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COMPARISON OF TRANEXAMIC ACID (TRANSAMIN®)™* AND TRADITIONAL THERAPY FOR SUDDEN DEAFNESS

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Abstract. The effectiveness of tranexamic acid treatment for sudden deafness was studied in detail. The results of treatment with tranexamic acid administration in 19 cases (25 ears) of sudden deafness and two historical control groups using various treatments were compared by the chi square contingency test. The data suggested that tranexamic acid treatment may be superior to traditional treatments especially if treatment is begun early. Among ears treated with tranexamic acid, 11 ears (44%) were healed or recovered remarkably, 8 ears (32%) recovered slightly and 6 ears (24%) were unchanged or worsened. Fibrinolysis in the inner ear may be the pathophysiology of sudden deafness. Treatment with tranexamic acid starting within 4 days after onset of symptoms was most effective in patients whose initial audiogram was flat or concave, initial average hearing loss at 5 frequencies (250 Hz, 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz) was between 23 dB and 76 dB (mean; 45.1 dB) and was not accompanied by dizziness.

Key words: sudden deafness, tranexamic acid, chi square contingency test.

Treatment of sudden idiopathic sensorineural hearing loss of undetermined cause still remains inconclusive although various treatments have been suggested (1-9). In 1976, 4 cases of sudden deafness of obscure origin in whom sensorineural hearing loss recovered completely following administration of tranexamic acid (10), an antiplasmin agent, were reported by Ohsaki *et al.* (11). In the present study, tranexamic acid was given to 19 patients (25 ears) with sudden deafness including the above mentioned 4 cases. The therapeutic effect of tranexamic acid among the 19 cases (25 ears) with sudden deafness was tested statistically against two historical control groups in which various modes of therapy had been attempted.

MATERIALS AND METHODS

Diagnostic criteria of sudden deafness. In April 1973, sudden deafness was recognized as a specific disease by the Ministry of Health and Welfare of Japan,

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and research into the epidemiology, etiology and treatment was started on a nationwide scale. The diagnostic criteria of sudden deafness were defined by the Sudden Deafness Research Committee of Japan in July, 1973 as follows:

Main symptoms. 1. Suddenly occurring deafness: Patient is able to state clearly that he noticed deafness on awakening from sleep or when working. 2. Obscure etiology (including uncertain cases): All cases lack a clear etiology for the sudden deafness (includes cases that have minor colds at, or shortly before, the time of onset). 3. Profound perceptive deafness: A) Perceptive deafness is not necessarily profound although the deafness may not be noticed in many cases if it is not profound. B) It is not determined by recruitment. C) Recovery and/or worsening of hearing acuity is not cyclic. D) In many cases deafness is unilateral, but in a few, deafness is bilateral concurrently.

Accessory symptoms. 1. Tinnitus: Tinnitus is mostly noticed just before or after the occurrence of deafness. 2. Dizziness, nausea and vomiting: Dizziness, which may be accompanied by nausea and vomiting, is occasionally noticed before or after deafness occurs but is not repeated. 3. Symptoms of other cranial nerves are absent.

Subjects. The subjects of this study were 19 patients seen in the Ear, Nose and Throat Clinic, Kobe Nishi-Shimin Hospital, Kobe, Japan between November 1974 and March 1975. Thirteen cases had unilateral and 6 cases bilateral deafneess. This group consisted of 8 males and 11 females. Six cases were in their forties, 3 in their thirties, fifties and sixties, 2 in their twenties, and 1 case each in teens and seventies (Tables 1, 2 and 3).

Treatment. Tranexamic acid was given intravenously and orally daily until hearing loss returned to normal or hearing acuity became fixed. The concentration of tranexamic acid in blood was maintained at approximately 10^{-3} mol in each patient; 5% tranexamic acid 250 mg (1 ml=50 mg) was injected intravenously once a day, while 1500 mg of tranexamic acid was given orally three times a day. All patients were treated in the outpatient clinic and the period of treatment for each patient is shown in Tables 1, 2 and 3.

Type of sudden deafness. Factors which are believed to influence the prognosis of sudden deafness were selected from data that were obtained at the first examination. These factors include the shape of the initial audiogram, the severity of hearing loss (arithmetical mean of hearing loss at 5 frequencies of 250 Hz, 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz, respectively), the time from onset of sudden hearing loss to the start of therapy, and the existence of dizziness.

Control groups. Historical control groups were identified from hospital records. Patients who received commonly used modes of therapy during the period July 1, 1971–June 30, 1973 were designated as control groups 1 and 2, for comparison with patients receiving tranexamic acid. Historical controls were identified from records in university hospitals, national hospitals and other large hospitals for the two year period ending in June 1973 when nationwide research by the Sudden Deafness Research Committee of Japan was started. Control group 1 included 362 ears treated with vasodilators, steroids and vitamins, while control group 2 included 312 ears treated with anticoagulants, drugs affecting

TABLE 1. HEALED OR REMARKABLY RECOVERED

Cases[a]	Age	Sex	Ear	Shape of audiogram	Hearing loss (Mean[b])	Hearing gain (Mean[b])	Gain/Loss ×100	Onset of therapy[c] (Day)	Period of therapy (Day)	Remarks
No. 1	48	M	L	Flat	23 dB	+11 dB	47.8%	1	32	Sudden deaf. at opposite side (cf. No. 13 in Table 2)
No. 2	51	M	L	Concave	48 dB	+34 dB	70.8%	2	17	
No. 3	35	F	R	Concave	48 dB	+39 dB	81.3%	4	18	
No. 4	31	M	R	High tone deaf.[e]	52 dB	+43 dB	82.7%	8	9	Malignant hypertension
No. 5	48	M	L	Concave	57 dB	+49 dB	86.0%	0	15	
No. 6	65	F	L	Flat	62 dB	+38 dB	61.3%	3	32	
No. 7[d]	44	F	R	Flat	76 dB	+47 dB	61.8%	2	36	
No. 8	45	F	R	Flat	41 dB	+23 dB	56.1%	2	16	
	45		L	Flat	27 dB	+11 dB	40.7%	2	16	
No. 9	19	F	R	Flat	23 dB	+15 dB	65.2%	4	21	
	19		L	Flat	39 dB	+31 dB	79.5%	4	21	
Mean	40.9				45.1 dB	+31.0 dB	66.7%	2.9	21.2	

a: All cases in this table were not accompanied by dizziness. *b*: Arithmetical mean of hearing acuity at 250 Hz, 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz. *c*: Period between deafness occurred and onset of therapy. *d*: Remarkably recovered. *e*: Gradual shape.

TABLE 2. SLIGHTLY RECOVERED

Cases[a]	Age	Sex	Ear	Shape of audiogram	Hearing loss (Mean[b])	Hearing gain (Mean[b])	Gain/Loss ×100	Onset of therapy[c] (Day)	Period of therapy (Day)	Remarks
No. 10	78	F	R	High tone deaf.[d]	57 dB	+21 dB	36.8%	0	21	
No. 11	20	M	R	High tone deaf.[d]	71 dB	+22 dB	31.0%	6	18	
No. 12	64	F	L	High tone deaf.[e]	82 dB	+26 dB	31.7%	121	40	
No. 13	48	M	R	Low tone deaf.	72 dB	+14 dB	19.4%	1	32	cf. No. 1 in Table 1.
No. 14	69	M	R	High tone deaf.[e]	65 dB	+23 dB	35.4%	14	29	
	69		L	High tone deaf.[e]	67 dB	+12 dB	17.9%	14	29	
No. 15	46	F	R	High tone deaf.[e]	28 dB	+11 dB	39.3%	11	17	Suffered influenza
	46		L	High tone deaf. (abrupt shape, only 8000 Hz)	40 dB	+21 dB	52.5%	11	17	
Mean	53.7[f]				57.1 dB[f]	+17.7 dB[f]	33.2%[f]	8.1[f]	23.3[f]	

a: No dizziness except Nos. 11 and 14, *b*, *c*: The same as shown in Table 1, *d*: Abrupt shape, *e*: Gradual shape, *f*: As it is thought to be an exception, No. 12 was excluded in the calculation.

TABLE 3. UNCHANGED (INCLUDING WORSENING)

Cases[a]	Age	Sex	Ear	Shape of audiogram	Hearing loss (Mean[b])	Hearing gain (Mean[b])	Gain/Loss ×100	Onset of therapy[c] (Day)	Period of therapy (Day)	Remarks
No. 16	47	F	R	High tone deaf.[d]	71 dB	+5 dB	7.0%	10	7	
No. 17[e]	50	F	L	Flat	76 dB	−14 dB	−18.4%	2	7	P. H.: Diabetes
No. 18	50	F	L	Total deaf.	88 dB	0 dB	0%	3	14	
No. 19	28	M	R	Total deaf.	92 dB	0 dB	0%	33	7	
No. 20	37	M	L	Total deaf.	92 dB	0 dB	0%	2	7	Suffered chr. hepatitis
	37		R	Total deaf.	92 dB	0 dB	0%	2	7	
Mean	41.5				85.2 dB	−1.8 dB	−1.9%	8.7	8.2	

a: No dizziness except Nos. 16 and 19, *b*, *c*: The same as shown in Tables 1 and 2, *d*: Gradual shape, *e*: Worsened.

the autonomic nervous system and stellate ganglion blocks. The results of control group therapy are shown in Table 4.

TABLE 4. PROGNOSIS BY TREATMENT AND INTERVAL FOLLOWING DISEASE ONSET[a]

Therapy	Onset of therapy[b] (Day)	Healed No.	%	Remarkably recovered No.	%	Slightly recovered No.	%	Unchanged or worsened No.	%	Total No.
Control 1 (vasodilators, steroids, vitamins) 1971-1973	0- 3	18	17.7	22	21.6	24	23.5	38	37.2	102
	4- 7	25	24.5	29	28.4	18	17.7	30	29.4	102
	8-14	7	7.5	14	14.9	23	24.5	50	53.1	94
	15-30	0	—	1	7.1	0	—	13	92.9	14
	⩾31	3	6.0	1	2.0	13	26.0	33	66.0	50
	Total	53	14.6	67	18.5	78	21.6	164	45.3	362
Control 2 (anti-coagulants, autonomic nervous agents, ganglion blockers) 1971-1973	0- 3	11	15.3	18	25.0	21	29.2	22	30.5	72
	4- 7	14	15.6	22	24.4	29	32.2	25	27.8	90
	8-14	8	9.8	18	22.0	23	28.0	33	40.2	82
	15-30	3	17.7	0	—	5	29.4	9	52.9	17
	⩾31	2	3.9	7	13.7	5	9.8	37	72.6	51
	Total	38	12.2	65	20.8	83	26.6	126	40.4	312
Tranexamic acid 1974-1975	0- 3	6	46.2	1	7.7	2	15.4	4	30.7	13
	4- 7	3	75.0	0	—	1	25.0	0	—	4
	8-14	1	16.7	0	—	4	66.6	1	16.7	6
	15-30	0	—	0	—	0	—	0	—	0
	⩾31	0	—	0	—	1	50.0	1	50.0	2
	Total	10	40.0	1	4.0	8	32.0	6	24.0	25

a: No. indicates number of ears (not patients' number).
b: Interval between disease onset and onset of therapy.

Therapeutic effects. The chi square contingency test was used for comparing therapeutic effects.

Standards of hearing recovery. Standards of hearing recovery were defined by the Sudden Deafness Research Committee of Japan in October 1974 and have been previously described (12). Standards of hearing recovery are summarized as follows:

Healed: 1. Cases who had recovered within 20 dB at 250 Hz, 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz, respectively. 2. Cases in whom the diseased ear recovered to the same auditory state as the healthy ear, and hearing acuity in the healthy ear was stable.

Remarkably recovered: Cases in whom arithmetical mean of hearing loss at 250 Hz, 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz was recovered by 30 dB or more.

Slightly recovered: Cases in whom arithmetical mean of hearing loss at above

5 frequencies recovered by 10 dB up to 30 dB.
Unchanged (including worsening) : Cases in whom arithmetical mean of hearing loss at above 5 frequencies changed within ± 10 dB.

RESULTS

Results and its classification of tranexamic acid treatment. Nineteen cases (25 ears) of sudden deafness were treated with tranexamic acid. Patients were divided into 3 groups based upon treatment response: healed or remarkably recovered, slightly recovered, and unchanged or worsened.

Each of the results was compared in regard to audiogram shape, severity of hearing loss, interval between hearing loss and treatment, and the presence or absence of dizziness. Results are given in Tables 1, 2 and 3.

In the healed or remarkably recovered 9 cases (11 ears) without dizziness (Table 1), therapies were started between the day of onset and day 8 after the onset of sudden hearing loss. The shape of audiogram was flat or concave in most cases, the severity of the average hearing loss in 5 frequencies was between 23 dB and 76 dB ($\bar{X}=45.1$ dB) and the amount of the average hearing improvement at 5 frequencies after therapy was from 11 dB to 49 dB ($\bar{X}=31.0$ dB).

In the slightly recovered 6 cases (8 ears) (Table 2), 4 cases (5 ears) were without dizziness and the remaining 2 cases (3 ears), with dizziness. Therapy was started between the day of onset and day 14 after onset except for one case on which therapy was started on day 121 after onset. Audiograms obtained before therapy showed the shape of high tone deafness in most cases and the severity of the average hearing loss at 5 frequencies was from 28 dB to 82 dB ($\bar{X}=57.1$ dB). The amount of average hearing improvement at 5 frequencies after therapy was between 11 dB and 26 dB ($\bar{X}=17.7$ dB).

In the unchanged or worsened 5 cases (6 ears) (Table 3), 3 were without dizziness; remaining two had dizziness. Therapy was started from day 2 to day 33 after onset. Audiograms showed the shape of total deafness in most cases and the severity of the average hearing loss at 5 frequencies was between 71 dB and 92 dB ($\bar{X}=85.2$ dB). The amount of average hearing improvement at 5 frequencies after therapy was from -14 dB to 5 dB ($\bar{X}=-1.8$ dB). However, one case who had concomitant diabetes mellitus showed the flat shape of sudden hearing loss in the initial audiogram, and subsequently worsened.

The percent of hearing recovery in the three categories was 66.7, 33.2 and -1.9%, respectively (Tables 1, 2 and 3). In the healed or remarkably recovered group (Table 1), patients Nos. 8 and 9 showed bilateral hearing loss. The percent hearing recovery was 56.1, 40.7 and 65.2, 79.5% in each ear, respectively. In the slightly recovered group (Table 2), patients Nos. 14 and 15 showed bilateral involvement, with the percent hearing recovery being 35.4,

17.9 and 39.3, 52.5% respectively. In the unchanged or worsened group (Table 3), patient No. 20 had 0% recovery in both ears. Of particular interest was a patient with bilateral involvement, whose left ear showed 47.8% recovery and right ear 19.4% recovery. Using the stated critera, this patient's left ear was grouped as healed or remarkably recovered (No. 1 in Table 1) and the right ear as slightly recovered (No. 13 in Table 2).

The results of treatment after the onset of hearing loss are shown in Table 4.

Statistical comparison of controls. When the results of control therapies were compared to each other by the chi square contingency test, the differences were not statistically significant (Table 4). When each control group was tested against the tranexamic acid treated group (Table 5), the results were statistically significant ($p<0.01$).

TABLE 5. CHI SQUARE CONTINGENCY TEST OF TREATMENT GROUPS BY PROGNOSIS

Therapy	Healed		Remarkably recovered		Slightly recovered		Unchanged		Total No.
	Obs.	Expect.	Obs.	Expect.	Obs.	Except.	Obs.	Expect.	
Control 1	53	52.31	67	68.88	78	87.52	164	153.29	362
Control 2	38	45.08	65	59.36	83	75.44	126	132.12	312
Tranexamic acid	10	3.61	1	4.76	8	6.04	6	10.59	25
Total	101		133		169		296		699

Obs.: Observed number, Expect.: Expected number.

DISCUSSION

Tranexamic acid, developed by Okamoto, S. and Okamoto, U. (13) in 1962 is an antiplasmin drug which is used clinically as a hemostatic agent to control oozing of blood in the plasmic or fibrinolytic state. The formula and chemical name of tranexamic acid (10) are $H_2N\text{-}CH_2\text{-}\langle\rangle\text{-}COOH$ and trans-4-aminomethylcyclohexane-carboxylic acid (abb. AMCHA). Its molecular weight is 157.

The material used in this study is Transamin, a brand name of tranexamic acid which is new investigational drug not approved for marketing by the Food and Drug Administration (F. D. A.) in the United States. Tranexamie acid (14) has the actions and uses of aminocaproic acid. It is reported to be 7 to 10 times more potent and to be less toxic than aminocaproic acid, produced by Lederle Laboratories under the name Amicar which is approved by the F. D. A..

When a new agent is thought to be effective for treating some diseases, it is necessary to evaluate objectively whether this new agent is in fact effective. Though double blind, controlled studies are well known techniques to evaluate drugs, the ethical problem of treating sudden deafness precludes this methodolo-

gy (2–4, 6, 12). For this reason historical controls were selected for comparison.

In data analysis, various parameters which were readily determined were used to evaluate prognosis. However, we consider that interval between disease onset and treatment have the greatest influence on the prognosis. In a limited 19 cases shown in Tabes 1, 2 and 3, age was not correlated with prognosis. We think, therefore, that other factors, *e.g.*, hearing loss and early treatment, are more closely related to the effectiveness of therapy.

As the molecular weight of tranexamic acid (10) is very low (157) compared with other drugs, we believe that tranexamic acid can easily reach the inner ear in adequate blood concentration.

In general, fibrinolysis might influence acceleration of permeability in tissue, tissue edema and extravascular red cell oozing (15, 16). If we assume that tranexamic acid, an antifibrinolytic agent, acts thus on the inner ear, then it would be logical to assume that sudden deafness is caused by an increase of fibrinolytic activity. Control of the fibrinolysis, especially in early stages, should be associated with better recovery of hearing.

Morimitsu *et al.* (17) recently proposed an idea about the pathophysiology of sudden deafness regarding meglumine diatrizoate treatment. Sudden hearing loss without vertigo could be due to a breakdown in the blood-cochlear barrier in the area of the *stria vascularis* with a subsequent decrease in the endocochlear DC potential. They suggest that because of the molecular weight and character of meglumine diatrizoate, the broken membrane pores are filled and the sodium pump is activated again to produce normal endolymph.

Schuknecht *et al.* (18, 19) performed autopsies the patients, 9 days to 20 years after the onset of sudden deafness. They showed atrophy of the organ of Corti, tectorial membrane and *stria vascularis*, suggesting viral labyrinthitis. On the other hand, Gussen (20) reported total loss of the organ of Corti, severe degenerative changes of *stria vascularis*, spiral ligament, outer sulcus cells and distal cochlear nerve fibers, and fresh hemorrhage in the temporal bone relating to the terminal subarachnoid hemorrhage. These occurred 2 months before death.

Regarding the pathological studies of sudden deafness within the time of cochlear dysfunction before irreversible changes occur, it is almost impossible to obtain specimens as no patients die so soon after the onset of sudden hearing loss without systemic serious complication. So, at present, it is reasonable to speculate about the pathophysiology of sudden deafness being reversible.

On the basis of clinical data in our series of 19 cases (25 ears) of sudden deafness, we classified cases assuming that fibrinolysis did occur in the inner ear in the group of healed or remarkably recovered as follow : therapy was started within day 4 after the onset of sudden hearing loss ; the shape of the initial

audiogram was flat or concave; the patients did not complain of dizziness; and the initial average hearing loss at 5 frequencies was between 23 dB and 76 dB. Among slightly recovered patients, fibrinolysis could have occurred, especially in the cases of high tone deafness, at an early stage following the onset of sudden deafness.

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