Efficacy of Thyrotropin-Releasing Hormone Analog for Protracted Disturbance of Consciousness due to Aneurysmal Subarachnoid Hemorrhage

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Objective: The efficacy of thyrotropin-releasing hormone tartrate (TRH-T) for treating prolonged disturbance of consciousness due to aneurysmal subarachnoid hemorrhage (SAH) remains unclear. The purpose of the present study was to determine whether TRH-T was really effective, and what was the recovery factor when it was valid. This was a retrospective study of a single facility. *Methods*: We treated 208 patients with aneurysmal SAH at our hospital between 2011 and 2017. Among them, we investigated 97 cases in which TRH-T was administered to prolonged disturbance of consciousness. Thirty one patients with Hasegawa dementia rating scale-revised (HDS-R) score less than 20 were included. Patients' HDS-R scores were evaluated 7 days after clipping the aneurysm and 2 days after completing a course of TRH-T treatment. HDS-R score increases of greater than or over equal to 8 and less than 8 were defined as good and poor outcomes, respectively. Outcomes were compared to 11 patients who did not receive TRH-T treatment. *Results*: Average initial and post-treatment HDS-R scores were 9 ± 6.6 and 19 ± 9.5, respectively. The good outcome group included 19 patients. Statistically significant differences in HDS-R score changes were observed between the group with initial HDS-R scores of 0-4 and the other groups. Poor outcomes were significantly correlated with age of greater than 60 years and initial HDS-R scores less than or over equal to 4 points. The improvement in HDS-R score was significantly greater in the TRH-T administration group than the control group. *Conclusions*: TRH-T was effective for treating prolonged disturbance of consciousness due to aneurysmal SAH, especially in young patients with HDS-R scores between 5 and 20.
Key Words: Aneurysm—Prolonged disturbance of consciousness—protirelin tartrate hydrate—subarachnoid hemorrhage—thyrotropin-releasing hormone analog

Abbreviations: HDS-R, Hasegawa dementia rating scale-revised; HK, Hunt and Kosnik; SAH, subarachnoid hemorrhage; TRH, thyrotropin-releasing hormone; TRH-T, thyrotropin-releasing hormone tartrate

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Introduction

Subarachnoid hemorrhage (SAH) due to ruptured cerebral aneurysms has a poor prognosis,[1,2] and many patients with SAH suffer side effects such as higher-order neurological dysfunction[3,4] or prolonged disturbance of consciousness.[5] There is some evidence that thyrotropin-releasing hormone tartrate (TRH-T) may be effective for treating prolonged disturbance of consciousness due to aneurysmal SAH.[6,7] However, the methods used to evaluate TRH-T efficacy in previous studies were not consistent. Moreover, to the best of our knowledge, there has been no report on the recovery factors following TRH-T treatment. The purpose of the present study was to determine whether TRH-T was really effective for patients of aneurysmal SAH with prolonged disturbance of consciousness, and what was the recovery factor when it was valid.

Materials and Methods

Our study was based on criteria from the Strengthening the Reporting of Observational Studies in Epidemiology statement. The study was approved by the Chiba Hokusoh Hospital Research Ethics Committee, Chiba, Japan. This was a retrospective study of a single facility.

Patient Characteristics

Flow diagram of patients' selection was shown in Figure 1. We treated 208 patients with aneurysmal SAH at our hospital between 2011 and 2017. Among 201 patients without 7 cases of data deficiency, 97 cases were treated with TRH-T analog for the treatment of prolonged disturbance of consciousness. In this study, we used the Hasegawa dementia rating scale-revised (HDS-R) score[8] as an indicator of disturbance of consciousness because the HDS-R score could be easily evaluated in a short time. The HDS-R scores less than 20 point were 38 cases, and HDS-R scores greater than or over equal to 20 point were 59 cases. Thirty one patients excluding 7 data loss cases from 38 cases with HDS-R score less than 20 were included in this study. This resulted in 8 male and 23 female patients (mean age, 60.7; range, 36−76). Patient characteristics, including SAH grading and aneurysm location, are presented in Table 1. We retrospectively reviewed data from patient charts, including admission data, laboratory test, imaging studies, and follow-up reports. The Hunt and Kosnik (HK) grade[9] was 1 in 1 patient, 2 in 12 patients, 3 in 12 patients, 4 in 4 patients, and 5 in 2 patients. Fisher group 3 was noted in 30 patients. Aneurysms were located in the anterior communicating artery in 16 patients, in the internal carotid artery in 7 patients, in the middle cerebral artery in 6 patients, in the basilar artery in 1 patient, and in the vertebral artery in 1 patient. During the same period, 11 patients with aneurysmal SAH were not treated with TRH-T because doctors judged their condition to be due to liver dysfunction, fever, and so on. The same patient data were extracted for this non-treatment group.

Treatment and Outcome Assessment

At our institution, we treat aneurysmal SAH by clipping in the acute stage (< 2 days). Perioperative care was performed according to a standardized protocol provided by the guidelines for managing aneurysmal SAH in Japan.[10]

We evaluated patients' HDS-R scores 7 days after clipping the aneurysm and 2 days after they completed a course of daily intravenous 2 mg TRH-T treatment. HDS-R score increases of greater than over equal to 8 and less than 8 were defined as good and poor outcomes, respectively.

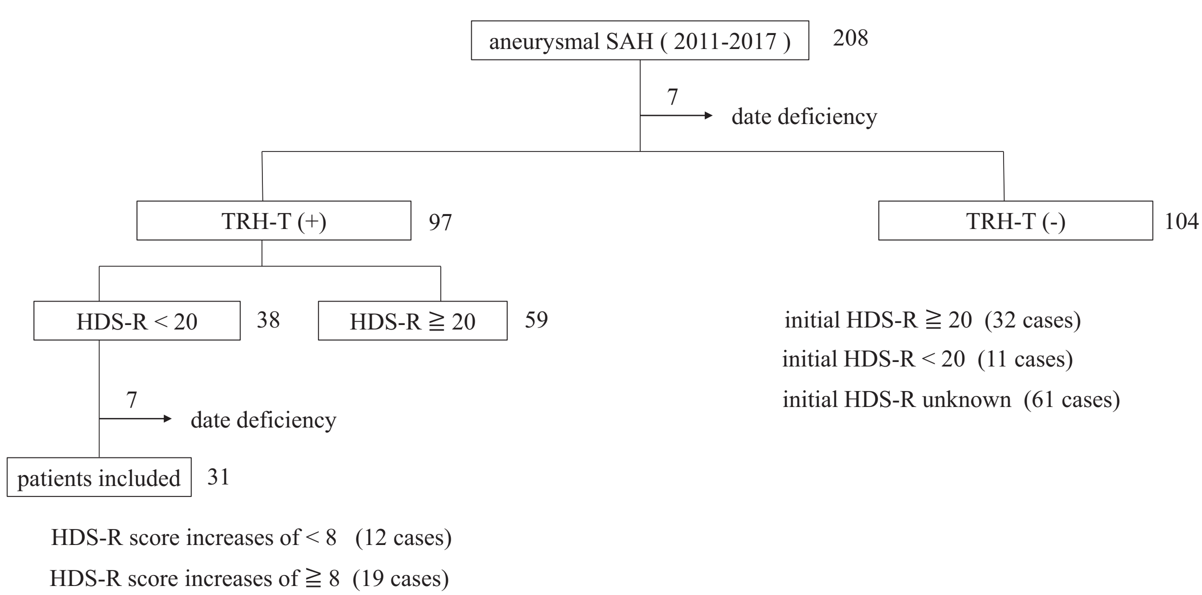

Figure 1. *Flow diagram of patients' selection.*

Table 1. *Patient characteristics*

Number of patient treating Aneurysmal SAH	208 cases (female 132 cases, mean age 61.4)
Number of patient included study (HDS-R score <20 point)	31 cases (31/208)
Sex (male:female)	8:23
Age	36-76 (mean:60.7)
Hunt and Kosnik grade	Grade1, 1case Grade2, 12cases Grade3, 12cases Grade4, 4cases Grade5, 2cases
Aneurysm location	ACA: 16cases IC: 7cases MCA: 6cases BA: 1case VA: 1case

Abbreviations: HDS-R, Hasegawa dementia rating scale-revised; SAH, subarachnoid hemorrhage.

Furthermore, we analyzed the factors related to poor outcomes. To control for the possibility that disorder of consciousness improved by the natural course, we compared outcomes between the TRH-T treatment group and the nontreatment group.

Statistical Analysis

Statistical analysis was performed using SPSS for Mac (V.21.0; SPSS, Armonk, NY). Variables are expressed as mean ± standard deviation, median (interquartile range, 25th−75th percentiles), or number of patients (%), where appropriate. The relationship between poor outcomes (<8 points) and clinical variables was investigated. Normally distributed continuous variables were compared using Student's *t* test, whereas non-normally distributed variables were compared using the Mann−Whitney *U* test. Multivariate logistic regression analysis was performed for all variables, including age, sex, aneurysm location, Fisher group, HK grade, and duration of TRH analog administration to determine the variables that were significantly associated with poor outcomes.

Differences with *P* values less than or over equal to .05 were considered statistically significant.

Results

Details of TRH-T analog treatment and efficacy are presented in Table 2. Average initial and post-treatment HDS-R scores were 9 ± 6.6 and 19 ± 9.5, respectively. TRH-T was administered on days 9−32 (mean treatment duration, 16.4 ± 3.7 days). As shown in Figure 2, patients with initial HDS-R scores of 0−4, 5−9, 10−14, and 15−20 points showed increases of 4 ± 5.4, 11.6 ± 3.8, 13.2 ± 7.9, and 8.5 ± 3.3 points, respectively. Statistically significant differences in HDS-R score changes were observed between the group with initial HDS-R scores of 0−4 and the other groups ($P = .031$). Nineteen patients (61.3%) were present in the good outcome group. As shown in Table 3, poor outcomes were significantly correlated with age of greater than 60 years ($P = .02$; odds ratio, 12.2; 95% confidence interval, 1.3−114) and initial HDS-R scores less than or equal to 4 points ($P = .0118$; odds ratio, 11.9; 95% confidence interval, 1.8-76). Furthermore, as shown in Table 4, multivariate logistic regression analyses showed that poor outcomes were significantly correlated with age greater than 60 years ($P = .012$) and initial HDS-R scores less than or equal to 4 points ($P = .04$).

The comparison between the TRH-T treatment group and nontreatment group is shown in Figure 3.

Table 2. *Details of treatment and efficacy of TRH-T analog*

Initial and post-treatment HDS-R score and day of administration	
Initial HDS-R score	0-20 point (mean; 9 point, SD 6.6)
Post-treatment HDS-R score	2-30 point (mean; 19 point, SD 9.5)
Day of administration TRH-T	9-32 day (mean; 16.4, SD 3.7)
Initial HDS-R score	**Average of increase of HDS-R point (SD)**
0-4	4 (5.4)
5-9	11.6 (3.8)
10-14	13.2 (7.9)
15-20	8.5 (3.3)

Abbreviations: HDS-R, Hasegawa dementia rating scale-revised; SD, standard deviation; TRH-T, thyrotropin-releasing hormone tartrate.

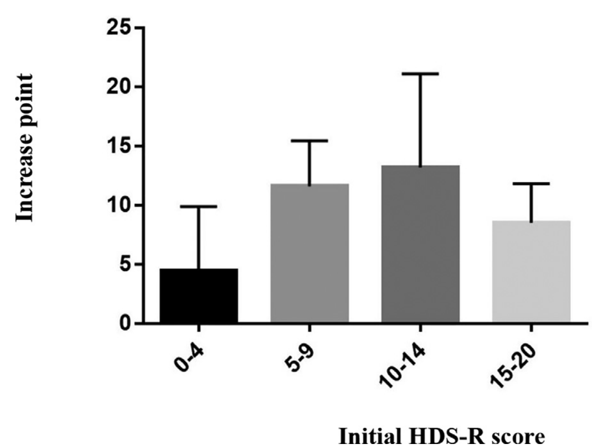

Figure 2. *Comparison of score increases when initial HDS-R scores are divided into 4 groups.*

Table 3. *Results of statistical analysis of risk factors for poor outcomes of TRH-T treatment*

Variable	Total	Good outcome (rise more than 8 points)	Poor outcome (rise less than 8 point)	*P* value*	Odds ratio
Mean age, yrs (SD)	60.7 (11)	56.3 (10.6)	67.6 (8.1)	**.0024**	
Over 60 (age) (%)	20 (64)	9 (47)	11 (91)	**.02**	12.2 (1.3-114)
Sex, female (%)	23 (74)	14 (73)	9 (75)	1.0	
Aneurysm location (posterior circulation) (%)	2 (6.4)	0 (0)	2 (17)	.5097	
Fisher group3 (%)	30 (97)	11 (92)	12 (100)	1.0	
H andK grade (severe 4, 5) (%)	6 (19)	3 (15)	3 (25)	.6526	
Initial HDS-R ≦4 point (%)	9 (29)	2 (10)	7 (58)	**.0118**	11.9 (1.8-76)
Span to administration of TRH analog	16.4 (3.7)	15.7 (1.6)	18 (5.6)	.202	

Abbreviation; HDS-R, Hasegawa dementia rating scale-revised; SD, standard deviation.
Data are expressed as number of patients (%), unless otherwise indicated.
*Variables showing significant difference by univariate analysis ($P < .05$) are indicated by boldface.

Table 4. *Multivariate logistic regression analysis of risk factors for poor outcomes following TRH-T treatment*

Variable	OR (95% CI)	*P* value*
Age > 60	6.3 (2.3-15)	**.012**
Initial HDS-R ≦ 4 point	8.4 (1.8-24)	**.04**
Sex (female)		.93
Aneurysm location (posterior circulation)		.245
Fisher group 3		.419
H and K grade (severe 4, 5)		.527

Abbreviations: CI, confidence interval; HDS-R, Hasegawa dementia rating scale-revised; OR, odds ratio.
*Variables showing significant difference by univariate analysis ($P < .05$) are indicated by boldface.

The groups did not differ significantly in terms of age, sex, aneurysm location, HK grade, or initial HDS-R score. Patients treated with TRH-T showed an HDS-R score increase of 10 ± 6.6 points, whereas the nontreatment group showed an increase of 3 ± 2.7 points. The difference in HDS-R score increases between the groups was statistically significant ($P = .0003$).

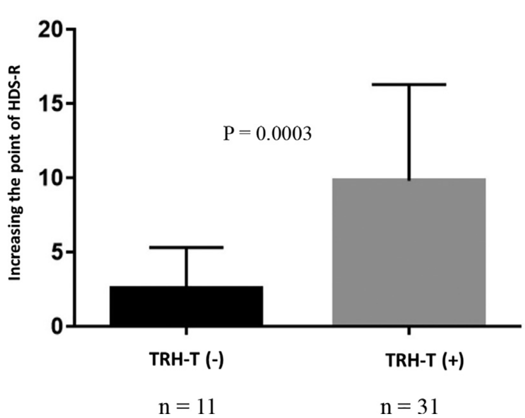

Figure 3. *Comparison between TRH-T treatment group and nontreatment group.*

Discussion

In the present study, TRH-T was effective for treating prolonged disturbance of consciousness due to aneurysmal SAH, especially in patients with HDS-R scores of less than 20 points. Poor outcomes were significantly correlated with age and initial HDS-R scores of less than 4 points. Therefore, TRH-T may be especially effective in young patients and in patients with initial HDS-R scores of greater than or over equal to 5 points. Despite improvements in treatment, aneurysmal SAH is still associated with high rates of mortality and morbidity.[3] Patients who survive treatment often suffer from side effects such as paresis, disturbance of consciousness, or higher-order neurological dysfunction; one-third of survivors never regain independence.[11] Rehabilitation after treatment for disturbance of consciousness, especially in young patients, is extremely important not only from the viewpoint of patient outcome but also from that of medical economics.[12,13] Causes of disturbance of consciousness due to aneurysmal SAH reportedly include extensive brain damage due to primary rupture, hydrocephalus, cerebral infarction due to cerebral vasospasm, and pituitary dysfunction.[14,15] Kreitschmann et al[15] reported that patients with aneurysmal SAH in the chronic stage after treatment have pituitary dysfunction in the form of growth and thyroid hormone deficiency. One report demonstrated that low T3 syndrome was associated with hydrocephalus and brain tumor, and that 43% of patients had aneurysmal SAH.[16,17]

Following brain injury, insufficient pituitary hormone secretion may occur in 30%−70% of cases.[16,18] Although the mechanism of underlying pituitary dysfunction in the chronic stage of aneurysmal SAH remains unclear, bleeding or subsequent surgical manipulation can damage hypothalamic structures. Pituitary dysfunction and low T3 syndrome are common complications in patients suffering from intracranial disorders and are associated with greater disease severity, a complicated clinical course, and greater mortality and handicap rates.[17,19,20]

Protirelin tartrate (TRH analog, HIRTONIN, Takeda, Japan and BOGNIN, Nichiiko, Japan) is currently used in Japan to promote recovery from disturbance of consciousness after aneurysmal SAH and head trauma due to its activation of the central nervous system.[21] Jun et al[6] demonstrated the positive effect of thyroid hormone replacement therapy on cognitive function in patients with aneurysmal SAH. However, few recent studies have assessed TRH-T treatment for disturbance of consciousness due to aneurysmal SAH.

In the present study, we evaluated TRH-T efficacy using HDS-R, a simple test for evaluating cognitive function and disturbance of consciousness. Jeong et al[22] reported that HDS-R scores are more influenced by demographic characteristics than MMSE, but that normative data contribute to improve diagnostic accuracy of dementia. By analyzing the outcomes, we found that older patients had poorer outcomes than younger patients and that a low initial HDS-R score was a significant factor for poor outcome. The natural prognosis of aneurysmal SAH was better in younger patients than in older ones, and younger patients had higher HDS-R scores than older patients.[23,24] Sano et al[7] administered TRH-T for aneurysmal SAH in a double-blind study and reported that 33% of patients in the placebo group had a good neurological outcome. Here, to control for the natural course of aneurysmal SAH, we compared outcomes between the TRH-T treatment group and the nontreatment group. The increase in HDS-R score was significantly higher for the TRH-T treatment group, supporting the effectiveness of TRH-T treatment. Although the 2 groups did not differ in demographic characteristics, the conditions (such as fever and liver dysfunction) of patients in the nontreatment group may have influenced HDS-R scores.

Limitations

This study has several limitations. First, the administration criteria for TRH-T were not clear; judgment of whether to use TRH-T depended on the attending doctors. Second, interpretation of the results is limited by the relatively small sample size and retrospective analysis. It was a major problem that there were many missing data. Third, we did not measure hormone levels, which could offer insight into the mechanism of improvement. Finally, there was a lack of evidence of setting outcome. To date, there are few reports about improving score of the HDS-R. Therefore, we defined increasing for 8 points as temporary expedient in this study. And then, we could obtain a significant difference by poor outcome and good outcome at 8 points. However, this definition and clinical meaning do not have enough scientific evidence.

Further research with prospective analysis, hormone measurements, a larger sample, and evidence of outcome setting criteria would help support the claim of this study.

Conclusions

TRH-T may improve disturbance of consciousness due to aneurysmal SAH, particularly for younger patients. Further study is needed to support this claim.

Conflicts of Interest

None of the authors have any conflicts of interest.

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