J. Phys. Ther. Sci. 35: 678–684, 2023

The Journal of Physical Therapy Science

Original Article

Factors associated with improvement in impaired consciousness during the acute phase of cerebral infarction: a prospective observational study

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Abstract. [Purpose] In this study, we investigated factors that contribute to improvement in impaired consciousness following cerebral infarction. [Participants and Methods] This prospective observational study included 186 patients with cerebral infarction. We investigated 21 variables including the rehabilitation status to determine factors that contribute to improvement in impaired consciousness. [Results] Improvement in impaired consciousness was correlated with age, delirium, the Japan Coma Scale score at initiation of rehabilitation, worsening, cerebral edema, and standing practice. [Conclusion] We conclude that the aforementioned factors may serve as predictors of possible improvement and that standing practice may contribute to improvement in impaired consciousness.
Key words: Impaired consciousness, Cerebral infarction, Acute phase

(This article was submitted May 18, 2023, and was accepted Jun. 28, 2023)

INTRODUCTION

Stroke is the second most common cause of mortality worldwide and the third longest disability-adjusted life years considering the degree and the duration of disability[1)].

Frequent impaired consciousness in the acute phase of stroke has a negative impact on physical and mental functions and activity capacity. For example, the patient's impaired consciousness may interfere with assessment and intervention, such as not being able to finish meals due to lack of sustained attention, requiring assistance to walk to the toilet due to insufficient muscle strength, and not being able to ensure the validity of higher brain function assessments necessary for driving. Therefore, therapists need to plan programs to anticipate future condition of impaired consciousness and to provide effective rehabilitation.

Previous studies reported that various factors at the time of admission were related to impaired consciousness during admission[2, 3)]. It was also reported that these factors were associated with serious complications and outcomes[3–5)]. Moreover, it was said that impaired consciousness at discharge was a predictor of some outcomes such as discharge outcome destination, death at 3 months, and severe disability[6)]. However, there is no investigation as to which factor affects improvement of impaired consciousness in patients with acute stroke. Clarifying such factors will contribute to the planning of rehabilitation program for the patients of acute stroke.

In addition to the timepoint of admission, factors that may influence the improvement of impaired consciousness should be considered as it relates to comorbidities, medication status, and even the implementation of rehabilitation. This is because it

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is said that rehabilitation in the acute phase improves functional disability and ADL[7–9]. We believe that clarifying the implementation of rehabilitation related to the improvement of impaired consciousness will assist in the practice of rehabilitation for people with impaired consciousness.

Stroke types are divided into cerebral infarction, cerebral hemorrhage, and subarachnoid hemorrhage. Of these, cerebral infarction accounts for 70% of all strokes in Japan[10], and it is the most frequently encountered cerebrovasucular disease in clinical situations.

Therefore in this study, we focus on factors that are associated with improvement of impaired consciousness in patients with cerebral infarction.

PARTICIPANTS AND METHODS

The study design was a prospective observational study. The hospital is an acute care hospital with an emergency center, with 480 beds and an average length of stay of about 12 days for all patients and about 20 days for stroke patients. The majority of stroke patients in the region are transported to this hospital for emergency treatment.

In this study, we followed the patients for 2 weeks from the start of rehabilitation, taking into account the average length of hospital stay at our hospital.

Rehabilitation for stroke patients begins the day following the onset date for occupational therapy and physical therapy, and as needed for speech and language therapy.

The study participants were patients with cerebral infarction who were admitted to our hospital between September 2021 and May 2022 and received prescriptions for rehabilitation. Patients who could not undergo magnetic resonance imaging (MRI) examination on admission, those who were clear consciousness at the start of rehabilitation, those who showed severe aphasia, and those who were discharged before the end of the 2-week observation period were excluded.

The following items were investigated: patient background (age, sex, volume of responsible lesion on admission, presence or absence of thalamic/brainstem lesions, mechanical thromboprophylaxis and worsening [cerebral infarction expansion, recurrence, or hemorrhagic infarction]), medical history (presence or absence of stroke and dementia), complications (degree of delirium, presence or absence of cerebral edema, infectious disease and dehydration/electrolyte abnormalities), evaluation results (impaired consciousness and stroke severity at the start of rehabilitation, impaired consciousness after 2 weeks, and improvement of impaired consciousness after 2 weeks compared to the start of rehabilitation), rehabilitation implementation status (rehabilitation time per day, whether or not the patient performed sitting practice, standing practice and walking practice), use of the medications to improve impaired consciousness (amantadine hydrochloride [Symmetrel®], citicoline [Nicoline®], and nicergoline [Sermion®]).

The following assessments were performed: responsible lesion volume at admission, level of consciousness at the start of rehabilitation and 2 weeks after rehabilitation, stroke severity at the start of rehabilitation, and delirium during hospitalization.

The volume of the source lesion at the time of admission to the hospital was measured using an Amin Ziostation2 workstation (AMIN, Tokyo, Japan). Ziostation2 is a workstation that can process MRI images in three dimensions, extract the cerebral infarction area from the images, and calculate the volume of the extracted area.

The Japan Coma Scale (JCS)[11] was used to assess the level of consciousness at the beginning and 2 weeks after rehabilitation. The JCS is an evaluation scale of consciousness level mainly used in Japan. The JCS evaluates the level of consciousness by dividing it into three major levels, each of which is further subdivided into three levels, for a total of nine levels (1, 2, 3, 10, 20, 30, 100, 200, and 300), and adding “clear consciousness” (0 as a proxy), making a total of 10 levels. This is a one-dimensional ordinal scale in which a higher score indicates a more severe impaired consciousness. Because the level of consciousness is unstable, it was assessed separately by the occupational therapist, physical therapist, and speech-language pathologist or nurse, and the lowest score was used.

Stroke severity at the beginning of rehabilitation was assessed by occupational therapists using the NIHSS[12], a severity rating scale widely used in the acute phase of stroke, which evaluates 11 functional impairments such as motor paralysis and sensory impairment on a 3–5 scale. The total score ranges from 0–40, with higher scores indicating more severe functional impairment.

The Japanese version of the Intensive Care Delirium Screening Checklist (ICDSC)[13] was used to assess delirium during hospitalization by occupational therapists based on nursing records. ICDSC is an internationally widely used scale for assessing delirium, which evaluates eight symptoms of suspected delirium, including changes in level of consciousness, lack of attention, and other symptoms. The total score ranges from 0–8, and a score of 4 or more is considered delirium. The ICDSC is a tool that enables retrospective evaluation of delirium from recorded data.

For statistical analysis, we divided patients into two groups. 1) improved group: patients who showed at least 1 step of improvement in the JCS level of consciousness two weeks after the start of rehabilitation; 2) non-improved group: patients not showed improvement. Factors associated with improvement in impaired consciousness were analyzed by univariate analysis. We first compared variables between the two groups. The qualitative variables of sex, presence or absence of thalamic/brainstem lesions, mechanical thromboprophylaxis, worsening, pre-existing stroke, pre-existing dementia, cerebral edema, infectious disease and dehydration/electrolyte abnormalities, whether or not the patient performed sitting, standing and walking practice, whether or not the patient used of consciousness-improving drugs were compared using χ^2 test. Quantitative variables were tested for normality with the Shapiro–Wilk test, and analyzed with the t-test for time of rehabilitation following a normal distribution, and with the Mann–Whitney U test for age, volume of responsible lesion at admission, degree of delirium, JCS at start of rehabilitation and after 2 weeks (JCS 0–300 was replaced by 0–9), and NIHSS at start of rehabilitation.

Next, multiple logistic regression analysis using the forced entry method was performed with the presence or absence of improvement in impaired consciousness (improvement: 1; no improvement: 0) 2 weeks after the start of rehabilitation as the dependent variable and all other variables as independent variables.

The odds ratios, 95% confidence interval (95% CI), and the discriminant accuracy of the overall model were calculated for the items that remained in the regression model, and the Hosmer–Lemeshow test was used to determine the goodness of fit of the model. To consider the influence of multicollinearity, a correlation matrix was obtained prior to multiple logistic regression analysis, and variables that were considered clinically significant when the absolute value of the correlation coefficient was 0.7 or higher were selected for examination. SPSS Ver 25.0 (IBM Japan, Tokyo, Japan) was used for these analyses, and the significance level was set at 5%.

This study was conducted with the approval from the Ethics Committee of Hirosaki University Graduate School of Health Sciences, (approval number: 2021-013).

RESULTS

A total of 186 out of 321 patients with cerebral infarction who underwent rehabilitation during the study period were included in the present study (Fig. 1).

Table 1 shows the attributes of the study participants. The mean (standard deviation) age was 79.8 years (± 10.3), and 98 (52.7%) were males and 88 (47.3%) were females.

Table 2 compares each variable between the improved groups (113 patients, 60.8%) and the non-improved group (73 patients, 39.2%). The improved group was younger than the non-improved group (p=0.004), contained more patients on mechanical thromboprophylaxis (p=0.044), fewer patients with worsening (p=0.011) and pre-existing dementia (p=0.040), and the delirium (p=0.002) and JCS after 2 weeks (p<0.001) were milder.

Table 3 shows the results of the multiple logistic regression analysis of factors related to the presence or absence of improvement in impaired consciousness. The results of the correlation matrix considering the influence of multicollinearity showed that the correlation coefficients between JCS at the start of rehabilitation and JCS after 2 weeks was 0.81 (p<0.001), that between JCS and NIHSS at the start of rehabilitation was 0.84 (p<0.001), and that between NIHSS at the start of rehabilitation and JCS after 2 weeks was 0.81 (p<0.001). Hence, JCS at the start of rehabilitation was included in the subsequent analysis.

In addition, the use of the medications to improve impaired consciousness was excluded from the analysis, as it caused a complete separation with 0 cells in the 2 × 2 crosstabulation table. The analysis showed that factors associated with the presence or absence of improvement in impaired consciousness were age (p=0.045; odds ratio, 0.957; 95% CI, 0.917–0.999), presence or absence of worsening (p=0.005; odds ratio, 0.178; 95% CI, 0.054–0.587), delirium (p=0.001; odds ratio, 0.556; 95% CI, 0.391–0.789), presence or absence of cerebral edema (p=0.017; odds ratio, 0.178; 95% CI, 0.044–0.730), JCS at the start of rehabilitation (p<0.001; odds ratio, 3.149; 95% CI, 1.970–5.032), and whether or not the patient performed standing practice (p=0.001; odds ratio, 17.221,95%CI 2.982–99.459). The results of the model were significant at p<0.001, and the result of the Hosmer–Lemeshow's test was p=0.684. The discriminant accuracy rate was 77.0%.

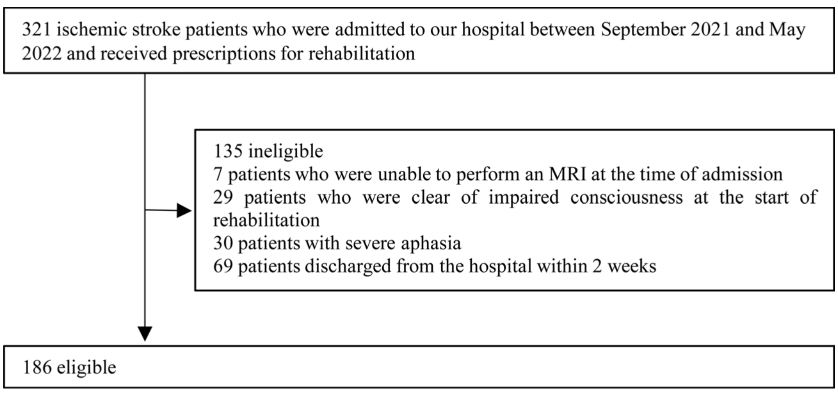

Fig. 1. Flow until enrolling target patients.

Table 1. Characteristics of patients (n=186)

Background		
Age (years)[a]		79.8 (10.3)
Sex[b]	Male: Female	98 (52.7): 88 (47.3)
Thalamic/brainstem lesions[b]	Yes: No	44 (23.7): 142 (76.3)
Volume of responsible lesion (mL)[a]		5.0 (19.1)
Mechanical Thromboprophylaxis[b]	Yes: No	20 (10.8): 166 (89.2)
Worsening[b]	Yes: No	30 (16.1): 156 (83.9)
Medical history		
Stroke[b]	Yes: No	63 (33.9): 123 (66.1)
Dementia[b]	Yes: No	24 (12.9): 162 (87.1)
Complication		
Delirium[a]		1.0 (2.0)
Cerebral edema[b]	Yes: No	47 (25.3): 139 (74.7)
Infectious disease[b]	Yes: No	24 (12.9): 162 (87.1)
Dehydration/electrolyte abnormalities[b]	Yes: No	25 (13.4): 161 (86.6)
Evaluate Results		
JCS at the start of rehabilitation[a]		2 (3)
JCS after 2 weeks[a]		2 (3)
NIHSS at the start of rehabilitation[a]		5.5 (11.0)
Rehabilitation implementation status		
Rehabilitation beginning day after onset (day)[a]		1 (0)
Rehabilitation time per day (min)[c]		69.8 (19.5)
Sitting practice[b]	Yes: No	157 (84.4): 29 (15.6)
Standing practice[b]	Yes: No	153 (82.3): 33 (17.7)
Walking practice[b]	Yes: No	124 (66.7): 62 (33.3)
Medication status		
Medications to improve impaired consciousness[b]	Yes: No	0 (0.0): 186 (100.0)

[a]: Median (Inter Quartile Range), [b]: number (%), [c]: Mean (standard deviation).
JCS: The Japan Coma Scale; NIHSS: National Institutes of Health Stroke Scale.

DISCUSSION

In this study, we examined factors related to the improvement of impaired consciousness in the acute phase, including the status of rehabilitation, and selected six factors: age, presence or absence of worsening, delirium, presence or absence of cerebral edema, JCS at the start of rehabilitation, and whether or not the patient performed standing practice. These factors are discussed below.

Regarding age and cerebral edema, being older and having cerebral edema had a negative effect on improvement of impaired consciousness. Both of these are risk factors for impaired consciousness on admission[2, 3)] and negative factors for outcomes such as reduced ADL capacity and increased mortality after 3 months[2, 3)], and being older and having cerebral edema were also shown to have a negative effect on the improvement of impaired consciousness. Regarding the relationship between age and cerebral edema, most older patients have severe cerebral atrophy, which may be less affected by cerebral edema. However, the results of this study, which were adjusted for these two factors by multivariate analysis, indicate that age and cerebral edema may be independent factors. In a previous study[2)], mortality rates were compared between two groups, those aged <65 years and those aged ≥65 years, stratified by the presence of cerebral edema. The mortality rate was higher in patients with cerebral edema aged ≥65 years than in those aged <65 years, indicating that age and cerebral edema may be factors independent of each other. The relationship between cerebral edema and older age, when considered in conjunction with the results of this and previous studies, suggests that these may be independent predictors.

Regarding the presence or absence of worsening, having a cerebral infarction exacerbation, recurrence, or hemorrhagic infarction had a negative impact on the improvement of impaired consciousness in this study. Previous studies have reported that the incidence of impaired consciousness in cerebral infarction is not less than 35%[3)], and patients with impaired consciousness on admission have a higher proportion of hemorrhagic infarction compared with those without impaired consciousness[3)]. Considering the results of this study together with the results of previous studies, it was inferred that cerebral exacerbation and recurrent and hemorrhagic infarction exacerbated the impaired consciousness and had a negative effect on the improvement of impaired consciousness.

Table 2. Comparison of variables between improved group and non-improved group

		Improved group (n=113)	Non-improved group (n=73)
Background			
Age (years)[a, *]		79 (12)	84 (10)
Sex[b]	Male: Female	50 (44.2): 63 (55.8)	38 (52.1): 35 (47.9)
Thalamic/brainstem lesionsb	Yes: No	25 (22.1): 88 (77.9)	19 (26.0): 54 (74.0)
Volume of responsible lesion (mL)[a]		5.0 (19.8)	5.2 (18.2)
Mechanical thromboprophylaxis[b, *]	Yes: No	17 (15.0): 96 (85.0)	4 (5.0): 69 (95.0)
Worsening[b, *]	Yes: No	12 (10.6): 101 (89.4)	18 (24.7): 55 (75.3)
Medical history			
Stroke[b]	Yes: No	41 (36.3): 72 (63.7)	22 (30.1): 51 (69.9)
Dementia[b, *]	Yes: No	10 (8.8): 103 (91.2)	14 (19.2): 59 (80.8)
Complication			
Delirium[a, **]		1 (1)	1 (2)
Cerebral edema[b]	Yes: No	25 (22.1): 88 (77.9)	22 (30.1): 51 (69.9)
Infectious disease[b]	Yes: No	16 (14.2): 97 (85.8)	8 (10.9): 65 (89.0)
Dehydration/electrolyte abnormalities[b]	Yes: No	12 (10.6): 101 (89.4)	13 (17.8): 60 (82.2)
Evaluate results			
JCS at the start of rehabilitation[a]		2 (3)	2 (3)
JCS after 2 weeks[a, **]		1 (2)	2 (3)
NIHSS at the start of rehabilitation[a]		5 (12)	6 (10)
Rehabilitation implementation status			
Rehabilitation time per day (min)[c]		63.7 (20.8)	63.8 (18.7)
Sitting practice[b]	Yes: No	97 (85.8): 16 (14.2)	60 (82.2): 13 (17.8)
Standing practice[b]	Yes: No	95 (84.0): 18 (16.0)	58 (79.4): 15 (20.6)
Walking practice[b]	Yes: No	79 (70.0): 34 (30.0)	45 (61.6): 28 (38.4)
Medication status			
Medications to improve impaired consciousness[b]	Yes: No	0 (0.0): 113 (100.0)	0 (0.0): 73 (100.0)

*p<0.05, **p<0.01.
[a]: Median (Inter Quartile Range), [b]: number (%), [c]: Mean (standard deviation).
JCS: The Japan Coma Scale; NIHSS: National Institutes of Health Stroke Scale.

With respect to JCS at the start of rehabilitation, patients with milder JCS at the start of rehabilitation showed poorer improvement in impaired consciousness. In previous studies examining the association between early impaired consciousness and outcomes such as mortality, acute hospital discharge destination, and ADL capacity[3–5], patients with initially milder impaired consciousness were reported to have better outcomes. It was expected that the improvement in impaired consciousness would also be better in the patients with mild impaired consciousness; however, the improvement in impairment consciousness was poor. One reason for this may be that the mild impaired consciousness patients had little room for improvement due to the ceiling effect.

Regarding delirium, severe delirium had a negative impact on the improvement of impaired consciousness. Delirium is often described as impaired consciousness[14], and in the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5), it is also considered a disturbance of attention (orientation, concentration, maintenance, and turnover) and consciousness[15]. In fact, patients with delirium experience a change in their level of consciousness within a short period of time[15]. Antipsychotic medications such as haloperidol (Serenace®) and risperidone (Risperdal®) are used as pharmacological treatment for delirium[14], and their sedative effects decrease the level of consciousness. Furthermore, delirium is a predictor of outcomes such as worse functional outcome, increased mortality, and prolonged hospital stay[16, 17]. These findings suggest that delirium may have contributed to the poor improvement in impaired consciousness.

With regard to the presence or absence of standing practice, the use of standing practice had a positive effect on the improvement of impaired consciousness. Previous studies[18, 19] reported that tilt table standing practice improved arousal and consciousness in patients with persistent disturbance of consciousness in the chronic phase, although at a different stage of illness than in this study. This can be explained by the theory of sensory stimulation programs[18]. The sensory stimulation program is based on the theory that intensive sensory stimulation enhances synaptic reinnervation and stimulates the reticular activating system, the center of consciousness. Although its effectiveness was not proven in a meta-analysis in 2002[20], a

Table 3. Factors associated with improvement of impaired consciousness

Related factors	Partial regression coefficient	Odds ratio	95% confidence interval	
			Lower	Upper
Age*	−0.044	0.957	0.917	0.999
Sex	−0.245	0.783	0.354	1.731
Thalamic/brainstem lesions	−0.714	0.490	0.190	1.264
volume of responsible lesion	−0.004	1.004	0.986	1.021
Mechanical thromboprophylaxis	1.483	4.405	0.896	21.666
Worsening**	−1.725	0.178	0.054	0.587
Previous strokes	0.307	1.360	0.594	3.110
Previous dementia	−1.004	0.366	0.098	1.365
Delirium**	−0.588	0.556	0.391	0.789
Cerebral edema*	−1.725	0.178	0.044	0.730
Infectious disease	0.723	2.061	0.383	11.094
Dehydration/electrolyte abnormalities	−0.537	0.584	0.144	2.373
JCS at the start of rehabilitation**	1.147	3.149	1.970	5.032
Rehabilitation time per day	0.003	1.003	0.981	1.026
Sitting practice	0.528	1.695	0.599	4.797
Standing practice**	2.846	17.221	2.982	99.459
Walking practice	1.077	2.935	0.799	10.781
Constant	−1.201	0.301		

Logistic regression analysis results with all variables as independent variables. Hosmer–Lemeshow test: p=0.684
Percentage of correct classifications: 77.0%
JCS at the start of rehabilitation and JCS after 2 weeks showed rs=0.81, JCS at the start of rehabilitation and NIHSS at the start of rehabilitation showed rs=0.84, and JCS after two weeks and NIHSS at the start of rehabilitation showed rs=0.81. Therefore, JCS at the start of rehabilitation was included in the analysis.
*p<0.05, **p<0.01.
JCS: The Japan Coma Scale; NIHSS: National Institutes of Health Stroke Scale.

2009 study[21)] reported that patients with brain injury who received a sensory stimulation program consisting of stimulation to the five senses (touch, taste, smell, hearing, and vision) during 30 min of training in the acute phase showed a significantly better level of consciousness than a control group. The standing posture is more stimulating than the supine or seated posture in terms of the amount of stimulation to the lower limbs and visual information from the surroundings, and it is assumed that the reticular activating system is activated. However, walking practice, which is considered more stimulating, was not identified as a predictor of improvement in impaired consciousness. This may be due to the fact that most of the patients who were able to perform walking exercises had only mild symptoms of impaired consciousness, and there was little room for improvement of impaired consciousness due to the ceiling effect. These results suggest that the standing posture may be useful for improving the level of consciousness of patients with impaired consciousness not only in the chronic phase but also in the acute phase of cerebral infarction.

These results suggest that age, delirium, presence or absence of cerebral edema, worsening and standing practice may predict improvement of impaired consciousness in patients with cerebral infarction, and that standing practice may contribute to improvement of impaired consciousness. On the other hand, the JCS at the start of rehabilitation was considered reasonable to exclude as a predictor because the ceiling effect of the JCS might not reflect the actual characteristics of impaired consciousness.

Limitations of this study include the following: predictive factors for cerebral hemorrhage and subarachnoid hemorrhage have not been investigated; the study was conducted at a single institution over a fixed period of time, which may have biased the severity of illness among the study participants; and regarding the effect of standing exercises, it is possible that multivariate analysis is insufficient to adjust for the bias in status between those who performed standing exercises and those who did not.

Conflict of interest

The authors declares that there is no conflict of interest.

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