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Original Article

Effects of Long-Term Rehabilitation on Functional Independence Measures and the Elucidation of Novel Prognostic Factors in Patients with Post-Stroke

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SUMMARY

Background: Although rehabilitation for the better quality of life reportedly improves motor and cognitive function in post-stroke patients, the factors that prevent good outcomes during rehabilitation are unclear. This study aimed to re-examine the effects of continuous and extensive long-term rehabilitation on motor, cognitive, and total functional independence measures (FIMs) in post-stroke patients in Japan and investigated the novel clinical factors that prevent improvements in FIMs on the top of known preventive factors such as hypertension, age, sex and stroke severity.
Methods: In this prospective observational study, 90 post-stroke patients, admitted to Sankuro Hospital for rehabilitation, were enrolled; the age was 61.4 ± 1.8 years old and 70% were male.
The acute phase of stroke treatment took place at mainly the Toyota Memorial Hospital or Toyota Kosei Hospital. In-hospital rehabilitation lasted 80 ± 39 (standard deviation) days. After discharge, all patients continued to receive rehabilitation twice or three times a week for next 12 months. We examined changes in motor, cognitive, and total FIMs and determined which factors negatively impacted improvements in FIMs.
Results: Rehabilitation for one year improved total and motor FIMs ($p < 0.01$), but not cognitive FIM. Plasma uric acid ($p < 0.01$ and $p < 0.05$) and albumin levels (both $p < 0.01$) were exclusively low in the patient groups with low total or motor FIMs.
Conclusions: In post-stroke patients, continuous and extensive rehabilitation improved total and motor FIMs, but not the cognitive FIM. We also found the differences in plasma uric acid and albumin levels between the groups with high and low total/motors FIMs.

1. Introduction

The incidence of stroke has increased worldwide and is not only a burden for patients but also a national and worldwide economic burden.[1,2] In Japan, the incidence of stroke and the mortality for stroke have been decreased because of the educational programs for the sufficient blood pressure control such as the less intake of salt and the promotion of daily exercise by the government.[3,4] Also, rehabilitation for post-stroke in Japan has provided the improvements of the motor and cognitive functions.[5] Most attention has been focused on the early phase of rehabilitation, which has been shown to improve motor and cognitive disturbances.[6] However, optimizing long-term rehabilitation to improve motor or cognitive dysfunction is also important. Furthermore, the factors that inhibit rehabilitation should be determined. Several studies focus on factors that attenuate or prevent improved motor and/or cognitive function during rehabilitation such as hypertension, age, sex, stroke severity and neglect.[7,8] However, when we have paid an attention to such factors, we still recognize that the beneficial effects of rehabilitation are limited and we need to find the additional factors to inhibit the beneficial effects of rehabilitation. The functional independence measure (FIM)[9] has been developed to provide a quantitative scale of activities of daily living: The FIM is an 18-item, 7-level scale developed to uniformly assess the severity of patient disability and the functional outcome of medical rehabilitation in terms of motor and cognitive abilities.

We aimed to determine the impact of extensive and early-onset and long-term rehabilitation on motor and cognitive dysfunction and the clinical factors that might prevent the beneficial effects of rehabilitation on total, motor, and cognitive dysfunction in Japanese post-stroke patients. We assessed the effects of extensive and early-onset rehabilitation for 1 year after discharge on FIM in post-stroke patients after the acute treatment of stroke. In addition, we investigated the clinical factors related to low total, motor, and cognitive FIMs.

2. Patients and methods

2.1. Study design

The present study was a retrospective observational study in Japan. The study was performed following the principles of the Declaration of Helsinki and the Japanese ethical guidelines for clinical research.

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2.2. Participants

We enrolled 90 post-stroke patients hospitalized at Sankuro Hospital. The inclusion criteria were as follows: (1) age between 20 and 99 years and (2) the existence of acute stroke treated at mainly Toyota Memorial Hospital or Toyota Kosei Hospital linked to Sankuro Hospital. These two hospitals for the patients with acute stroke are in the level of high standard among the Japanese hospitals for the treatment of acute stroke. The treatment for stroke at an acute phase followed the Japanese Guidelines for the Management of Stroke 2015.[10] The patients received the rehabilitation as a specialized post-stroke rehabilitation program administered by physicians, physical therapists, occupational therapists, and speech therapists within 3 days after admission, in line with the definition in a previous study.[11] The exclusion criteria included overt cardiovascular disease, serious liver and kidney diseases, pregnancy or lactation during treatment and rehabilitation period, and active malignancy requiring treatment. The target number of patients for recruitment was 90. The study protocol was approved by the external ethics committee of the Evidence Founder Club at Osaka (EU20160915-2); the Committee decided that based on the Japanese Clinical Research Guidelines, it was not essential to obtain informed consent from patients selected for inclusion in this study because the study was a retrospective observational study. Instead, we made a public announcement in accordance with the Ethics Committee's request and the Japanese Clinical Research Guidelines.

2.3. Procedures

After extensive and comprehensive treatment of stroke in the acute phase at Toyota Memorial Hospital, the patients were transferred to Sankuro Hospital for chronic rehabilitation, and we measured clinical parameters, including a blood analysis and total, motor, and cognitive FIMs[9,12] at the onset of hospitalization. We provided in-hospital rehabilitation to post-stroke patients at Sankuro Hospital. Rehabilitation was provided following the Japanese guidelines of rehabilitation.[13] At Sankro Hospital, the physical, occupational, and speech therapies were continuously provided for an average of 60–180 min three times a week depending on the status of the patients until discharge from Sankuro Hospital. In Japan, rehabilitation provided by physicians and therapists is reimbursed by the universal healthcare insurance system. Sankuro Hospital provided averagely 90 days in-hospital standard rehabilitation for post-stroke patients in Japan, and after discharge from Sankuro Hospital, we provided 60–180 min of standard rehabilitation twice or three times a week for next 12 months as an outpatient clinic.

2.4. Outcomes

The first primary outcome of the study was the improvement of motor, cognitive, and total FIM for 1 year after discharge. The secondary outcome was the identification of clinical factors related to no improvement of FIM.

2.5. Statistical analysis

The total number of subjects was estimated to be 90, based on the feasibility of patient enrollment in Sankuro Hospital. All analyses were performed at Brain Share, Co (Mr. M. Moriyasu) using the statistical analysis software SPSS, version 25 for Windows (IBM Corp., Armonk, NY, USA).

2.6. Role of the funding source

The sponsors of the study were THE OKAZAKI SHINKIN BANK. At Okazaki city, Aichi Prefecture, Japan, and Medical Information Research Association at Osaka city. The sponsors had no role in the study design, data collection, data analysis, and data interpretation or in the writing of the report. The corresponding author had full access to all the data in the study at the end of the study and had final responsibility for the decision to submit for publication.

3. Results

Of 300 patients hospitalized between October 2015 and March 2018 for rehabilitation for post-stroke, 90 patients completed in-hospital rehabilitation and the follow-up rehabilitation for 1 year. The other 210 patients declined the rehabilitation within 1 year because of physical and economic reasons.

Table 1 presents the baseline characteristics of the enrolled patients. Seventy and 30% of the patients were cerebral infarction cerebral hemorrhage, respectively, and modified Rankin Score was 3–5. At the phase of acute stroke, 60% and 40% of the patients experienced dysphagia and unilateral neglect, respectively. They received the standard care for stroke at stroke care units.[10] Figure 1 shows the improvements in total (A), motor (B), and cognitive (C) FIMs, where X and Y axes are FIMs at the onset of rehabilitation and

Table 1
Patient characteristics at hospitalization.

Age (years old)	61.4 ± 1.8
Gender (M:F)	63:27
stroke type (hemorrahge:infarction)	41:49
Modified Rankin Score	3.6 ± 0.3
Total FIM at entry	84.5 ± 2.5
Motor FIM at entry	56.7 ± 2.0
Cognitive FIM at entry	27.8 ± 0.8
Dysphagia (+:-)	37:53
Unilateral neglect (+:-)	35:55
AST (U/L)	23.7 ± 1.1
ALT (U/L)	28.0 ± 2.3
γGT (U/L)	40.8 ± 3.9
TP (g/dL)	6.9 ± 0.1
ALB (g/dL)	3.8 ± 0.1
TG (mg/dL)	146.3 ± 11.5
Tcho (mg/dL)	173.2 ± 4.7
HDL-C (mg/dL)	40.2 ± 1.7
LDL-C (mg/dL)	99.8 ± 4.9
Glu (mg/dL)	127.2 ± 4.4
HbA1c (%)	6.2 ± 0.2
UA (mg/dL)	5.4 ± 0.2
Na (mEq/L)	137.6 ± 0.4
CRP (mg/dL)	0.6 ± 0.1
WBC (/uL)	7067 ± 222
RBC (10^4/uL)	425.1 ± 7.1
Hb (g/dL)	12.9 ± 0.2
Hct (%)	38.7 ± 0.5
PLT (10^4/uL)	27.0 ± 0.9

Values are mean ± SD or real numbers.
Abbreviations: AST, plasma aspartate aminotransferase levels; ALT, plasma alanine aminotransferase levels; γGTP, plasmaγ-glutamyl transpeptidase levels; TP, plasma total proten levels; ALB, plasma albumin levels; TG, plasma triglyceride levels; Tcho, plasma total cholesterol levels levels; HDL-C, plasma HDL cholesterol levels; LDL, plasma LDL cholesterol levels; Glu, plasma glucose levels; HBA1c, plasma hemoglobin A1c levels; UA, plasma uric acid levels; Na, plasma sodium levels; CRP, plasma C-reactive protein levels; WBC, blood white blood cell counts; Hb, blood hemoglobin levels; Hct, hematocrit values; PLT, blood platelet levels.

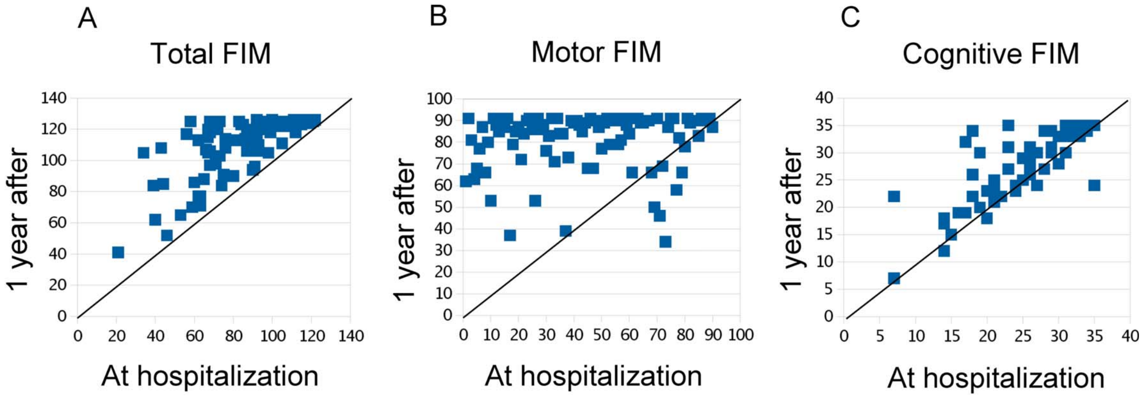

Figure 1. Changes in total, motor, and cognitive FIMs from the time of hospitalization to one year after discharge in stroke patients who received continuous rehabilitation.

1 year after rehabilitation, respectively. Total (84.5 ± 2.5 to 110.4 ± 2.0, $p < 0.01$) and motor (56.7 ± 2.0 to 80.7 ± 1.4, $p < 0.01$) FIMs improved, but cognitive FIM did not change significantly (27.8 ± 0.8 to 29.7 ± 0.7, ns). Tables 2 and 3 show the clinical data of patients after classification based on total FIM ≥ 105 or total FIM < 105 and motor FIM ≥ 77 or FIM < 77, respectively. In patients with either low total or motor FIM, both plasma uric acid and albumin levels among the available clinical parameters including age, sex, stroke severity, stroke type, dysphagia, and unilateral neglect were significantly lower. The reason for cut-off points of 105 and 77 of total and motor FIMs are derived from the upper values of the lowest quarter of tetrameric division of total and motor FIMs, respectively.

4. Discussion

Two major conclusions can be made from the present investigation. First, long-term rehabilitation of post-stroke patients provided better physical quality of life (QOL) but not cognitive QOL. Second, low plasma uric acid or albumin levels were linked to no improvements in total or motor FIMs. These results indicate the importance of rehabilitation in improved physical QOL. The low plasma uric acid and albumin levels are inhibitory clinical factors for rehabilitation-induced improvements and maintenance of QOL. Long-term rehabilitation of post-stroke patients and the exclusion of low plasma uric acid and albumin levels are necessary for stroke patients. However, before reaching this intriguing observational conclusion, we should consider several issues that need to be clarified.

First, the relationship between motor and cognitive FIM should be examined, because it is plausible that cognitive disorders cause motor disorders or vice versa. Cognitive disorder may decrease the willingness of patients to exercise and, thus, decrease the motor FIM. On the other hand, decreases in motor FIM may decrease cognitive FIM, because motor neurons may affect brain function via the afferent neurons. Indeed, the autonomic nervous system includes

Table 2
The data at the hospitalization between the groups with Total FIM < or ≥ 105.

	Total FIM < 105	Total FIM ≥ 105	p value
Age (years old)	67.5 ± 4.6	59.6 ± 1.8	0.065
Gender (M:F)	12:8	51:19	0.28
stroke type (hemorrhage %)	55	43	0.43
Modified Rankin Score	3.4 ± 0.6	3.7 ± 0.8	0.11
Dysphagia (%)	50	39	0.45
Unilateral neglect (%)	45	37	0.54
AST (U/L)	21.2 ± 2.0	24.5 ± 1.3	0.19
ALT (U/L)	22.2 ± 3.5	30.0 ± 2.8	0.14
γGT (U/L)	29.7 ± 5.0	44.5 ± 4.9	0.098
TP (g/dL)	6.6 ± 0.2	7.0 ± 0.1	0.045
ALB (g/dL)	3.2 ± 0.2	3.9 ± 0.1	0.01
TG (mg/dL)	145.7 ± 27.5	146.5 ± 12.1	0.97
Tcho (mg/dL)	159.2 ± 7.1	178.5 ± 5.7	0.065
HDL-C (mg/dL)	40.5 ± 3.3	40.1 ± 2.0	0.90
LDL-C (mg/dL)	88.6 ± 4.8	104.6 ± 6.3	0.10
Glu (mg/dL)	126.2 ± 8.0	127.6 ± 5.3	0.89
HbA1c (%)	5.8 ± 0.3	6.2 ± 0.2	0.26
UA (mg/dL)	4.3 ± 0.5	5.7 ± 0.2	0.004
Na (mEq/L)	138.1 ± 0.6	137.4 ± 0.5	0.48
CRP (mg/dL)	0.8 ± 0.3	0.5 ± 0.1	0.27
WBC (/uL)	6605 ± 437	7224 ± 256	0.22
RBC (10^4/uL)	415.7 ± 13.4	428.4 ± 8.4	0.44
Hb (g/dL)	12.4 ± 0.4	13.1 ± 0.2	0.18
Hct (%)	37.9 ± 1.0	38.9 ± 0.6	0.44
PLT (10^4/uL)	24.8 ± 1.8	27.5 ± 1.0	0.089

Values are mean ± SD or real numbers.
Abbreviations are same as in Table 1.

Table 3
The data at the hospitalization between the groups with Motor FIM < or ≥ 77.

	Motor FIM < 77	Motor FIM ≥ 77	p value
Age (years old)	66.0 ± 4.5	59.9 ± 1.8	0.14
Gender (M:F)	13:9	50:18	0.28
stroke type (hemorrhage %)	55	43	0.43
Modified Rankin Score	3.6 ± 0.8	3.7 ± 0.7	0.52
Dysphagia (%)	50	31	0.17
Unilateral neglect (%)	50	36	0.21
AST (U/L)	21.6 ± 1.7	24.5 ± 1.4	0.24
ALT (U/L)	23.5 ± 4.2	31.2 ± 3.9	0.13
γGT (U/L)	30.3 ± 5.0	45.0 ± 4.4	0.092
TP (g/dL)	6.7 ± 0.1	7.0 ± 0.1	0.12
ALB (g/dL)	3.5 ± 0.2	3.9 ± 0.1	0.00001
TG (mg/dL)	155.3 ± 28.5	142.3 ± 11.0	0.60
Tcho (mg/dL)	160.1 ± 6.6	179 ± 5.9	0.062
HDL-C (mg/dL)	40.3 ± 3.0	40.1 ± 2.0	0.96
LDL-C (mg/dL)	87.4 ± 4.5	104.8 ± 6.5	0.10
Glu (mg/dL)	133.6 ± 9.0	124.8 ± 5.1	0.37
HbA1c (%)	6.0 ± 0.3	6.2 ± 0.3	0.65
UA (mg/dL)	4.4 ± 0.5	5.7 ± 0.2	0.049
Na (mEq/L)	137.3 ± 0.7	137.7 ± 0.5	0.65
CRP (mg/dL)	0.85 ± 0.3	0.48 ± 0.11	0.15
WBC (/uL)	6800 ± 420	7173 ± 262	0.45
RBC (10^4/uL)	414.0 ± 12.0	429.0 ± 9.0	0.36
Hb (g/dL)	12.5 ± 0.4	13.0 ± 0.3	0.23
Hct (%)	38.0 ± 0.9	39.0 ± 0.7	0.40
PLT (10^4/uL)	24.3 ± 1.4	28.1 ± 1.1	0.060

Values are mean ± SD or real numbers.
Abbreviations are same as in Table 1.

more afferent neurons than efferent neurons. Many reports show that exercise reduces the severity of cognitive disorders.[14] However, we found no relationship between motor and cognitive FIMs in the present study, which is in conflict with previous data.[15] The first possibility is that cognitive FIM was relatively high in the present patient population and there was no chance for cognitive FIM improvement. The relatively high cognitive FIM may be due to the younger age of patients (61.4 years) in the present study. The second possibility is that cognitive FIM cannot be improved by 12 months-rehabilitation for Japanese post-stroke patients, and we may need to longer or more extensive rehabilitation to improve cognitive FIM. The third possibility is that the sample size of 90 patients may not be sufficient to observe the improvement of cognitive FIM, although we provided the cognitive rehabilitation following the Japanese rehabilitation guideline for post-stroke. However, we can state that rehabilitation is less effective for cognitive FIM than the motor FIM.

The second issue is related to nutrition. Nutritional disorders revealed by the low plasma albumin levels may inhibit improvements in total and motor FIMs. Severe malnutrition was associated with poor functional outcomes, measured by FIMs in patients with ischemic stroke.[16,17]

The third issue is the effects of plasma uric acid on FIM. Meat produces amino acids in addition to uric acid and insufficient amino acid intake along with low uric acid levels may affect the physical condition of post-stroke patients and, thus, the motor FIM.[18,19]

4.1. Limitations of the present study

First, we did not know the physiological or neurohormonal mechanisms that account for the present phenomenon. We should clarify these observations in experimental studies. Second, this is a single-center study, and we need to confirm the present finding in other hospitals with multicenter trials. Third, the number of enrolled patients was not large. Of 300 patients hospitalized between October 2015 and March 2018 for rehabilitation for post-stroke, 90 patients completed in-hospital rehabilitation and the follow-up rehabilitation for 1 year. The other 210 patients declined the rehabilitation within 1 year because of physical and economic reasons. Therefore, the number of 90 is the feasible number, but not derived from the statistical prediction. The present findings should be confirmed in a larger number of patients. Fourth, this is a single-arm observation study. To gain a better understanding of the effects of long-term rehabilitation, we should set another arm where rehabilitation is not applied to the post-stroke patient. However, this long-term rehabilitation protocol is standard for stroke patients, and ethical limitations prevent denying rehabilitation care. Fifthly, the rehabilitation in the present study lasted for 12 months after the discharge, and the longer rehabilitation may change the present results. Although this may be true, the length for the insurance reimbursement for the rehabilitation after stroke is limited by the Japanese government. Therefore, we need to set 360 days for the present investigation.

Lastly, this study lacked the data about premorbid functioning and other predictors which are important determinants of rehabilitation outcome in post-stroke patients. However, this is a retrospective study using the clinical data from ordinary routine rehabilitation and care, so we could not obtain the further important data. We should investigate the comprehensive next study in the near future.

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Conflicts of interest

All authors have completed and submitted the ICMJE Form for disclosure of potential conflicts of interest.

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