

## 적절한 재활치료의 시점: 문헌상의 근거에 대한 고찰

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### Optimal Timing of Rehabilitation: Overview of the Evidence in the Literature

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Stroke results in chronic disability which is a major burden in various ways and thus regaining functional independence is an important goal for the stroke patients and caregivers. Early rehabilitative training after stroke onset takes place in most stroke centers. However, optimal timing of rehabilitation after stroke remains controversial and debate on the complications and other issues induced by the early rehabilitation is still ongoing despite considerable amount evidence in the literature that supports early rehabilitation. There is uncertainty about whether very early mobilization within 24 to 48 hours of stroke onset improves outcome after stroke. Emphasis on early mobilization with increasing frequency and dose of mobilization in the early phase of stroke may contribute to improved functional outcomes after stroke. In this article, superiority of the very early mobilization after stroke is demonstrated by reviewing supporting evidence from animal studies by showing changes in task performance and anatomy, clinical comparative data by comparing outcome measurement scores, AVERT studies, a large scale randomized controlled trial currently in progress to provide sufficient clinical evidence, and the current Clinical Practice Guidelines. (**Brain & NeuroRehabilitation 2012; 5: 1-5**)

**Key Words:** early mobilization, rehabilitation, stroke

### Introduction

Is earlier rehabilitation the better? and what evidence is there for supporting early rehabilitation for stroke patients? These are important questions to answer because the timing of rehabilitation initiation is modifiable, unlike many other predictors of functional recovery after stroke (eg, age, premorbid function). Regaining functional independence is an important goal for people who have experienced stroke.<sup>1</sup> Customizing the optimal rehabilitation resources to meet the needs of the patients is challenging. The mismatch between the patient's needs and the provided therapies may fail to achieve preferred outcomes.<sup>2</sup> Challenging the patients to higher-order tasks

as early as possible is associated with better outcomes.<sup>3</sup> Earlier and more intensive out-of-bed activity after stroke would reduce time to unassisted walking and improve independence in activities of daily living.<sup>1</sup> Adaptive plasticity in the lesioned side of the brain as well as the healthy side by rehabilitational training was observed in many clinical and experimental studies.<sup>4</sup> Horn et al.<sup>2</sup> found earlier rehabilitation admission and higher level activities early in the rehabilitation process are associated with better stroke outcome.

To clarify the extent of improvement in terms of motor function and define the optimal time window for rehabilitation interventions, numerous compelling studies in the literature provided sufficient evidence to persuade that earlier the stroke patients are able to participate in rehabilitation, the better they will do overall. We intend to provide evidence based references to ascertain the importance of early rehabilitation by categorizing several studies into animal studies, clinical comparative studies, AVERT trials and the Clinical Practice Guideline (CPG).

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## 1) Animal Studies

Animal studies have shown that earlier rehabilitation results in improved motor recovery and delayed rehabilitation resulted in worse motor recovery. In 1999, Risedal et al.<sup>4</sup> reported the negative effect of early training after focal brain ischemia in their animal study, by demonstrating more prominent increased infarct volume and thalamic atrophy in the early training group than the standard and late rehabilitation group. The functional recovery was also seen delayed in the early training group, whereas the late rehabilitation group swam shorter distance, and found platform earlier than the early training group in the water maze test. Such findings were hypothesized to relate to the increased glutamate release and peri-infarct cortical hyperexcitability. Since publication of this study, studies on early rehabilitation faltered for a while.

In 2003, Schallert et al.<sup>5</sup> reported that the brain seems to be "primed" to "recover" in early stages of acute stroke. Animal studies have shown markedly reduced dendritic arborisation when therapy is delayed for several weeks post-stroke.<sup>6,7</sup> In a study on determination of the period during which the post-stroke brain is most sensitive to physical rehabilitation to maximize the functional gains from rehabilitation, Biernaskie et al.<sup>8</sup> subjected animals to 5 weeks of rehabilitation beginning at days 5, 14 and 30 poststroke. Comparing the changes in functional tasks of staircase reaching, narrow-beam-walking, cylinder test of forelimb use and ladder-rung walking test, ER5 demonstrated significant improvement compared to the ER 14, ER 30 and social housing. They also observed the amount of dendritic growth in the undamaged motor cortex was associated with both lesion size and improved functional outcome. The efficacy of rehabilitative therapy is influenced by time of commencement and it declines with time, and improved outcome was associated with greater growth of dendritic complexity of layer V neurons. These findings suggest heightened sensitivity of the post-stroke brain when exposed to early initiation of rehabilitation, and that early rehabilitation initiation is associated with significant functional gains and enhanced structural plasticity.

## 2) Clinical Comparative Data

Paolucci et al.<sup>9</sup> compared 135 stroke patients who received rehabilitation 1) within the first 20 days (short onset), 2) 21~40 days (medium onset) and 3) 41~60 days (long onset) while provided with same physical therapy program. Their outcome revealed Barthel Index (BI) scores in the short onset group improved at significantly greater rate than the other two groups with highest rehabilitation efficiency (improvement in score on each scale/length of rehabilitation stay) on the BI.

In a study comparing the impact of early and delayed admission to rehabilitation on functional outcomes in stroke patients, Salter et al.<sup>10</sup> grouped 435 patients by interval from stroke onset to rehabilitation admission (5~30 days vs 31~150 days) and compared the differences in length of rehabilitation stay and functional outcome variables. The results demonstrated that early-admission group experienced significantly better functional improvement than the delayed-admission group. In sub-group analysis, there were statistically significant differences in mean admission and discharge FIM scores, FIM change and length of stay (LOS) between patients admitted 0~15 and 16~30 days post-stroke as well as between patients admitted 16~30 days and 31~60 days post-stroke. Patients admitted 31/60 days post-stroke were also compared with those 91/150 days post-stroke, and they found a trend toward increasing LOS ( $p = 0.08$ ) and lower discharge FIM scores ( $p = 0.08$ ). They concluded that despite substantial functional improvements that can be achieved over the course of rehabilitation admission even in those with delay in admission to rehabilitation following stroke, such gains take significantly longer to achieve and are inferior to those with earlier admission to rehabilitation.

Associations between days from stroke symptom onset to rehabilitation admission and rehabilitation outcomes of discharge total FIM, discharge motor FIM, discharge activities of daily living (ADL) FIM, and discharge mobility FIM scores, as well as rehabilitation LOS in moderate to severe stroke patients were studied after controlling for a variety of confounding variables including age, sex, race, ambulation independence and ADL independence prior to admission by Maulden et al.<sup>11</sup> in a cohort

study of 6 inpatient rehabilitation facilities. In the moderately impaired group, more days from stroke onset to rehabilitation admission was associated significantly with longer rehabilitation LOS while the severely impaired group did not show any association between days from symptom onset to rehabilitation admission with LOS. Both of the moderately and severely impairment groups with fewer days between onset to inpatient rehabilitation showed better functional outcomes at discharge, whereas only the moderately impaired group with fewer days between onset to acute inpatient rehabilitation showed shorter rehabilitation LOS.

In a Cochrane database systemic review, Bernhardt et al.<sup>12</sup> compared the benefits and harms of very early mobilization commenced within 48 hours of stroke, with conventional care. Although they found insufficient evidence to support or refute the efficacy of routine very early mobilization after stroke compared with conventional care, and despite no significant difference on any secondary outcomes, they found fewer patients who received early and frequent mobilization were dead or disabled at three months.

Clinical comparative data suggests that delay in stroke rehabilitation is associated with worse outcomes.

### 3) A Very Early Rehabilitation Trials for Stroke (AVERT)

AVERT, a multicenter, randomized, controlled trial involving over 2,000 patients from 15~20 hospitals participating in Australia, New Zealand, Singapore, Malaysia, Northern Ireland, Scotland, Wales and England, is to determine if very early mobilization (VEM) of stroke patients in addition to standard care compared to standard care (SC) alone is more effective in lowering mortality, disability, and severity of complications and improving quality of life. Patients are randomly allocated to SC or VEM for which additional physiotherapy and nursing were given over the intervention period of 14 days, or until the patient is discharged from stroke unit care, whichever is sooner. The aim is to reduce both the personal and community burden of stroke by establishing the efficacy, cost effectiveness and potential mechanisms of VEM.

In a AVERT phase II trial on the safety and feasibility of SC and VEM, the safety outcomes of number of death at 3 months, adverse events, compliance with physiologic

monitoring criteria, and patient fatigue after interventions, and feasibility outcomes of "dose" of mobilization and "contamination" of SC, were recorded and compared. Safety outcomes were similar between groups while high VEM dose and faster time to first mobilization were successfully achieved, concluding that VEM within 24 hours of acute stroke appears safe and feasible.<sup>13</sup> Further results from the phase II AVERT on hypothesis that VEM would reduce time to assisted walking and improve independence in activities of daily living (ADL) demonstrated that VEM group returned to walking significantly faster with 3.5 median days taken to return to walking 50m in comparison to SC group showing 7 days, and more VEM patients were independent in ADLs (Barthel Index) and motor function (Rivermead Motor Assessment) than SC patients. It provides novel evidence that earlier and more intensive mobilization in the acute phase of stroke can accelerate recovery of meaningful physical outcomes (BI, Rivermead, walking).<sup>1</sup> Alongside a phase II AVERT, cost effectiveness of VEM compared with SC was assessed by determining the costs from medical records and interview as 3, 6, and 12 months. The VEM group incurred significantly less costs at 3 months (VEM: AUD 13,559; SC: AUD 21,860;  $p = 0.02$ ) and the mean per patient total cost at the 12-months assessment (VEM: AUD 17,564; SC: AUD 29,750;  $p = 0.03$ ), demonstrating the cost effectiveness of the VEM.<sup>14</sup> Another phase II AVERT explored whether VEM affected complication type, number and severity by recording complications to 3 months by a blinded assessor and classified by a neurologist. Immobility-related complications showed no significant difference between SC and VEM. They found falls and UTI were the most common complications while older age and longer LOS are the factors associated with experiencing an immobility-related complications. Higher prevalence of stroke-related complications was seen in the VEM group at 3 months but not at 12 months while higher NIHSS score at baseline and smoking history were associated with experiencing a stroke-related complication. They concluded that VEM promotes recovery, reduce complications and consequently reduce LOS.<sup>15</sup>

AVERT phase III is currently in commencement to provide greater certainty regarding the efficacy and the cost effectiveness of VEM in the recovery of physical inde-

pendence after stroke, hence a better quality of life and cost effective therapy, and ultimately reduce the global burden of stroke.

#### 4) Clinical Practice Guidelines Recommendations

Multiple studies with different classes of evidence depending on the specific aspects of rehabilitation support recommendations of rehabilitation assessment and early initiation of basic rehabilitation services. Most of elements are supported by Class I to Class IIa, Level B to C evidence.<sup>16</sup> Recommendations with Level I evidence include the delivery of poststroke care in a multidisciplinary rehabilitation setting or stroke unit, early patient assessment via the NIH Stroke Scale, early initiation of rehabilitation therapies, swallow screening testing for dysphagia, an active secondary stroke prevention program, and proactive prevention of venous thrombi. Standardized assessment tools should be used to develop a comprehensive treatment plan appropriate to each patient's deficits and needs, as well as medical therapy for depression or emotional lability is strongly recommended. A speech and language pathologist should evaluate communication and related cognitive disorders and provide treatment when indicated.<sup>17</sup> Clinical Practice Guidelines recommend rehabilitation therapy start as early as possible, once medical stability is achieved,<sup>18</sup> with exception of the more severe stroke patients in whom the benefits of earlier rehabilitation would not be expected to be as great. The Korean CPG Recommendations on Initiation of Rehabilitation state 1) Rehabilitation therapies for acute stroke patients should initiate as early as possible once medical stability is reached (A, Ia), and 2) it is advisable to initiate rehabilitation within 72 hours of stroke onset (B, III).

## Conclusion

The brain is "primed" to recover early post-stroke and there is emerging evidence supporting early admission to stroke rehabilitation. The current evidence from the animal studies, clinical comparable data, AVERT trials and the CPG strongly suggests that acute stroke patients should be admitted to the specialized stroke rehabilitation or have access to comparable therapies in acute care as

soon as they are able to participate following the onset of the stroke. Earlier rehabilitation results in improved motor recovery and delays in stroke rehabilitation is associated with worse outcomes even when medical comorbidities and stroke severity are taken into account.

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