Outcome After Mobilization Within 24 Hours of Acute Stroke
A Randomized Controlled Trial

Antje Sundseth, MD; Bente Thommessen, PhD; Ole Morten Rønning, PhD

Background and Purpose—Very early mobilization (VEM) is considered to contribute to the beneficial effects of stroke units, but there are uncertainties regarding the optimal time to start mobilization. We hypothesized that VEM within 24 hours after admittance to the hospital would reduce poor outcome 3 months poststroke compared with mobilization between 24 and 48 hours.

Methods—We conducted a prospective, randomized, controlled trial with blinded assessment at follow-up. Patients admitted to the stroke unit within 24 hours after stroke were assigned to either VEM within 24 hours of admittance or mobilization between 24 and 48 hours (control group). Primary outcome was the proportion of poor outcome (modified Rankin scale score, 3–6), whereas secondary outcomes were death rate, change in neurological impairment (National Institutes of Health Stroke Scale score), and dependency (Barthel Index 0–17).

Results—Fifty-six patients were included (mean age ±SD, 76.9 ± 9.4 years), 27 were in the VEM group and 29 were in the control group. VEM patients had nonsignificant higher odds (adjusted for age and National Institutes of Health Stroke Scale score on admission) of poor outcome (OR, 2.70; 95% CI, 0.78–9.34; P = 0.12), death (OR, 5.26; 95% CI, 0.84–32.88; P = 0.08), and dependency (OR, 1.25; 95% CI, 0.36–4.34; P = 0.73). The control group, having milder strokes (National Institutes of Health Stroke Scale score ±SD: control group, 7.5 ± 4.2; VEM, 9.2 ± 6.5; P = 0.26), had better neurological improvement (P = 0.02).

Conclusions—We identified a trend toward increased poor outcome, death rate, and dependency among patients mobilized within 24 hours after hospitalization, and an improvement in neurological functioning in favor of patients mobilized between 24 and 48 hours. Very early or delayed mobilization after acute stroke is still undergoing debate, and results from ongoing larger trials are required. (Stroke. 2012;43:2389-2394.)

Key Words: early mobilization ■ outcome ■ randomized controlled trial ■ stroke

Stroke is one of the most frequent causes of death and long-term disability in the Western world.1,2 Because of demographic changes, estimates indicate an increasing prevalence of stroke and stroke-related burden in future decades.3 Thrombolytic treatment in acute stroke is the most potent acute treatment, but it is currently only available for a minor proportion of stroke patients. Stroke unit treatment has demonstrated the greatest population benefit, because most cases are eligible for this intervention. Compared with treatment in general medical wards, treatment in stroke units reduces mortality, disability, and the need for long-term institutional care.4

The aspects that are responsible for the effect of stroke units are still uncertain, although very early mobilization (VEM) is considered an important component for an improved outcome.5-7 Early deaths not caused by the stroke itself are often associated with complications of immobilization such as infections, particularly lung infections, and thromboembolism. Data, including those from animal experiments, indicate that early mobilization and training after stroke are important to utilize brain plasticity8-11 and to hasten recovery, in addition to preventing complications.12,13 In contrast, the penumbra is vulnerable to decreased blood flow that, as some authors suggest, could be caused by any activity comprising head elevation.13,14 Little is known about the effect of exercise on the penumbra, ie, if motor activity might harm the penumbra by stimulating the release of excitatory substances.

Monitoring vital parameters and upholding physiological homeostasis in acute stroke are major components in stroke unit care.15 A disadvantage of early mobilization could be reduced access to monitoring vital parameters and, consequently, delayed detection of derangement of physiological homeostasis. Some studies indicate that continuous obse-
viation in an intensive stroke unit may be better in relation to reducing death and poor outcome than discontinuous observation, as performed in conventional stroke units. Patients accessible for therapeutic interventions for cerebral revascularization, such as intravenous/intra-arterial thrombolysis or embolectomy, and who are more intensively monitored may have their early mobilization postponed. In Scandinavia, most patients are mobilized early according to national guidelines, but those receiving endovascular interventions are often bedridden for at least 24 hours.

The optimal time for mobilization is unknown; therefore, it seems important to clarify whether all stroke patients should be mobilized immediately after admittance for an acute stroke or if they should be immobilized for the first 1 or 2 days. A number of studies of VEM vs delayed mobilization after stroke have been conducted, but only A Very Early Rehabilitation Trial Phase II (AVERT II) met the criteria for randomized controlled trials and timing of mobilization of the Cochrane review from 2009. The findings of VEM within 24 hours of stroke onset appearing to be safe and feasible have later been supported by the Very Early Rehabilitation or Intensive Telemetry after Stroke Pilot Trial (VERITAS). Both studies were small, with 71 and 32 patients included, respectively.

Because early mobilization is suggested to be one of the most important causes for the beneficial effect of comprehensive stroke care, we hypothesized that early mobilization out of bed after stroke onset would enhance improvement. The aim of our study was to identify whether VEM within 24 hours after admittance to a hospital reduces poor outcome 3 months poststroke compared with first mobilization between 24 and 48 hours.

Subjects and Methods
We conducted a randomized controlled trial to compare the two treatments, with the main objective of this study being to identify and compare the proportion of poor outcome (modified Rankin scale [mRS] score 3–6) 3 months poststroke. Secondary outcomes were death rate at 3 months, change in neurological impairment assessed by the change in the National Institutes of Health Stroke Scale (NIHSS) score at admittance to 3 months poststroke, dependency assessed by the Barthel Activities of Daily Living Index at 3 months, and type and number of all complications within 3 months after stroke.

Study Settings
The Akershus Early Mobilization in Stroke Study (AKEMIS) was conducted at the stroke unit of the Department of Neurology, Akershus University Hospital, between January 1, 2007 and October 31, 2007, and from January 12, 2009 to February 28, 2010. Patients were treated according to the European Stroke Organisation’s guidelines for management of ischemic stroke 2008. The stroke unit was staffed by a specialist multidisciplinary team of senior and resident neurologists, a nursing staff, physiotherapists, occupational therapists, a speech therapist, and a social worker, and the standardized protocol for diagnosis, observation, and acute treatment, including early rehabilitation and the prevention of complications, was followed. Early mobilization out of bed several times per day is a component of early rehabilitation and a key feature of stroke unit care in Scandinavia.

Study Design
The study was a prospective, randomized, controlled study with a blinded assessment at the end of follow-up.
score 8–16) or severe (NIHSS score >16). Global functioning was measured by mRS. A mRS score 0 to 2 was defined as good outcome and mRS score 3 to 6 was defined as poor outcome. Activities of Daily Living score was assessed by the 10-item Barthel Index at days 4 to 5 and 3 months poststroke. Independence in activities of daily living was defined as Barthel Index ≥18. Complications within 3 months after stroke were classified as follows: (1) stroke-related (recurrent stroke or intracerebral hemorrhage, transient ischemic attack, postapoplectic epilepsy); (2) immobility-related (deep vein thrombosis, pulmonary embolism, bedsores, pneumonia, urinary tract infection, and falls); and (3) comorbidity-related (angina pectoris, myocardial infarction).

Ethics
The study was approved by the Regional Committee for Ethics in Medical Research and by the Data Protection Authorities. All participants or their first-degree relatives gave their written informed consent.

Statistical Analysis
The sample size was calculated to be 123 patients in each group (95% confidence interval [CI], margin of error 5%) to detect a difference of 20% in the proportions of patients dead or with poor outcome at 3 months follow-up on the basis of results from stroke unit studies with the best effect. However, because of slow recruitment, the inclusion of patients had to be stopped before reaching the calculated sample size.

The $\chi^2$ statistics and unpaired 2-sample t tests were used to determine differences among background variables. Differences between groups in poor outcome, death, and dependency are presented in proportions and odds ratios (OR) with 95% CI. Outcome analyses were adjusted for age and NIHSS score on admission with multivariable regression analyses. Three-month mortality was analyzed by Fisher exact test. Between-group differences in neurological impairment were analyzed by unpaired 2-sample t tests and Mann-Whitney U test for nonparametric samples. Neurological improvement in each group was evaluated with paired-samples t test and Wilcoxon signed rank test. Differences between the groups in the proportion of patients having any complications and compared with ≥2 complications were analyzed by $\chi^2$ statistics and Fisher exact test, respectively.

In a few patients, the exact time to first mobilization was not registered accurately and medical records were studied to calculate the mean value on the basis of the earliest and latest possible times of mobilization. Between-group differences in the median time from symptom onset and from hospitalization to first mobilization were analyzed by Mann-Whitney U test. $P<0.05$ was used as level of significance. Statistical analyses were performed on an intention-to-treat basis using SPSS 17.0.

Results
In total, 65 patients were randomized and, of these, 9 were excluded; 7 patients had a misdiagnosis of stroke that was detected by a stroke neurologist the day after admission and 2 patients were recruited into the study >24 hours after stroke onset. Of the remaining 56 patients, 27 were randomized to VEM in the VEM group and 29 were randomized to delayed mobilization in the CG. Two patients in the VEM group and 1 in the CG were lost to follow-up regarding disability and impairment but were alive at 3 months according to the Norwegian resident registration. Enrollment into the study is shown in the Figure.

The baseline characteristics and risk factors of the 56 patients studied were similar for both groups, except for a significantly higher prevalence of diabetes (VEM 2 of 27 [7%] vs CG 8 of 29 [28%]; $P=0.05$) and a trend toward more patients with mild stroke in the CG (VEM 16 of 27 [59%] vs CG 21 of 29 [72%]; $P=0.07$; Table 1).

The median time to first mobilization from stroke onset was 13.1 hours for the VEM group (interquartile range [IQR], 8.5–25.6 hours) and 33.3 hours for the CG (IQR, 26.0–39.0 hours; $P=0.001$), and from admission to hospital the median time was 10.0 hours for the VEM group (IQR, 3.3–24.0 hours) and 26.3 hours for the CG (IQR, 24.0–35.6 hours; $P=0.001$). Five of our VEM patients (mean age, 82.4 years; mean NIHSS score on admission, 15) were not mobilized according to the protocol. Instead, 3 were mobilized within 48 hours and the remaining 2 were mobilized within 72 hours. One patient in the CG (age 90 years; NIHSS score on admission, 6) commenced first mobilization 85 hours after admission.

Primary Outcome: Poor Outcome
At 3 months follow-up, more patients in the VEM group had a poor outcome compared with those in the CG (mRS score
Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>VEM, n=27</th>
<th>CG, n=29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>76.5 (9.7)</td>
<td>77.3 (9.3)</td>
</tr>
<tr>
<td>Male</td>
<td>11 (41)</td>
<td>14 (48)</td>
</tr>
<tr>
<td>Stroke risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>20 (74)</td>
<td>22 (75)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>13 (48)</td>
<td>13 (45)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>11 (41)</td>
<td>7 (24)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>7 (26)</td>
<td>10 (35)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (7)</td>
<td>8 (28)</td>
</tr>
<tr>
<td>Smoking</td>
<td>8 (30)</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>8 (30)</td>
<td>9 (31)</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left side</td>
<td>18 (67)</td>
<td>18 (62)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>5 (19)</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Oxfordshire stroke classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TACI</td>
<td>4 (15)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>PACI</td>
<td>9 (33)</td>
<td>11 (38)</td>
</tr>
<tr>
<td>POCI</td>
<td>2 (7)</td>
<td>5 (17)</td>
</tr>
<tr>
<td>LACI</td>
<td>7 (26)</td>
<td>5 (17)</td>
</tr>
<tr>
<td>TOAST classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>8 (30)</td>
<td>9 (31)</td>
</tr>
<tr>
<td>Large vessel</td>
<td>2 (7)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Small vessel</td>
<td>6 (22)</td>
<td>8 (28)</td>
</tr>
<tr>
<td>Other/undetermined</td>
<td>6 (22)</td>
<td>6 (21)</td>
</tr>
<tr>
<td>NIHSS score on admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All: mean (SD)</td>
<td>9.2 (6.5)</td>
<td>7.5 (4.2)</td>
</tr>
<tr>
<td>Mild (0–8)</td>
<td>16 (59)</td>
<td>21 (72)</td>
</tr>
<tr>
<td>Moderate (8–16)</td>
<td>5 (19)</td>
<td>6 (21)</td>
</tr>
<tr>
<td>Severe (&gt;16)</td>
<td>6 (22)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>mRS score on admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All: mean (SD)</td>
<td>3.9 (0.9)</td>
<td>3.8 (0.7)</td>
</tr>
<tr>
<td>mRS score 3–5</td>
<td>24 (89)</td>
<td>28 (97)</td>
</tr>
<tr>
<td>Barthel Index on days 4–5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>10.3 (7.3)*</td>
<td>14.1 (5.6)†</td>
</tr>
<tr>
<td>Time to first mobilization, median hr (IQR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>From stroke onset</td>
<td>13.1 (8.5–25.6)</td>
<td>33.3 (26.0–39.0)</td>
</tr>
<tr>
<td>From admission</td>
<td>10.0 (3.3–24.0)</td>
<td>26.3 (24.0–35.6)</td>
</tr>
</tbody>
</table>

3–6: VEM 15 of 25 [60%] vs CG 11 of 28 [39.3%]. The difference between the groups was not statistically significant either before (OR, 2.32; 95% CI, 0.77–9.34; P = 0.14) or after adjusting for age and NIHSS score on admission (OR, 2.70; 95% CI, 0.78–9.34; P = 0.12). Patients not mobilized according to the randomization were included in an on-treatment analysis that showed the same trend toward poorer outcome in the VEM group.

Secondary Outcomes: Death

In total, 9 patients (16.1%) were dead at the 3-month follow-up, 7 (25.9%) in the VEM group and 2 (6.9%) in the CG. The odds of being dead appeared higher in the VEM group compared with the CG (OR, 4.73; 95% CI, 0.89–25.21; P = 0.07). Still, after adjustment for age and NIHSS score on admission, the difference in mortality did not reach significance (OR, 5.26; 95% CI, 0.84–32.88; P = 0.08).

All 3 in-hospital deaths were in the VEM group. They occurred 4 to 12 days after stroke onset (Figure) and were caused by the initial stroke. The mean age of these patients was 84 years (range, 80–92 years), and their NIHSS scores on admission were 6, 9, and 20, respectively. The other 6 patients died between 14 to 72 days after stroke. The cause of death was recurrent stroke in 2 patients, pulmonary cancer and pneumonia in 1, and unknown causes in 3.

Change in Neurological Impairment

In addition to the change in NIHSS scores from admission to the 3-month follow-up for patients who survived for 3 months, the mean values of the NIHSS scores on admission and at the 3-month follow-up are presented in Table 2. The neurological improvement from admission to follow-up was highly significant in both groups (P < 0.001), although the improvement was significantly better in the CG patients (P = 0.02).

Dependency

The in-hospital disability obtained by Barthel Index was higher in the VEM group than in the CG (Table 1). At the 3-month follow-up, both groups had a median Barthel Index of 19 (VEM IQR 7–20 vs CG IQR 6–20). The odds of being dependent 3 months after stroke were higher in the VEM group, but did not reach significance before (OR, 1.21; 95% CI, 0.41–3.63; P = 0.73) or after adjustment for age and NIHSS score on admission (OR, 1.25; 95% CI, 0.36–4.34; P = 0.73).

Complications

The proportion of patients with at least 1 complication within 3 months after stroke was the same in the 2 groups (VEM 18 of 27 [67%] vs CG 19 of 29 [66%]; P = 0.93). The proportion of VEM patients experiencing 2 or 3 complications was nonsignificantly higher than that of CG patients (VEM 8 of 18 [44%] vs CG 3 of 19 [16%]; P = 0.08). The 2 groups had...
comparable numbers of stroke-related, immobility-related, and comorbidity-related complications (data not shown).

**Discussion**

In this randomized trial, we could not confirm our hypothesis that VEM after stroke onset (within 24 hours after admittance to a hospital) reduces poor outcome compared with mobilization between 24 and 48 hours after admittance. In contrast, we found a nonsignificant trend toward poorer outcome, and higher death rate and dependency among patients mobilized within the first 24 hours after hospitalization. Among those who survived 3 months, there was an improvement in neurological function in favor of patients mobilized between 24 and 48 hours.

Recently, there have been 2 phase II studies conducted on VEM after stroke, the AVERT II in Australia and VERITAS in the United Kingdom. The objective of both studies was to compare safety and feasibility of VEM (commencing within 24 hours of stroke onset) with standard care (SC) mobilization.[17,18] Both studies had similar inclusion criteria, recruiting patients older than 18 years with a first or recurrent stroke. Patients with severe prestroke comorbidity or disability (AVERT II: premorbid mRS score >3; VERITAS: premorbid mRS score >2) were excluded.[20] In addition, AVERT II had predefined physiological inclusion criteria regarding blood pressure, heart rate, oxygen saturation, and temperature.[17] A key distinction between our study and the 2 other studies was the only intervention in AKEMIS was the different timing of mobilization, as opposed to AVERT II and VERITAS, in which the VEM group additionally obtained a higher total dose of mobilization than the SC group.[20] Hence, a direct comparison of these 3 small studies is not possible. However, their results are interesting, because they, so far, are the only randomized controlled trials evaluating VEM after stroke, which is supposed to be an important aspect of stroke unit treatment.

The proportion of deaths in the present study corresponds to the results from AVERT II.[17] This study also had a higher proportion of deaths in the VEM group compared with the SC group (21% vs 9%).[17] As in the present study, the treatment groups in AVERT II were imbalanced, with more severe strokes on admission in the VEM group than in the CG and SC groups.[17] After adjustment for stroke severity on admission in both studies, the differences in mortality were still nonsignificant. In VERITAS, only 1 patient (3%) was dead at the 3-month follow-up,[19] however, the patients were younger, had milder strokes, and had less stroke risk factors.[17]

The proportion of patients with a good outcome in the VEM group of our study was the same as that in AVERT II (mRS score 0–2: AKEMIS 10 of 25 [40%] vs AVERT II 15 of 38 [39.5%]).[17] Both studies had similar times from stroke to first mobilization in the VEM group.[17] The percentage of patients with a good outcome in our CG was relatively comparable with that of VERITAS VEM patients (mRS score 0–2: AKEMIS 17 of 28 [60.7%] vs VERITAS 12 of 16 [75%]).[19] In VERITAS, the mobilization of VEM patients was more often started on the second day after stroke onset and at approximately the same time as in our CG.[19]

The results regarding functional outcome and dependency of our CG differed from those of the SC groups from the 2 other studies. The median time to first mobilization from stroke onset in the CG and SC group of all 3 studies was relatively equal and varied from 30.8 to 33.3 hours.[17,19] Hence, the timing of the first mobilization could not explain the differences. As a result, this could lead to a hypothesis that the outcome can be influenced by both the amount of treatment and the time of mobilization.

The results of the CG in the present study, along with the comparable VEM group in VERITAS, indicate that mobilization starting 1 day after stroke onset does not increase the risk of death, poor outcome, or dependency. There was not a difference in the proportion of patients experiencing complications within 3 months of stroke onset or in the number of immobility-related complications between our groups. The difference in change in neurological improvement between our groups should be interpreted with caution because of the imbalance in case fatality and the exclusion of nonsurvivors from this analysis.

Theoretically, the ischemic penumbra, which is assumed to exist at least 3 to 16 hours and possibly up to 48 hours,[34,35] may turn into infarcted tissue. Unstable physiological hemostatic factors can negatively affect residual blood flow and the duration of the flow disturbance and, thereby, the outcome of the penumbra.[36] AVERT II did not register any patients having 3 consecutive blood pressure declines of >30 mm Hg in their first 3 mobilization attempts[17] and none of our patients had a severe blood pressure decline or loss of consciousness in connection with mobilization.

There are uncertainties about the localization and extent of the penumbra in humans,[35,37] although it must be presumed that the penumbra is larger in most cortical strokes. Therefore, factors influencing the fate of the penumbra may have larger impact in these strokes.

In a study of residual blood flow velocity in acute middle cerebral artery occlusion, an improvement of mean flow velocity was observed when lowering the patient’s head position from 30 to 0 degrees.[14] On the basis of this, a flat positioning was recommended for up to 24 hours after admission for some patients,[14,38] whereas others even support bed rest for at least 2 days.[13] However, reduced blood flow velocity in the middle cerebral artery is not synonymous with a reduced cerebral blood flow; consequently, the importance of blood flow velocity for the ischemic penumbra is uncertain.

The strength of the present study is its prospective and randomized controlled design with blinded assessment at the end of follow-up. We recruited patients across the severity spectrum, and the validity of our findings regarding the effect of early mobilization is strengthened by the fact that we managed to start the intervention very early. The recruitment to the study was, however, difficult because of the fact that the patients were admitted too late to the hospital to be included within 24 hours of stroke onset. In addition, patients who were candidates for thrombolytic treatment were not eligible according to our exclusion criteria. The low power attributable to the small sample size is a limitation of the present study and requires that the results are interpreted with
caution. Further, it emphasizes the need for larger randomized controlled trials that address the effect of early mobilization within 24 hours, such as the ongoing AVERT Phase III study.

Conclusions

The present study shows a nonsignificant trend toward poorer outcome and higher death rate and dependency among patients mobilized within 24 hours of hospitalization who had more severe strokes on admission. Because our study had limited power, it is impossible to draw reliable conclusions in terms of the effect of VEM on stroke survival and functional outcome. We need further results from randomized controlled trials addressing the effect of mobilization within 24 hours of stroke onset.

Acknowledgments

The authors thank the staff of their stroke unit for help in performing this study.

Sources of Funding

The principle investigator was paid by the South-Eastern Norway Regional Health Authority.

Disclosures

None.

References

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Stroke. 2012;43:2389-2394; originally published online June 14, 2012;
doi: 10.1161/STROKEAHA.111.646687

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

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