Early Mobilization After Stroke

An Example of an Individual Patient Data Meta-Analysis of a Complex Intervention

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Background and Purpose—Very early mobilization (VEM) is a distinctive characteristic of care in some stroke units; however, evidence of the effectiveness of this approach is limited. To date, only 2 phase II trials have compared VEM with standard care: A Very Early Rehabilitation Trial (AVERT) in Australia and the recently completed Very Early Rehabilitation or Intensive Telemetry after Stroke trial in the United Kingdom. The Very Early Rehabilitation or Intensive Telemetry after Stroke protocol was designed to complement that of AVERT in a number of key areas. The aim of this analysis was to investigate the impact of VEM on independence by pooling data from these 2 comparable trials.

Methods—Individual data from the 2 trials were pooled. Overall, patients were between 27 and 97 years old, had first or recurring stroke, and were treated within 36 hours after stroke onset. The primary outcome was independence, defined as modified Rankin scale score of 0 to 2 at 3 months. The secondary outcomes included complications of immobility and activities of daily living. Logistic regression was used to assess the effect of VEM on outcome, adjusting for known confounders including age, baseline stroke severity, and premorbid modified Rankin scale score.

Findings—All patients in AVERT and Very Early Rehabilitation or Intensive Telemetry after Stroke were included, resulting in 54 patients in the VEM group and 49 patients in the standard care group. The baseline characteristics of VEM patients were largely comparable with standard care patients. Time to first mobilization from symptom onset was significantly shorter among VEM patients (median, 21 hours; interquartile range, 15.8–27.8 hours) compared with standard care patients (median, 31 hours; interquartile range, 23.0–41.2 hours). VEM patients had significantly greater odds of independence compared with standard care patients (adjusted odds ratio, 3.11; 95% confidence interval, 1.03–9.33).

Conclusions—Planned collaborations between stroke researchers to conduct trials with common protocols and outcome measures can help advance rehabilitation science. VEM was associated with improved independence at 3 months compared with standard care. However, both trials are limited by small sample sizes. Larger trials (such as AVERT phase III) are still needed in this field. **(*Stroke*. 2010;41:2632-2636.)**

Key Words: early ambulation ■ meta-analysis ■ rehabilitation ■ stroke

Stroke rehabilitation trials are often small and, therefore, underpowered.[1] Meta-analysis offers advantages for increasing statistical power and providing a more precise estimate of effect than that of individual studies.[2] Rehabilitation treatments are described as complex interventions in that they contain several interacting components.[3] A lack of understanding of the interventions' mechanisms and the use of multiple and different outcome measures make meta-analysis of complex interventions difficult.[4] Therefore, heterogeneity is considered a more complicated issue in the synthesis of complex interventions compared to that of simple interventions.

Individual patient data meta-analysis may offer a retrospective solution to dealing with heterogeneity in complex intervention research. However, being able to adjust for variations prospectively at a trial level should also be considered. For example, this may include ensuring the standardization of a complex intervention undergoing evaluation to establish that it is reproducible.

The complex intervention described in this article, very early mobilization (VEM), involves starting mobilization (ie, getting out of bed, standing, and walking) early after stroke and continuing at frequent intervals. Standardizing VEM

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The data for this pooled analysis were used for the purposes that they were originally intended. Participants in the individual trials have previously given informed consent to participate in their respective trial and as a result have agreed that their data can be used to investigate the specified research question.

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poses a challenge in that the VEM protocol differs according to patient capability and delivery can be difficult, particularly because variations in care between different units are known to exist.[5] This has important implications for the validity of complex intervention trials, approaches used in meta-analysis, and the longer-term success of clinical implementation.

To date, 2 phase II trials of early mobilization have already been conducted: the A Very Early Rehabilitation Trial (AVERT) in Australia and the Very Early Rehabilitation or Intensive Telemetry after Stroke (VERITAS) in the United Kingdom. The VERITAS protocol was intentionally matched to that of AVERT in a number of key areas. The aim of this analysis is to estimate the pooled effect of VEM in relation to independence at 3 months. In addition, the effect of VEM on the risk of complications 1 week after stroke and activities of daily living 3 months after stroke also are investigated.

Materials and Methods

Both trials were designed to compare the feasibility and safety of a VEM protocol with usual stroke care mobilization practices. AVERT is a multicenter, randomized trial and VERITAS is a single-center, randomized trial with a 2×2 factorial design to investigate the combined effect of VEM and automated physiological monitoring.[6,7] Both trials used computer-generated, blocked randomization procedures and used opaque envelopes to conceal group allocation. In AVERT, patients were stratified by stroke severity and hospital site.

The inclusion and exclusion criteria were similar for both trials. Both trials recruited patients older than 18 years with a new or recurrent stroke and excluded patients with severe prestroke disability or comorbidities. There was no upper age limit in either trial. In AVERT, severe prestroke disability was defined as a premorbid modified Rankin scale (mRS) score >3, and in VERITAS it was defined as a premorbid mRS score >2.

The key principles of the VEM intervention protocol used in AVERT were adopted in VERITAS with respect to the timing, nature, and frequency of the intervention. Both trials aimed to get patients up to sit, stand, and walk within 24 hours, or as soon after the point of recruitment as possible, and continued mobilization throughout the day. The time to trial recruitment from onset of stroke symptoms was slightly shorter in AVERT (<24 hours) than in VERITAS (<36 hours). VEM was delivered for 14 days by a team of nurses and therapists in AVERT but was predominately nurse-led for 7 days in VERITAS. Both groups received usual mobilization practices from ward staff.

To measure time spent in mobilization activity in AVERT, ward staff recorded time spent in therapy with trial patients. This was measured for the intervention period of 14 days, or earlier if the patient was discharged. In AVERT, the total dose of mobilization for each treatment group (in minutes) across the length of stay was calculated. In VERITAS, an accelerometer was used to measure time (in minutes) spent sitting/lying, standing, and stepping for patients. An accelerometer is a device used to objectively measure physical activity.[8] This was measured on days 3, 4, and 5, with recordings on the first day considered most reliable (personal communication). In VERITAS, time spent upright, defined as the time spent standing or stepping, was calculated.

In the pooled analysis, the primary outcome was independence at 3 months as measured by mRS ≤2 and Barthel Index ≥18. The secondary outcomes were early complications of immobility and activities of daily living at 3 months. Activities of daily living were measured by the Barthel Index. Complications were defined as stroke-related, immobility-related, comorbidity-related, or any others. Complications of immobility included falls, pneumonia, chest infection, deep venous thrombosis, and pulmonary embolism. Complications were assessed on day 5 for VERITAS and on day 7 for AVERT. Complications were collected from medical records by a blinded assessor. Variables from both data sets were matched and combined if the same outcome measure was used. Data were routinely checked and, when appropriate, verified against the published trial analysis results.

Statistical Analysis

Univariate analysis was used to compare patient characteristics at baseline between the 2 individual trials and between treatment groups in the pooled analysis. In addition, time to first mobilization and time spent mobilizing were compared between the treatment groups using summary data from the trials.

Multivariate analysis was used to assess the combined effect of VEM on independence at 3 months. Logistic regression was performed to adjust for known confounders, including age, baseline stroke severity, and premorbid mRS score. The effect of including other additional variables was also explored in separate models. These include automated monitoring, the factorial design used in VERITAS, and variables as informed by the univariate analysis ($P<0.10$). A similar method of univariate and multivariate analysis was performed for the secondary outcomes. Analyses were conducted with STATA version 10.1 and Review Manager version 5.

Results

All patients in AVERT (n=71) and VERITAS (n=32) were included in the pooled analysis. No patients were lost to follow-up at 3 months. AVERT had 33 patients in the standard care (SC) group and there were 38 patients in the VEM group, whereas VERITAS had 8 patients in each of the 4 treatment groups, 16 patients received early mobilization, and 16 patients received standard mobilization practices.

The pooled analysis showed the baseline characteristics of patients were comparable between treatment groups (Table 1). It is worth noting that VERITAS excluded patients with mRS >2; therefore, the number of patients in the mild-to-moderate disability category (premorbid mRS, 2–3) was small. Furthermore, there were some differences in the patient baseline characteristics between the 2 trials. VERITAS patients had a lower mean age than AVERT patients (65.3 years vs 74.7 years). AVERT had a higher proportion of patients with risk factors for stroke than VERITAS, such as hypertension (70.4% vs 37.5%), atrial fibrillation (31.0% vs 6.2%), and current smokers (40.6% vs 14.1%). More patients had moderate or severe stroke in AVERT than in VERITAS (57.8% vs 28.1%). The proportion of patients in AVERT with total anterior circulation syndrome was higher than that of VERITAS (22.5% vs 9.4%).

In AVERT, the first time to mobilization was significantly shorter for the VEM group (median, 18.1 hours; interquartile range [IQR], 12.8–21.5 hours) compared to that of the SC group (30.8 hours; IQR, 23.0–40.0 hours; $P<0.001$). Similarly, in VERITAS the time to mobilization was also shorter for the VEM group (median, 27.3 hours; IQR, 26.0–29.0 hours) compared to SC group (median, 31.8 hours; IQR, 23.0–46.8 hours); however, this was not significantly different. In AVERT, the total dose of mobilization (defined as therapy time) in the intervention period for the VEM group was double that of SC group (VEM, 167 minutes; IQR, 62–305 minutes; vs SC, 69 minutes; IQR, 31–115 minutes; $P=0.003$). Dose of mobilization was defined as the mean time spent upright in VERITAS; 61.3 (SD, 53.6) minutes and 42.2 minutes (SD, 56.7) were observed in the VEM and SC groups, respectively.

Table 1. Patient Demographics and Characteristics at Baseline by Treatment Groups

	SC	VEM	*P*
N of patients	49	54	
Age (mean, SD)	72.0 (11.6)	71.6 (14.2)	0.86
Female	27 (55.1%)	22 (40.7%)	0.15
Stroke risk factors			
Hypertension	32 (65.3%)	30 (55.6%)	0.31
Atrial fibrillation	12 (24.5%)	12 (22.2%)	0.79
Coronary heart disease	18 (36.7%)	11 (20.4%)	0.07
Diabetes	7 (14.3%)	13 (24.1%)	0.21
Current smoker			
Yes	13 (26.5%)	10 (15.5%)	0.33
No	36 (73.5%)	44 (81.5%)	
Premorbidity (mRS score)			
No or mild symptoms (0–1)	41 (83.7%)	39 (72.2%)	0.16
Mild-to-moderate disability (2–3)	8 (16.3%)	15 (27.8%)	
Living arrangements on admission			
Home alone	17 (34.7%)	11 (20.4%)	0.24
Home not alone	30 (61.2%)	39 (72.2%)	
Other	2 (4.8%)	4 (7.4%)	
Stroke history			
Previous stroke	7 (14.3%)	15 (27.8%)	0.10
NIHSS score			
Total score (mean, SD)	8.7 (6.0)	9.7 (7.1)	0.71
Mild (1–7)	24 (49.0%)	29 (53.7%)	
Moderate/severe (>8)	25 (51.0%)	25 (46.3%)	
Oxfordshire classification			
TACS	9 (18.4%)	10 (18.5%)	0.21
PACS	17 (34.7%)	17 (31.5%)	
LACS	10 (20.4%)	10 (18.5%)	
POCS	5 (10.2%)	14 (25.9%)	
ICH	6 (12.2%)	3 (5.6%)	
Unknown	2 (4.1%)	0 (0%)	

Entries are n (%), unless stated otherwise.

ICH indicates intracerebral hemorrhage; LACS, lacunar circulation syndrome; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; PACS, partial anterior circulation syndrome; POCS, posterior circulation syndrome; SC, standard care; TACS, total anterior circulation syndrome; VEM, very early mobilization.

Significant testing used the χ^2 test for categorical variables and a *t* test or Mann-Whitney *U* test for continuous variables.

The pooled analysis showed that the time to first mobilization from symptom onset was significantly shorter among VEM patients (median, 21 hours; IQR, 15.8–27.8 hours) compared with SC patients (median, 31 hours; IQR, 23.0–41.2 hours).

Table 3. Number of Patients With Early (≤7 Days After Stroke) Complications

	SC	VEM
N of patients	49	54
N of complications		
1	12	9
2	5	6
3	5	2
4	2	1
5	1	1
Any complication*	25 (51.0%)	19 (35.2%)
Immobility-related complication		
Deep vein thrombosis/pulmonary embolism	1	0
Fall	7	3
Pneumonia/chest infection/aspiration	13	8
Urinary tract infection	5	0
Any immobility-related complication*	17 (68.0%)	7 (36.8%)

SC indicates standard care; VEM, very early mobilization.

*One patient may experience ≥1 complication.

Overall, the proportion of VEM patients who were independent at 3 months was higher than that of the SC group; the pooled absolute risk difference was 15.3% (95% confidence interval, −4.0%–38.0%). Patients who underwent VEM were 3-times more likely to be independent at 3 months than were SC patients (adjusted odds ratio, 3.11; 95% confidence interval, 1.03–9.33; Table 2). A similar effect was observed for independence in activities of daily living using Barthel Index (adjusted odds ratio, 4.41; 95% confidence interval, 1.36–14.32). Additional models that included additional variables such as automated monitoring (model 2, Table 2) and a history of heart disease (model 3, Table 2) gave similar results, suggesting that these factors did not have a confounding effect on VEM.

A greater percentage of SC patients (51.0%) experienced at least 1 complication when compared with VEM patients (35.2%; Table 3). Immobility-related complications accounted for 68.0% of complications in the SC group and 36.8% in the VEM group. The risk of experiencing early complications of immobility in VEM patients was significantly lower than that of SC patients (adjusted odds ratio, 0.20; 95% confidence interval, 0.10–0.70). VEM patients had a higher level of activities of daily living at 3 months than SC patients: median Barthel Index scores were 20 (IQR, 16.5–20) and 17 (IQR, 12–20), respectively.

Table 2. Odds Ratios for Independence at 3 Months

				Adjusted OR (95% CI)		
Independence	SC, n (%)	VEM, n (%)	Unadjusted OR (95% CI)	Model 1*	Model 2†	Model 3‡
Modified Rankin scale score (0–2)	17 (34.7)	27 (50.0)	2.02 (0.89–4.60)	3.11 (1.03–9.33)	3.20 (1.10–9.70)	3.10 (1.03, 9.28)
Barthel Index (18–20)	20 (40.8)	30 (57.4)	2.90 (1.24–7.15)	4.41 (1.36–14.32)	4.58 (1.39–15.10)	4.34 (1.32, 14.30)

CI indicates confidence interval; OR, odds ratio; SC, standard care; VEM, very early mobilization.

*Adjusted for trial identification, age, baseline National Institutes of Health Stroke Scale total score, premorbid modified Rankin scale score, †automated monitoring, and ‡history of coronary heart disease.

Discussion

This analysis approach has shown a favorable effect of VEM in acute stroke patients on independence at 3 months. In both AVERT and VERITAS, patients received earlier and more frequent mobility practice than that routinely provided. There were no significant differences in baseline characteristics between the treatment groups. This provides some confidence that this treatment effect is a result of consistent delivery of VEM and that the individual studies were estimating the same effect. Although time to mobilization was shorter for VEM patients in both trials, this was not significant in VERITAS. This may be attributable to the difficulty in recruiting patients to VERITAS early after stroke, with delayed hospital admission being a potential contributing factor.[7] Not being able to access patients early within a trial setting made it challenging to mobilize patients more rapidly than usual. This was particularly relevant for patients most severely affected, and gaining assent from the nearest relative had further time implications. It should also be noted that once the patient was recruited and randomized in VERITAS, there was no delay to commencing the first mobilization, with the time between randomization to first mobilization being significantly smaller for VEM patients than SC patients. An exploration of time to first mobilization across baseline stroke severity (data not shown) suggests little difference in time between mild stroke patients and moderate-to-severe stroke patients.

A similar treatment effect on the secondary outcomes for each of the 2 trials was observed. Patients in both trials who underwent VEM appeared to have a lower rate of complications associated with immobility in the acute stages. Reduction in immobility-related complications is one of the proposed mechanisms by which VEM may improve outcome.[9] An association between early mobilization and reduced number of complications, such as pneumonia, is yet unproven and results of previous studies vary.[9,10]

This individual patient data meta-analysis, by adjusting for confounders, has provided a more reliable estimate of effect than previously reported in the individual studies.[6,7] This has important implications considering that regaining independence in activities such as walking after stroke is thought to be one of the most important rehabilitation goals for patients.[11–13] The ongoing AVERT phase III trial will determine the impact of VEM practices in a larger sample.[14]

Overall, this analysis has provided an example of how researcher collaboration with deliberate matching of protocol and outcome measures can allow data from 2 similar trials of methodological quality to be combined. Using such an approach to demonstrate the replication of a complex intervention in different settings is likely to improve confidence in the intervention. If such practice was more widely adopted, then the process of synthesizing the evidence would be more transparent and robust.[15] Collaboration among international stroke rehabilitation trialists has the potential to provide country-specific information. Synthesizing the data in this way could inform the statistical planning of the main analysis with regard to predefining categories for subgroup analysis and highlighting potential prognostic factors.

The main limitation of this analysis is small sample size. The size of the overall treatment effect therefore only can be indicative. Given the small sample size of the individual studies, this pooled analysis should only be considered as an illustration of the method, rather than allowing any confident deductions to be made regarding the effectiveness of VEM. The ongoing AVERT phase III trial will address this by testing VEM in much a larger population, across a spectrum of patient types, and across a number of countries.

Accelerometer use in stroke patients is still relatively novel and the reliability of certain devices is not yet explicit.[8] This explains the relatively high rate of missing data recorded in VERITAS. If VEM is shown to be efficacious, then its implementation into clinical practice will require a robust monitoring system. As demonstrated in VERITAS, one method may be to measure patients' physical activity levels using an accelerometer and comparing post-implementation levels to a baseline before its introduction.

More work is required to develop an evidence base around the implementation of complex interventions in stroke rehabilitation, especially around the standardization of interventions. It has been stated that complex interventions may work best if tailored, for example, to patient type and local circumstances rather than being completely standardized.[3] Finally, the development of process of care indicators and the long-term monitoring of complex interventions in clinical practice to ensure adherence of guidelines and equity of care should be the major focus of research once evidence of benefit has been established. Translation of research findings to clinical practice remains a significant challenge in health care.

Conclusion

This pooled analysis has provided a more precise estimate of effect for VEM in relation to independence at 3 months after stroke than that previously reported. However, the cost-effectiveness and future implementation of VEM only can be determined by the ongoing larger trial. Combining individual patient data has emphasized the importance of sharing protocols and agreeing outcome measures to reduce variations between trials and ensure comparability of trials of complex intervention. Any subsequent synthesis therefore is more likely to be valid.

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Disclosure

None.

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