June 2018

Hello members.

We are continuing this month focusing on early mobilization. Last week we provided a systematic review and meta-analysis of very early mobilization. Conclusions. **A few published stroke guidelines do recommend mobilization 24-48 hrs after stroke onset-but evidence remains insufficient.**

This week, we want to delve into the "A Very Early Rehab Trial" AVERT trials after stroke. We provide a summation of the history of the trials, Phase II, Phase III, and a dose-response analysis of the intervention. This is a great topic for journal clubs at your facility. The graphs, data, analyses are very well explained and chocked full of details. Abstracts and links are below.

Next week, we will review Dr. Bernhardt’s interpretation of whether we are ready for very early mobilization implementation.

Are you doing early mobilization? As typical with research, we get a small snapshot but not the entire picture. Who? How? When? are still not known.

**A very early rehabilitation trial for stroke (AVERT). Brief history**

**Protocol publication.**

**Summary.**

- A randomized controlled trial of Very Early Mobilization (VEM) versus standard of care (SOC). Blinded assessment of outcome and intention to treat.
  - **Hypothesis.** VEM (in addition to standard care) compared to SOC will
    - Reduce death and disability at 3-months
    - Reduce the number and severity of complications
    - Improve quality of life at 12 months
    - Be cost-effective.
  - **Inclusion.**
    - Over 18 years, stroke admit, within 24 hours of symptoms
    - Able to arouse patient
  - **Exclusion.**
    - Modified rankin scale >2 (moderate to severe disability) before stroke
    - Rapid early deterioration or rapidly deteriorating disease.
    - Unstable coronary or other medical condition
  - **Stratification.** National Institute of Health Stroke Scale (NIHSS)
    - Mild NIHSS 1-7
Phase II. Safety and Feasibility
- Hypothesis. Very early rehab will be safe and feasible.
- Interventions. SOC + VEM or VEM until discharge or 14 days.
  - Monitoring BP, HR, sats pre mobilization.
  - VEM assist the patient to upright and out of bed-sitting or standing, 2x/day 6 days/week. Hoists were used when necessary.
- Outcomes.
  - Safety. Number of deaths at 3 months.
  - Feasibility. Higher dose of mobilization in VEM would be achieved.
- Results.
  - 71 patients recruited, 2 dropouts. (87% ischemic stroke) 33 SOC, 38 VEM
  - Mean age 74.7 (12.5) years.
  - SAFETY. No differences in deaths between the 2 groups, after adjusting for balance imbalance in stroke severity and premorbid rankin.
  - FEASIBILITY. Total dose of mobilization VEM 167 (62-305) minutes. SOC 69 (31-115).
  - Secondary outcome rankin of 0-2 at 3 months. SOC 30.3% and VEM 39.5%, not significant (p = 0.05).
- Conclusion. Safe and feasible.

Phase III. Efficacy
- Hypothesis. VEM would improve functional outcome at 3 months, reduce immobility-related complications and accelerate walking recovery, improve quality of life at 12 months, and be cost effective.
- Methods. Same as above.
- Outcomes. Modified Rankin scale (mRS). Favorable outcome (0-2) and poor (3-6). Time to achieve unassisted walking over 50 m. Deaths.
  - Highly recommended to read the statistical analysis, excellent description and will informs the outcomes.
- Results.
  - VEM 1054, SOC 1050.
  - More patients in the SOC had a favorable outcome on mRS than VEM after adjusting for age, NIHSS.
  - Walking unassisted by 3 months, adjusted odds ratio 0.83, p = 0.143, no difference between groups.
  - Deaths VEM 8%, SOC 7% Odds ratio 1.34, p = 0.113.
  - Subgroup analyses reported, but authors report they were not powered to detect these differences.
- Conclusion. Clinical hypothesis-VEM would lead to fewer complications-but no difference between groups.

Follow up analyses on data. Dose-response analysis in AVERT. Must read paper, so many wonderful tables, graphs!
- Methods.
  - Dose-response: time from stroke to first mobilization; median number of out of bed sessions per day; median minutes out of bed per day.
  - 2 models adjusted for age, baseline NIHSS. Model 1. Times out of bed.
  - Model 2. Minutes out of bed.
  - Favorable outcome mRS 0-2 at 3 months.
- Results.
  - Greater time from stroke to first mobilization was associated with reduced odds of favorable outcome (0.99, p = 0.036). OR patients who started mobilization earlier after stroke had improved odds of favorable outcome.
  - Keep time to first mobilization and frequency the same, every extra 5 minutes out of bed per day reduced the odds of favorable outcome.
  - BUT increasing the frequency of session there was a 13% favorable outcome.
  - Increasing session frequency reduced the odds of death by 20%. But nonfatal severe adverse events showed less associations.
- Conclusion.
Potential beneficial effect of increasing frequency out of bed, but not the amount of time helps reduce disability at 3 months.

Results need to be confirmed in further RCT’s.


BACKGROUND AND PURPOSE: Very early rehabilitation, with an emphasis on mobilization, may contribute to improved outcomes after stroke. We hypothesized that a very early rehabilitation protocol would be safe and feasible. METHODS: We performed a randomized, controlled trial with blinded outcome assessment. Patients at <24 hours after stroke were recruited from 2 Melbourne metropolitan stroke units. Patients were randomly assigned to receive standard care (SC) or SC plus very early mobilization (VEM) until discharge or 14 days (whichever was sooner). The primary safety outcome was the number of deaths at 3 months. The primary feasibility outcome was a higher "dose" of mobilization achieved in VEM. Secondary safety outcomes included adverse events (including falls and early neurologic deterioration), compliance with physiologic monitoring criteria, and patient fatigue after interventions. Secondary feasibility outcomes included "contamination" of standard care. RESULTS: Overall, 18% of patients screened were suitable for recruitment. Seventy-one patients were recruited and randomized, with 2 dropouts by 12 months. The majority experienced ischemic strokes (87%). The group mean +/- SD age was 74.7 +/- 12.5 years, and 58% (n=41) had a National Institutes of Health Stroke Scale score >7. There was no significant difference in the number of deaths between groups (SC, 3 of 33; VEM, 8 of 38; P=0.20). Almost all deaths occurred in patients with severe stroke. Secondary safety outcomes were similar between groups. The intervention protocol was successfully delivered, achieving VEM dose targets (double SC, P=0.003) and faster time to first mobilization (P<0.001). CONCLUSIONS: VEM of patients within 24 hours of acute stroke appears safe and feasible. Intervention efficacy and cost-effectiveness are currently being tested in a large randomized, controlled trial.


Abstract

BACKGROUND:
Early mobilisation after stroke is thought to contribute to the effects of stroke-unit care; however, the intervention is poorly defined and not underpinned by strong evidence. We aimed to compare the effectiveness of frequent, higher dose, very early mobilisation with usual care after stroke.

METHODS:
We did this parallel-group, single-blind, randomised controlled trial at 56 acute stroke units in five countries. Patients (aged ≥18 years) with ischaemic or haemorrhagic stroke, first or recurrent, who met physiological criteria were randomly assigned (1:1), via a web-based computer generated block randomisation procedure (block size of six), to receive usual stroke-unit care alone or very early mobilisation in addition to usual care. Treatment with recombinant tissue plasminogen activator was allowed. Randomisation was stratified by study site and stroke severity. Patients, outcome assessors, and investigators involved in trial and data management were masked to treatment allocation. The primary outcome was a favourable outcome 3 months after stroke, defined as a modified Rankin Scale score of 0-2. We did analysis on an intention-to-treat basis. The trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN1260600185561.

FINDINGS:
Between July 18, 2006, and Oct 16, 2014, we randomly assigned 2104 patients to receive either very early mobilisation (n=1054) or usual care (n=1050); 2083 (99%) patients were included in the 3 month follow-up assessment. 965 (92%) patients were mobilised within 24 h in the very early mobilisation group compared with 623 (59%) patients in the usual care group. Fewer patients in the very early mobilisation group had a favourable outcome than those in the usual care group (n=480 [46%] vs n=525 [50%]; adjusted odds ratio [OR] 0.73, 95% CI 0.59-0.90; p=0.004). 88 (8%
patients died in the very early mobilisation group compared with 72 (7%) patients in the usual care group (OR 1.34, 95% CI 0.93-1.93, p=0.113). 201 (19%) patients in the very early mobilisation group and 208 (20%) of those in the usual care group had a non-fatal serious adverse event, with no reduction in immobility-related complications with very early mobilisation.

**INTERPRETATION:**
First mobilisation took place within 24 h for most patients in this trial. The higher dose, very early mobilisation protocol was associated with a reduction in the odds of a favourable outcome at 3 months. Early mobilisation after stroke is recommended in many clinical practice guidelines worldwide, and our findings should affect clinical practice by refining present guidelines; however, clinical recommendations should be informed by future analyses of dose-response associations.


**Abstract**
Objective: Our prespecified dose-response analyses of A Very Early Rehabilitation Trial (AVERT) aim to provide practical guidance for clinicians on the timing, frequency, and amount of mobilization following acute stroke.

Methods: Eligible patients were aged ≥18 years, had confirmed first (or recurrent) stroke, and were admitted to a stroke unit within 24 hours of stroke onset. Patients were randomized to receive very early and frequent mobilization, commencing within 24 hours, or usual care. We used regression analyses and Classification and Regression Trees (CART) to investigate the effect of timing and dose of mobilization on efficacy and safety outcomes, irrespective of assigned treatment group.

Results: A total of 2,104 patients were enrolled, of whom 2,083 (99.0%) were followed up at 3 months. We found a consistent pattern of improved odds of favorable outcome in efficacy and safety outcomes with increased daily frequency of out-of-bed sessions (odds ratio [OR] 1.13, 95% confidence interval [CI] 1.09 to 1.18, \(p < 0.001\)), keeping time to first mobilization and mobilization amount constant. Increased amount (minutes per day) of mobilization reduced the odds of a good outcome (OR 0.94, 95% CI 0.91 to 0.97, \(p < 0.001\)). Session frequency was the most important variable in the CART analysis, after prognostic variables age and baseline stroke severity.

Conclusion: These data suggest that shorter, more frequent mobilization early after acute stroke is associated with greater odds of favorable outcome at 3 months when controlling for age and stroke severity.

**Classification of evidence:**
This study provides Class III evidence that shorter, more frequent early mobilization improves the chance of regaining independence after stroke.


**DETAILED article not reviewed above.**

**Abstract**
**BACKGROUND**
Mobilising patients early after stroke [early mobilisation (EM)] is thought to contribute to the beneficial effects of stroke unit care but it is poorly defined and lacks direct evidence of benefit.

**OBJECTIVES**
We assessed the effectiveness of frequent higher dose very early mobilisation (VEM)
DESIGN
We conducted a parallel-group, single-blind, prospective randomised controlled trial with blinded end-point assessment using a web-based computer-generated stratified randomisation.

SETTING
The trial took place in 56 acute stroke units in five countries.

PARTICIPANTS
We included adult patients with a first or recurrent stroke who met physiological inclusion criteria.

INTERVENTIONS
Patients received either usual stroke unit care (UC) or UC plus VEM commencing within 24 hours of stroke.

MAIN OUTCOME MEASURES
The primary outcome was good recovery [modified Rankin scale (mRS) score of 0-2] 3 months after stroke. Secondary outcomes at 3 months were the mRS, time to achieve walking 50m, serious adverse events, quality of life (QoL) and costs at 12 months. Tertiary outcomes included a dose-response analysis.

DATA SOURCES
Patients, outcome assessors and investigators involved in the trial were blinded to treatment allocation.

RESULTS
We recruited 2104 (UK, n=610; Australasia, n=1494) patients: 1054 allocated to VEM and 1050 to UC. Intervention protocol targets were achieved. Compared with UC, VEM patients mobilised 4.8 hours [95% confidence interval (CI) 4.1 to 5.7 hours; p < 0.0001] earlier, with an additional three (95% CI 3.0 to 3.5; p < 0.0001) mobilisation sessions per day. Fewer patients in the VEM group (n=480, 46%) had a favourable outcome than in the UC group (n=525, 50%) (adjusted odds ratio 0.73, 95% CI 0.59 to 0.90; p=0.004). Results were consistent between Australasian and UK settings. There were no statistically significant differences in secondary outcomes at 3 months and QoL at 12 months. Dose-response analysis found a consistent pattern of an improved odds of efficacy and safety outcomes in association with increased daily frequency of out-of-bed sessions but a reduced odds with an increased amount of mobilisation (minutes per day).

LIMITATIONS
UC clinicians started mobilisation earlier each year altering the context of the trial. Other potential confounding factors included staff patient interaction.

CONCLUSIONS
Patients in the VEM group were mobilised earlier and with a higher dose of therapy than those in the UC group, which was already early. This VEM protocol was associated with reduced odds of favourable outcome at 3 months cautioning against very early high-dose mobilisation. At 12 months, health-related QoL was similar regardless of group. Shorter, more frequent mobilisation early after stroke may be associated with a more favourable outcome.

FUTURE WORK
These results informed a new trial proposal [A Very Early Rehabilitation Trial - DOSE (AVERT-DOSE)] aiming to determine the optimal frequency and dose of EM.

Join us on Facebook and twitter @APTAStrokeSIG and Instagram #StrokePT