A Very Early Rehabilitation Trial after stroke (AVERT): a Phase III, multicentre, randomised controlled trial

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Scientific summary

The AVERT RCT

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Scientific summary

Background

The last two decades has seen a substantial change in the way that stroke patients are managed. We now have several interventions available that have good evidence of benefit for acute stroke patients. Arguably the most important of these is stroke unit care, which comprises a complex package of specialist multidisciplinary stroke care involving nurses, therapists and doctors. However, this is a complex intervention and it is difficult to provide firm advice on the key components of stroke unit care. Many descriptive studies have reported that early mobilisation (EM) (starting out of bed, sitting, standing and walking early after stroke) is believed to be an important contributor to the benefit of stroke units. However, EM is poorly described and defined. This trial focuses on very early mobilisation (VEM) commencing within 24 hours of stroke onset as a key component of stroke unit care.

Very early mobilisation comprises the commencement of sitting, standing and walking training out of bed after stroke within 24 hours of stroke onset, using a clinical protocol that tailors the activity to the severity of stroke. The biological rationale for VEM is based on the following.

1. There is good evidence that bed rest is often harmful.
2. Some of the most common and serious complications after stroke are those related to immobility.
3. Modern concepts of brain recovery after injury suggest a window of opportunity for exploiting brain plasticity and encouraging repair.

However, there are also concerns about the potential harm of VEM and, in particular, due to reduced cerebral blood flow caused by adopting an upright position too early. In view of these uncertainties, Professor Julie Bernhardt of the University of Melbourne began the A Very Early Rehabilitation Trial (AVERT) programme of work. This comprised Phase I observational studies, followed by a Phase II safety and feasibility randomised controlled trial (RCT) and, finally, the main multicentre international RCT (AVERT Phase III) that is reported here.

Objectives

The primary aim of this trial was to investigate the effectiveness of a protocol to implement VEM after stroke; with commencement of frequent out-of-bed activity within 24 hours of stroke onset, compared with usual care (UC).

The objectives of AVERT were to address four main questions.

1. Does VEM reduce death and disability at 3 months post stroke?
2. Does VEM reduce the number and severity of complications at 3 months post stroke?
3. Does VEM improve quality of life (QoL) at 12 months post stroke?
4. Is VEM cost-effective?

Methods

The AVERT was a pragmatic, prospective, parallel-group, multicentre, international, RCT with blinded assessment of outcomes and an intention to treat analysis. The National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme grant supported the UK component of the trial.

Setting
Acute stroke units in 56 hospitals in five countries: UK (England, Scotland, Northern Ireland and Wales), Australia, New Zealand, Malaysia and Singapore.

Participants
Acute stroke patients (confirmed first or recurrent stroke, cerebral infarct or intracerebral haemorrhage) who were admitted to a stroke unit within 24 hours of symptom onset. Treatment with recombinant tissue plasminogen activator (rtPA) was allowed with the agreement of the responsible clinician. Exclusion criteria included significant premorbid disability, competing care needs or acute medical instability.

Procedures
Informed consent was obtained from the patient or their nominated representative. Patients were invited to take part in a trial that was testing 'different types of rehabilitation'. Baseline data were entered on the AVERT Online electronic data capture system prior to randomisation.

Randomisation
After entry of baseline data, the online system allocated the patient to a treatment group using a 1 : 1 ratio, with computer-generated block randomisation stratified for site and severity. Patients were allocated to receive either UC alone or VEM in addition to UC. The VEM intervention commenced as soon as patients were recruited and lasted for 14 days, or until the patient was discharged from the stroke unit (whichever was sooner). Following randomisation, baseline patient data were collected on baseline demography, mobility scale for acute stroke, star cancellation test and time to first mobilisation (TTFM).

Interventions
The AVERT intervention protocol was followed for all patients randomised. Regardless of intervention group, the AVERT nurses and physiotherapists recorded information about all mobilisations via the online trial system.

Usual care was provided at the discretion of the individual sites. Trial staff documented usual stroke unit care at their site. At each site, UC was monitored to ensure that UC did not change, or changes were clarified.

The VEM intervention comprised the following key features.

- It was to begin within 24 hours of stroke onset.
- It was to focus on out-of-bed sitting, standing and walking activities.
- VEM was delivered in at least three out-of-bed sessions in addition to UC.
- Nursing and physiotherapy mobilisations were titrated according to patient functional level.

Patients allocated to VEM were managed by physiotherapy and nursing staff trained in the study procedures (AVERT nurses and physiotherapists), who followed a prescribed approach based on the baseline assessment of patient abilities from level one (fully dependent) to level four (little or no dependence). Usual risk assessments and lifting policies were applied to all mobilisations. Prior to, and during, the first mobilisation, an assessment of physiological variables was required and mobilisation was stopped if physiological variables changed beyond specified limits. VEM activities were repeated and varied as appropriate and could be reduced if associated with excessive fatigue. Nurses and therapists frequently worked together, but on Saturdays the AVERT nurse was responsible for providing and recording mobilisations.

The UC group received usual post-stroke care and the number and type of mobilisations were not prescribed but were recorded. AVERT Online was used to record therapy and nursing input to both VEM and UC groups and any deviations to the protocol were documented and reported. Care was taken not to record VEM interventions in the routine clinical records.

Blinding

Several steps were taken to maintain the integrity of the trial.

- Patients and families were not told of their allocation group.
- Treatment allocation was not written in the medical records.
- AVERT staff ensured that other staff were not aware of treatment allocation.
- The blinded outcome assessor was remote from the ward and did not have contact with any clinical care.

Outcomes

The primary outcome was survival without major disability [modified Rankin scale (mRS) score of 0–2] at 3 months after stroke. Secondary efficacy outcomes were an assumption-free ordinal shift across the range of the mRS, time (days) to walk 50 m unassisted and the proportion of patients achieving unassisted walking by 3 months. Secondary safety outcomes at 3 months were fatal and non-fatal serious adverse events (SAEs). SAEs of interest were neurological (stroke progression and recurrent stroke) and immobility related (pulmonary embolism, venous thrombosis, urinary tract infection, pressure sores and pneumonia). All fatal and non-fatal SAEs were reported according to standard definitions and independently adjudicated. At 12 months, an assessment of health-related quality of life (HRQoL) was made, using the assessment of quality of life, with costs assessed using a resources questionnaire.

Subgroup analyses were prespecified for age, stroke severity, stroke subtype (infarct or haemorrhage), treatment with rtPA and TTFM, as well as an exploratory analysis of association between treatment dose and patient outcome.

Sample size

We estimated that a sample of 2104 patients would be required to provide an 80% power to detect a significant intervention effect ($p = 0.05$) with adjustments for 5% drop-in and 10% drop-out. The trial was powered to detect an absolute risk reduction of a poor outcome (mRS score of 3–6) of at least 7.1%. The statistical and cost analysis plans were prespecified and published in advance. The primary outcome analysis used a binary logistic regression model with treatment group as an independent variable and mRS at 3 months as the dependent variable, with intention-to-treat analysis. Baseline stroke severity and age were included as treatment covariates.

A series of subgroup and exploratory analysis were prespecified to explore the range of any treatment effect and to allow analysis of association between treatment dose and patient outcome.

Results

A total of 25,237 patients were admitted within 24 hours of stroke onset, of whom 23,133 were ineligible. Main reasons for ineligibility were a lack of available recruiting staff on duty, medical instability or premorbid disability. A total of 2104 patients were recruited between July 2006 and October 2014; 1054 received VEM and 1050 received UC. A total of 34 patients were found to have a non-stroke diagnosis and 26 were never mobilised. These patients remained within the intention-to-treat analysis.

Baseline characteristics were well matched between groups. The median time to randomisation was 18 hours after stroke, 80% were experiencing a first stroke and 45% were classified as having moderate–severe stroke (National Institutes of Health Stroke Scale score of > 7). A total of 26% were aged > 80 years and 24% received rtPA.

Patients allocated to VEM began mobilisation within 24 hours of stroke and maintained earlier and higher levels of out-of-bed activity than UC patients. However, it was noted that the median TTFM in the UC group reduced during the study period. Overall, 965 (92%) VEM patients were mobilised within 24 hours compared with 623 (59%) in the UC group. There were no substantial regional differences in the delivery of the intervention.

Primary outcome

A total of 2083 (99%) patients were included in the 3-month follow-up.

At 3 months, fewer patients in the VEM group had a favourable outcome (mRS score of 0–2) than in the UC group. A total of 480 (46%) VEM patients had a favourable outcome compared with 525 (50%) in the UC group. This resulted in the significant difference between groups on the prespecified analysis [adjusted odds ratio (aOR) 0.73, 95% confidence interval (CI) 0.59 to 0.90; $p = 0.004$]. Sensitivity analysis produced similar results and unadjusted analysis of the primary outcome showed a similar (but borderline significant) direction of effect ($p = 0.068$). Subgroup analysis of the primary outcome showed a consistent pattern favouring UC across all the main subgroups. There was a suggestion of poorer outcomes with VEM in patients with severe stroke and intracerebral haemorrhage but these did not achieve statistical significance (test for interaction $p > 0.05$).

Secondary outcomes

Assumption-free ordinal analysis across the whole mRS did not show a significant difference between groups (aOR 0.94, 95% CI 0.85 to 1.03; $p = 0.193$). Similarly, there were no significant differences in walking ability (aOR 1.04, 95% CI 0.94 to 1.15; $p = 0.459$), case fatality at 3 months (aOR 1.34, 95% CI 0.93 to 1.93; $p = 0.113$) or non-fatal SAEs (incidence rate ratio 0.88, 95% CI 0.72 to 1.07; $p = 0.194$). For HRQoL, the median assessment of QoL (interquartile range) for the VEM group was 0.47 (0.07–0.81) and for the UC group was 0.49 (0.08–0.81) ($p = 0.865$).

Tertiary outcomes

Further prespecified analyses explored the relationship between treatment received and patient outcomes. These indicated that a favourable outcome (mRS score of 0–2), survival and recovery of walking at 3 months were positively associated with an increased frequency of mobilisation sessions. In contrast, a more prolonged duration of out-of-bed mobilisation activity was associated with a poorer outcome. This pattern was observed in logistic regression analysis and confirmed with a classification and regression tree analysis.

Meta-analysis of early mobilisation trials

We identified a total of nine RCTs, including AVERT, that had tested EM (within 48 hours) after stroke compared with UC. Across all trials, the median delay to starting mobilisation was 18.5 hours in the EM group and 33.3 hours in the UC group. EM showed non-significant increase in the odds of death or dependency (odds ratio 1.10, 95% CI 0.94 to 1.29).

Conclusions

This is the largest randomised trial of its kind and required strong interdisciplinary collaboration. Most patients underwent first mobilisation within 24 hours of stroke but the earlier, more frequent, higher-dose mobilisation was associated with a poorer outcome than UC. As usual stroke unit care varied from site to site and is complex in nature. It is oversimplistic to simply advise UC.

The AVERT results raise several important research questions; in particular, what are the physiological and molecular changes induced that may be harmful in some patients, who should we target for EM and how do we best describe the key characteristics of EM. These questions are being taken forward in a more detailed meta-analysis. We also propose to undertake a further dose–response trial (AVERT–DOSE) to explore the effect of frequency and dose of rehabilitation on efficacy and safety outcomes.

Trial registration

This trial is registered with the Australian New Zealand Clinical Trials Registry number ACTRN12606000185561, and Current Controlled Trials ISRCTN98129255 and ISRCTN98129255.

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This report

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