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Very early versus delayed mobilisation after stroke (Review)

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Very early versus delayed mobilisation after stroke

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ABSTRACT

Background

Very early mobilisation is performed in some stroke units and recommended in acute stroke clinical guidelines. It is unclear whether very early mobilisation independently improves outcome after stroke.

Objectives

To determine the benefits and harms of very early mobilisation (commenced within 48 hours of stroke) compared with conventional care.

Search methods

We searched the Cochrane Stroke Group Trials Register (last searched April 2008). In addition, we searched 25 databases including the Cochrane Central Register of Controlled Trials (*The Cochrane Library* Issue 3, 2007), MEDLINE (1950 to August 2007), EMBASE (1980 to September 2007), CINAHL (1982 to December 2006), and AMED (1985 to January 2007). We also searched relevant ongoing trials and research registers (searched January 2007) and the Chinese medical database Wanfangdata (searched March 2007), handsearched journals, searched reference lists and contacted researchers in the field.

Selection criteria

Unconfounded RCTs of acute stroke patients, comparing an intervention group that started out of bed mobilisation within 48 hours of stroke and aimed to reduce time to first mobilisation and/or increase the amount or frequency (or both) of mobilisation, with conventional care.

Data collection and analysis

One review author eliminated obviously irrelevant records; two review authors independently applied selection criteria to remaining studies. The primary outcome was death or poor outcome (dependency or institutionalisation) at the end of scheduled follow up. Secondary outcomes included mortality, dependency, institutionalisation, activities of daily living (ADLs), quality of life, time to walking, adverse events (e.g. deep vein thrombosis) and patient mood.

Main results

One study, involving 71 participants, was included. In this study the experimental group had earlier and more frequent mobilisation than the control group (median 18.1 hours post stroke for experimental group versus 30.8 hours control; 167 minutes of mobilisation (interquartile range (IQR) 62 to 305) during admission for experimental group versus 69 (IQR 31 to 115) minutes control). Fewer patients who received early and frequent mobilisation were dead or disabled at three months, but this was not statistically significant and the confidence intervals were wide (odds ratio (OR) 0.67, 95% confidence interval (CI) 0.25 to 1.79, $P = 0.42$). No significant difference on any secondary outcomes of interest were found.

Authors' conclusions

We found insufficient evidence to support or refute the efficacy of routine very early mobilisation after stroke, compared with conventional care. More research is required to determine the benefits and harms of very early mobilisation after stroke.

PLAIN LANGUAGE SUMMARY

Very early versus delayed mobilisation after stroke

The impact of very early mobilisation on recovery after stroke is not clear. Care in a stroke unit is recommended for patients early after stroke and results in reduced disability and an increased likelihood of returning home. Very early mobilisation (helping patients to get up out of bed very early and often after stroke symptom onset) is performed in some stroke units and is recommended in many acute stroke clinical guidelines. However, this review identified only one small trial (71 participants) which found no difference in death and dependency at three months between those who undertook an early intensive mobilisation protocol and those who did not. No significant harms were identified and a small reduction in non serious adverse events was found. At present there is insufficient evidence to support or refute the effects of routine very early mobilisation after stroke and several trials are currently ongoing.

BACKGROUND

Stroke presents a major global public health challenge, with 5.5 million people dying from stroke each year (WHO 2003) and many more living with chronic disability (Wolfe 2000). We know that treatment in a stroke unit (compared to treatment in a general medical ward) reduces the odds of being dead or disabled at 12 months post stroke (SUTC 2007). However, relatively little is known about which components of acute stroke unit care may be responsible for better outcomes (Langhorne 1998; Langhorne 2002). Early rehabilitation is described as an important feature of stroke unit care (Langhorne 1998), but there is only limited information about what early rehabilitation entails and who provides it. In addition to the uncertainties surrounding the optimal amount of rehabilitation that can be provided early after stroke, exactly how early rehabilitation should start is controversial. Early mobilisation (getting patients up and out of bed within 24 to 48 hours of stroke) as part of a rehabilitation package is an established feature of acute stroke unit care in many Scandinavian hospitals. In other parts of the world, patients are restricted to bed for some days (Diserens 2006) before mobilisation is allowed. In some cases these differences in practice reflect concerns about the possibil-

ity that early mobilisation may have a detrimental effect on the vulnerable ischaemic penumbra (Diserens 2006) although there is little evidence to support this view (Bernhardt 2007), while in other cases they are likely to reflect historical practices. Although very early mobilisation has been recently recommended in a number of acute stroke clinical guidelines (Adams 2003; NSF 2007), only indirect evidence currently supports these recommendations (Indredavik 1999). It is not known whether very early mobilisation independently improves outcome after stroke.

OBJECTIVES

To determine whether very early mobilisation (started as soon as possible and no later than 48 hours after onset of symptoms) in acute stroke patients improves recovery (primarily the proportion of independent survivors) in comparison with conventional care.

METHODS

Criteria for considering studies for this review

Types of studies

We sought all unconfounded randomised trials, with or without blinding, of very early mobilisation within 48 hours of symptom onset compared with conventional care (that is, normal practice or no routine intervention).

Types of participants

Participants in trials had to have a definite clinical diagnosis of stroke (focal neurological deficit of cerebrovascular origin) and could be mobilised within 48 hours of stroke onset. There were no age restrictions.

Types of interventions

Very early mobilisation was defined as any intervention delivered with the aim of reducing the time from stroke onset to first mobilisation (first out of bed episode), and increasing the amount of out of bed physical activity (e.g. participation in activities of daily living (ADLs) such as walking to toilet, transferring on/off toilet, sitting out of bed, standing and walking). Any form of very early mobilisation was considered irrespective of the number and discipline of staff assisting; and dose or duration of intervention. Conventional care was defined as usual mobilisation practice.

Types of outcome measures

Primary outcomes

(1) Death or a poor outcome: the number of patients who died or remained dependent (Barthel score < 15 or equivalent and/or admission to institutional care or modified Rankin Score 3 to 6) at end of scheduled follow up. Institutional care was defined as care within a residential home, nursing home, or hospital at follow up or at discharge.

Secondary outcomes

- (1) Death: number of deaths from any cause.
- (2) Death or dependence: the number of patients dead or physically dependent.
- (3) The number of patients requiring institutional care.
- (4) Performance in activities of daily living.
- (5) Performance in extended activities of daily living (community and domestic activities).
- (6) Patient subjective health status/quality of life.
- (7) Time to walking unassisted (without help from another person) reported alone or as a component of a functional mobility scale.

- (8) Potential adverse events: number and/or severity of adverse effects including deep vein thrombosis (DVT), non fatal pulmonary embolism (PE), incidence and grade of pressure sores (using standardised grading scale), number of incontinent episodes over 24 hours, severity of incontinence, chest infection, falls and physiological variables (blood pressure, oxygen, temperature) recorded.
- (9) Patient mood.

All secondary outcomes of interest were for follow up at three to 12 months after stroke.

Search methods for identification of studies

See: 'Specialized register' section in [Cochrane Stroke Group](#)

We searched the Cochrane Stroke Group Trials Register, which was last searched by the Review Group Co-ordinator on 14 April 2008. In addition, we systematically searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 3, 2007); MEDLINE (1950 to August 2007) ([Appendix 1](#)); EMBASE (1980 to September 2007); CINAHL (1982 to December 2006); PsycINFO (1806 to December 2006), the Allied and Complementary Medicine Database (AMED, 1985 to January 2007), The Physiotherapy Evidence Database (PEDro (<http://www.pedro.fhs.usyd.edu.au/>) 1929 to December 2006), REHABDATA (<http://www.naric.com/research/rehab/>, searched 1956 to December 2006), Center for International Rehabilitation Research Information and Exchange (CIRRIE, (<http://cirrie.buffalo.edu/>) 1990 to December 2006), OTSeeker (searched 22 January 2007), SPORTDiscus (1830 to November 2006), Digital Dissertations (1743 to December 2006), Wanfangdata (<http://www.wanfangdata.com/>, searched March 2007), Science Citation Index Expanded (1900 to December 2006), Social Sciences Citation Index (1956 to December 2006), Arts and Humanities Citation Index (1975 to December 2006), British Association of Occupational Therapists Library Collection (searched January 2007) and the British Association/College of Occupational Therapists Thesis Collection (searched January 2007). In January 2007 we searched the following trials and research registers; the Meta Register of Controlled Trials (mRCT, <http://www.controlled-trials.com/mrct/>), ClinicalTrials.gov, the UK National Research Register (NRR), the Australian Clinical Trials Registry (ACTR), the Netherlands Trial Register, the UK Department of Health Research Findings Register (ReFeR) and Index to UK Theses.

We used the search strategy for MEDLINE and modified it to suit other databases ([Appendix 1](#)). There was no language restriction and we arranged translation of relevant Chinese papers.

- (1) We handsearched all available years of the following journals:
 - *Advances in Occupational Medicine and Rehabilitation* (1996 to 1999);
 - *Advances in Clinical Neurosciences and Rehabilitation* (2001 to 2006);
 - *Advances in Clinical Rehabilitation* (1987 to 1990);

- *Archives of Occupational Therapy* (renamed *Occupational Therapy and Rehabilitation*) (1922 to 2006);
- *Canadian Journal of Rehabilitation* (1987 to 1999);
- *Chinese Journal of Physical Medicine and Rehabilitation* (1980 to 2006);
- *European Journal of Physical Medicine and Rehabilitation* (1991 to 1999);
- *International Journal of Rehabilitation and Health* (1995 to 2000);
- *Journal of Rehabilitation Administration* (1987 to 2006);
- *Rehabilitation* (1948 to 49, 1951 to 1977);
- *Rehabilitation in Canada* (1963 to 1972);
- *Rehabilitation Nursing Research* (1992 to 1996);
- *Topics in Stroke Rehabilitation* (1995 to 2006).

(2) We contacted a number of relevant researchers and Drs Lorraine Smith, Andrea Di Lauro and Julie Bernhardt provided responses to our requests.

(3) We searched the references lists of all relevant papers.

Data collection and analysis

Selection and identification of relevant trials

We selected trials for inclusion based on the described inclusion criteria. Two review authors (MT and JMC) independently read the titles (and abstracts if available) of all the references identified and eliminated any obviously irrelevant studies. We obtained the full text for remaining studies and, based on the inclusion criteria (types of studies, types of participants, aims of interventions, outcome measures), two review authors (MT and JMC) independently classified these as eligible, not eligible or unsure. Any trials classified as not eligible by the review authors were excluded. Three review authors (MT, JMC and LL) made decisions about inclusion, and we resolved differences in opinion regarding trial eligibility by discussion between all review authors. If further information was needed to reach consensus, we contacted trialists and attempted to obtain the missing information. Papers and abstracts in Chinese were reviewed by one researcher fluent in Chinese and with medical training (JW or WZ, see [Acknowledgements](#)). One review author (MT) assessed a short English description of the decision made.

Assessment of methodological quality

One review author (MT), who had no involvement in any included studies, evaluated the methodological quality of included trials. This review author extracted information for each included trial about the method of randomisation and allocation concealment, blinding of outcome assessment and any intention-to-treat analyses.

Data extraction

Our primary aim was to obtain standardised data through collaboration with the original trialists. Two review authors (MT and JMC) extracted data from published sources using a standard data recording form. We extracted important quality indicator data such as concealment of randomisation, blinding of outcome evaluation, and intention-to-treat analysis, and graded these as present or unclear. In addition, we extracted data relating to all primary and secondary outcomes of interest, as well as important imbalances in prognostic factors, comparison (details of the intervention in the treatment and control groups, details of co-intervention(s) in both groups) and other relevant outcomes not prespecified in the protocol (for example, exertion).

All the extracted data were checked for agreement between review authors, with a third review author (LL) arbitrating any items where consensus could not be reached. If necessary, we contacted trialists to request more information, clarification or missing data.

Data analysis

We planned to compare interventions that commenced mobilisation earlier and aimed to improve the frequency or amount (or both) of mobilisation, delivered by any member of the acute stroke unit staff, versus delayed mobilisation (or conventional care) on primary and secondary outcome parameters. Binary (dichotomous) outcomes were analysed with a fixed-effect model, as odd ratios (OR) with 95% confidence intervals (CI). For continuous outcomes standardised mean difference (SMD) with a random-effects model was used to take account of any statistical heterogeneity. We planned to examine the statistical heterogeneity between studies using the I-squared (I^2) statistic. Substantial heterogeneity was determined as a value greater than 50%. We used the Cochrane Review Manager software, RevMan 4.2 ([RevMan 2006](#)), for analyses.

Sensitivity analysis

We planned sensitivity analyses to evaluate the effect of differences in methodological quality (method of randomisation, allocation concealment, intention-to-treat analysis and blinding of final assessment), time to first mobilisation and amount of mobilisation.

RESULTS

Description of studies

A total of 39 trials of interest were identified by September 2007, of which 28 were excluded ([Asberg 1989](#); [Chu 2003](#); [Di Lauro 2003](#); [Duan 2006](#); [Gong 2003](#); [Gu 2006](#); [Guan 2001](#); [Hamrin](#)

1982; Huang 2001; Huang 2003; Kreisel 2005; Li 2003; Li 2004; Lin 2005; Liu 2004; Raicevic 2000; Pan 2004; Qian 2003; Qian 2004; Song 2005; Truscott 1974; Wang 2006; Xi 2003; Xiao 2004; Xue 2004; Zeng 2004; Zhang 1998; Zhao 2003). Nineteen of these studies were published in Chinese language journals and required translation to English. These trials were excluded for various reasons detailed in [Characteristics of excluded studies](#). Eight studies have not been assessed at this time as we have been unable to obtain full references and we have been unsuccessful in obtaining any further information from the authors (Gorbunov 2003; Hara 2001; Izumi 2001; Li 1999; Nilsson 2003; Toyota 2001; Xu 2001; Zielke 2003). Two trials are currently ongoing (AVERT III; VERITAS) and there are no data available. Details of these trials are reported in [Characteristics of ongoing studies](#). This left one trial, AVERT Phase II (AVERT II) which was included in the review. This trial compared very early mobilisation versus conventional care within stroke units.

Patient characteristics

The inclusion and exclusion criteria for patients in AVERT II are shown in [Characteristics of included studies](#). In AVERT II only those patients regarded as meeting the World Health Organization criteria (Hatano 1976) definition of a stroke were included. The mean age of all stroke 71 patients was 74.7 years. Fifty-four per cent were male and 87% had suffered an ischaemic stroke that affected the right side in 51% of cases. For 75% of patients, this was their first-ever stroke. Of the common risk factors for stroke, 70% of the group presented with hypertension, 28% with ischaemic heart disease, 27% with hypercholesterolaemia and 54% were either current smokers or had previously smoked. Stroke severity was measured using the National Institutes of Health Stroke Scale (NIHSS) (Brott 1989) and classified as mild (NIHSS 0 to 7), moderate (NIHSS 8 to 16) or severe (NIHSS > 16) stroke. Stratified randomisation was used to balance stroke severity between groups. The mean baseline NIHSS was 10, and 58% of the sample had experienced moderate or severe stroke. There were no significant baseline imbalances between groups in important prognostic factors.

Outcomes and length of follow up

For the AVERT II study, the primary outcome was death at three months. Secondary outcome measures included: serious adverse events at three months (any event that was life-threatening, incapacitating or prolonged hospital admission and patient acuity); non-serious adverse events (all other adverse events that did not meet the 'serious' criteria) at three months post stroke; falls during intervention phase and at three months; deterioration within seven days of stroke onset, perceived exertion immediately following mobilisations; and hypotensive episodes during mobilisation. Deterioration was defined according to the European Progressing

Stroke Study definition (Barber 2004), on the Scandinavian Stroke Scale, a two or greater worsening in either consciousness, leg or eye movement scores, or a three or greater worsening in speech score. Falls during the intervention (whether serious or non-serious events) and at three months were reported separately. Disability was measured using the modified Rankin Scale (mRS) with a score of 3 to 6 indicating poor outcome.

As AVERT II was a Phase II (pilot) trial, feasibility outcomes included time to first mobilisation and total 'dose' (minutes) of mobilisation throughout the acute intervention period.

Follow up for AVERT II occurred at seven and 14 days post stroke, then at three, six and 12 months; however, with the exception of disability on the modified Rankin Scale (which was reported at six and 12 months), published data for this study are limited to the three-month time point.

Proportion of people followed up

In AVERT II, 100% of patients were followed up at three months. Two patients (3%) were lost to follow up at 12 months (both in the intervention group).

Intervention characteristics

In AVERT II, the experimental intervention aimed to provide the first mobilisation within 24 hours of stroke. A nurse and physiotherapy team performed mobilisations, which aimed to assist the patient to be upright and out of bed (sitting, standing or walking) at least twice a day, six days per week. Physiological monitoring of blood pressure, heart rate and temperature was done prior to each mobilisation within the first three days of stroke. The experimental intervention was additional to conventional care. Frequent mobilisations continued until 14 days post stroke or discharge. Patients in the experimental group received the first mobilisation at a median time of 18.1 (interquartile rate (IQR) 12.8 to 21.5) hours post stroke. All patients in this group were mobilised within 48 hours. Patients received a median of 167 (IQR 62 to 305) minutes of mobilisation during the acute stroke unit admission. Median length of stay was six days (IQR 1 to 19).

The control group received conventional stroke unit care only, which included a mobilisation component. Patients in the control group received first mobilisation at a median time of 30.8 (IQR 23.0 to 39.9) hours post stroke. Not all patients were mobilised within 48 hours of stroke onset in this group. A median of 69 (IQR 31 to 115) minutes of mobilisation was provided to this group during the acute stroke unit admission. Median length of stay was seven days (IQR 2 to 22).

Risk of bias in included studies

Method of randomisation and allocation concealment

[AVERT II](#) used computer-generated randomisation. Allocation was concealed by opaque envelopes.

Blinding of outcome assessment

[AVERT II](#) had clear blinding of outcome assessor.

Intention-to-treat analysis

[AVERT II](#) performed an intention-to-treat analysis.

Follow up

In [AVERT II](#), all patients (100%) completed follow up at three months (primary outcome point). Two patients (3%) were lost to follow up at 12 months (both in the intervention group).

Effects of interventions

Primary outcome

Death or a poor outcome (Outcome 1.1)

Data were available from [AVERT II](#) (71 participants) for the outcome death or a poor outcome at three months. There was a non-significant reduction in the number of patients dying or having a poor outcome in those patients who received very early mobilisation (23/38, 60.5%) compared with the control group (23/33, 69.7%) at three months (OR 0.67, 95% CI 0.25 to 1.79, $P = 0.42$).

Secondary outcomes

Death (Outcome 1.2)

Data were available from [AVERT II](#) (71 participants) for the outcome death at end of scheduled follow up. There was a non-significant increase in the number of patients who died in the very early mobilisation group (8/38, 21.1%) compared with controls (3/33, 9.1%) at three months (OR 2.67, 95% CI 0.64 to 11.03, $P = 0.18$).

Death or dependence (Outcome 1.3)

The modified Rankin Scale was used in [AVERT II](#) to measure outcome at three months. Using this scale, 'poor outcome' is equivalent to 'dependence', therefore the results for outcome 1.3 are the same as for the primary outcome (outcome 1.1).

Institutional care at end of scheduled follow up

No data were available for this outcome.

Performance in activities of daily living

No data were available for this outcome.

Performance in extended activities of daily living (community and domestic activities)

No data were available for this outcome.

Patient subjective health status/quality of life

No published data were available for this outcome.

Time to walking unassisted (without help from another person)

No published data were available for this outcome.

Potential adverse events

Data on serious adverse events were available for [AVERT II](#) (71 participants). No data were available for individual adverse events of interest, such as deep vein thrombosis, pulmonary embolism, fracture, pressure sores, chest infection, incontinence, blood pressure, oxygen or temperature. However, data for early deterioration within seven days and falls were both available. Summary data for non-serious adverse events were also available.

Serious adverse events were defined as any event that was life-threatening, incapacitating or prolonging hospital admission and patient acuity. There was no statistically significant difference in the total number of serious adverse events occurring between the very early mobilisation and control groups when analysed as a between-group comparison (experimental group 15, control group 14, $P = 0.85$).

Data on the number of falls experienced were available from [AVERT II](#). There was no statistically significant difference in falls rate between groups at three months when analysed as a between-group comparison during the intervention period (experimental group 19.7/1000 bed days, (95% CI -2.1 to 41.4), control group 22.8/1000 bed days, (95% CI 0.4 to 45.3), $P = 0.81$) or in the total number of falls at three months (experimental group 27, control group 28, $P = 0.51$).

Data on deterioration at seven days were available from [AVERT II](#). Fewer patients in the early and intensive group deteriorated (early mobilisation; 8/38, 21.1%: conventional care; 9/33, 27.3%) but this was not statistically significant (OR 0.71, 95% CI 0.24 to 2.12, $P = 0.54$).

At three months, there were significantly fewer non-serious adverse events in the very early mobilisation group compared with

the control group when analysed as a between-group comparison (experimental group 61, control group 76, $P = 0.04$). Non-serious adverse events included adverse events that were not life threatening, incapacitating, led to prolonged hospital admission or an increase in patient acuity.

Patient mood at the end of scheduled follow up

No published data were available for this outcome.

Sensitivity analysis

There were insufficient data to carry out any sensitivity analyses.

DISCUSSION

This systematic review aimed to assess the benefits or harms of very early mobilisation compared with conventional practice. We conducted a comprehensive search of 26 citation and clinical trial registries and attempted to contact researchers in the field to identify unpublished studies. We identified only three eligible RCTs, with two trials currently underway in Scotland ([VERITAS](#)) and Australia ([AVERT III](#)). The identified [AVERT II](#) trial (Australia) was a small safety and feasibility study including 71 participants that compared patients who undertook an early (within 24 hours of stroke onset) and more frequent mobilisation protocol with patients who commenced usual care mobilisation later. However, the majority of patients in both groups were mobilised within 48 hours of stroke. In the included study, which was of high methodological quality, there was no difference found in death and disability between groups, no significant harms were identified and the only significant benefit identified was a lower rate of non-serious adverse events in the very early mobilisation group. Given these results, there is insufficient evidence of benefit or harm to recommend commencing mobilisation within 48 hours after stroke.

Clearly there is research interest in this field, with 39 relevant trials identified. Despite this significant body of potentially relevant research, very few studies met the inclusion criteria. One of the major problems we identified during our search for relevant research, was that the term 'early rehabilitation' was used to define interventions spanning a wide time interval. For example, some authors used the term 'early' to describe an intervention that commenced within 48 hours post stroke ([Xue 2004](#)), while other authors described interventions commencing within three months of stroke as 'early' interventions ([Li 2002](#)). It is likely that what clinicians and researchers consider as early rehabilitation is strongly dependent on when rehabilitation usually commences within their healthcare system. This may vary considerably between countries.

The most common reason for trial exclusion in this review was that the mobilisation interventions in the experimental group commenced more than 48 hours after stroke symptom onset, with over

140 studies in this category. Also, a few studies failed to detail the time from stroke onset, instead noting time from admission (e.g. [Asberg 1989](#); [Gao 2001](#)). Given that it can take patients hours or even days to reach hospital following a stroke, these studies failed to provide a precise time point from stroke onset to commencing intervention and consequently the trials could not be included. Other studies provided insufficient information about the timing of the intervention to allow confirmation that the trial met the inclusion criteria ([Hamrin 1982](#); [Raicevic 2000](#)). Author contact has been attempted for these studies and we are awaiting responses. Finally, poor definition of the intervention content and dose was also a problem in this review. It was not uncommon to find interventions only broadly defined with limited information about how much mobilisation was delivered by whom, how often and over what time frame (days/weeks). Once again, we have attempted to contact the authors to seek further information and await a response.

We recommend that researchers and clinicians move to using a common terminology. We have proposed the term 'very early' rehabilitation used to indicate interventions commencing within two days, and 'early' as those commencing three to seven days following stroke onset ([Bernhardt 2007](#)). In this time-critical field of research, it is also important that researchers clearly define when interventions commenced (hours) and that the time is estimated from the start of stroke symptom onset.

Our review identified a substantial number of trials (51 RCTs, 6596 participants) from China that addressed the topic of early rehabilitation following stroke. We understand that current usual practice in many places in China is for little or no organised rehabilitation to be provided to patients following stroke. It is therefore likely that these trials, many of which have been undertaken over the past five years, reflect increasing interest in the provision of rehabilitation to people with stroke. Unfortunately, all the 19 relevant trials identified in this review failed to meet the inclusion criteria because they provided either a complete multidisciplinary rehabilitation program or package (for example, [Xue 2004](#)) which may or may not include a mobilisation component, and compared this with no rehabilitation, or did not provide details of the time of commencement of mobilisation (for example, [Zhang 1998](#)). In view of this rapidly growing body of Chinese research and the difficulties associated with acquisition and translation of Chinese research, forming partnerships with Chinese researchers on the topic of early rehabilitation would be beneficial.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence regarding the benefits or harms of very early mobilisation after stroke to make any recommendation on the practice. This review found no evidence to suggest that the

practice should be discontinued in countries where very early mobilisation is a well established part of stroke unit care (Indredavik 1999). However, there is insufficient evidence to suggest that the practice should be adopted more broadly.

Implications for research

Larger, high-quality trials of very early mobilisation are needed before any clear indication about the harms and benefits of the practice can be established. These studies need to clearly define the timing of commencement of mobilisation interventions, and timing should be provided from time of stroke symptom onset, not admission. Researchers and journal editors must ensure publications fulfil CONSORT guidelines (Moher 2001) with adequate description of the experimental and control interventions. AVERT III, a large (2104 participants) multicentre trial of very early mobilisation versus standard care is currently ongoing with results not expected until early 2011. This and related trials are likely to make a considerable contribution to our understanding of the implications of very early mobilisation on stroke patient outcome.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

AVERT II

Methods	Randomised controlled trial of very early and intensive mobilisation versus standard care Computer generated blocked randomisation, stratified by stroke severity and clinical site, opaque envelopes Blinded outcome assessment, patients blind to group	
Participants	Melbourne, Australia 71 participants: 38 intervention, 33 control Mean age: 74.7 years 53.5% male Mean NIHSS 10 Inclusion criteria: acute stroke patients admitted within 24 hours of symptom onset to a stroke unit, able to react to verbal commands, systolic BP 120 to 220 mmHg, oxygen saturation > 92% (with or without supplementation), heart rate 40 to 100, temperature < 38.5 C Exclusion criteria: premorbid mRS > 3, deterioration within first hour of admission to stroke unit, direct admission to intensive care, concurrent progressive neurological disorder, acute coronary syndrome, severe heart failure, lower limb fracture, palliative care	
Interventions	Very early mobilisation plus standard care versus standard care alone The very early mobilisation group commenced mobilisation (upright and out of bed at least twice a day) as soon as practical, aiming to have first mobilisation within 24 hours of stroke onset This continued daily for 14 days post stroke or until discharge Participants were monitored during mobilisation within the first three days Mobilisation was delivered by a nurse/physiotherapist team	
Outcomes	Mortality 'Severe' adverse events 'Non-severe' adverse events Deterioration Perceived exertion (Borg scale) Total dose of mobilisation Time from stroke onset to first mobilisation mRS (disability) Contamination (increase in mobility in a random sample of standard care participants)	
Notes	Follow-up period: primary outcome 3 months, final follow up 12 months	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

mRS: modified Rankin scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Asberg 1989	Quasi-randomised
Chu 2003	Timing not stated
Di Lauro 2003	No time difference between groups
Duan 2006	Timing not stated, additional psychotherapy and cognitive therapy
Gong 2003	Timing not stated, non randomised
Gu 2006	Timing not stated
Guan 2001	Timing not stated, confounded by additional psychotherapy and swallowing therapy
Hamrin 1982	Confounded by rehabilitation package (a large number of components of stroke unit care versus none), pseudo-RCT
Huang 2001	Timing not stated
Huang 2003	Therapy was started <1 day (ischaemic) or < 3 days (haemorrhagic) Both types of patients were analysed together as a group Contact attempted to further elaborate this study - this was unsuccessful
Kreisel 2005	No time difference of therapy between groups
Li 2003	Timing not stated
Li 2004	Timing not stated
Lin 2005	Timing not stated, confounded by additional psychotherapy, cognitive therapy
Liu 2004	No control < 48 hours, confounded by additional functional electrical stimulation
Pan 2004	Timing not stated
Qian 2003	Timing not stated
Qian 2004	Timing not stated
Raicevic 2000	Timing not stated Possibly passive therapies - not mobilisation

(Continued)

Song 2005	Timing not stated
Truscott 1974	Not an RCT (observational)
Wang 2006	Timing not stated
Xi 2003	Quasi-randomised, uncertain when out of bed
Xiao 2004	Timing not stated
Xue 2004	Intervention was the earlier delivery of a rehabilitation package that included mobilisation and other therapies considered to potentially confound the results (speech therapy, swallowing therapy, psychological therapy including anti-depressants)
Zeng 2004	Confounded by Chinese medicine, timing uncertain, quasi-randomised
Zhang 1998	Timing not stated
Zhao 2003	Uncertain timing: 'as soon as state of illness was stable'

RCT: randomised controlled trial

Characteristics of ongoing studies [ordered by study ID]

AVERT III

Trial name or title	A Very Early Rehabilitation Trial: Phase III (AVERT III)
Methods	
Participants	Plan to recruit 2104 stroke patients Admitted to stroke unit within 24 hours of onset, premorbid mRS < 3
Interventions	Additional early mobilisation, three times a day for 14 days or discharge, or standard care (control)
Outcomes	mRS at 3 months, evaluations of adverse effects, health-related quality of life, cost effectiveness and cost utility, long-term efficacy, activity limitation, dose response, patient severity and staff injury
Starting date	July 2006
Contact information	A/Prof Julie Bernhardt
Notes	Estimated trial duration: 5 years

VERITAS

Trial name or title	Very Early Rehabilitation or Intensive Telemetry After Stroke (VERITAS)
Methods	
Participants	Plan to recruit 20 stroke patients Admitted to hospital within 24 hours, no premorbid severe disability
Interventions	Very early mobilisation (similar to AVERT protocol) or intensive physiological monitoring, or both, or standard care (control)
Outcomes	mRS at 3 months, adverse events, patient activity, neurological deterioration, Barthel index at 1 week and 3 months, walking speed (1 week and discharge), patient satisfaction, resource allocation
Starting date	March 2007
Contact information	Prof Peter Langhorne
Notes	Recruitment completed in January 2008 Follow up ongoing

mRS: modified Rankin scale

DATA AND ANALYSES

Comparison 1. Very early mobilisation versus standard care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or a poor outcome	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Death or poor outcome at 3 months	1	71	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.25, 1.79]
2 Death	1	71	Odds Ratio (M-H, Fixed, 95% CI)	2.67 [0.64, 11.03]
2.1 Mortality at 3 months	1	71	Odds Ratio (M-H, Fixed, 95% CI)	2.67 [0.64, 11.03]
3 Death or dependence	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Death or dependence at 3 months	1	71	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.25, 1.79]

Analysis 1.1. Comparison 1 Very early mobilisation versus standard care, Outcome 1 Death or a poor outcome.

Review: Very early versus delayed mobilisation after stroke

Comparison: 1 Very early mobilisation versus standard care

Outcome: 1 Death or a poor outcome

Analysis 1.2. Comparison 1 Very early mobilisation versus standard care, Outcome 2 Death.

Review: Very early versus delayed mobilisation after stroke

Comparison: 1 Very early mobilisation versus standard care

Outcome: 2 Death

Analysis 1.3. Comparison 1 Very early mobilisation versus standard care, Outcome 3 Death or dependence.

Review: Very early versus delayed mobilisation after stroke

Comparison: 1 Very early mobilisation versus standard care

Outcome: 3 Death or dependence

APPENDICES

Appendix I. MEDLINE search strategy

MEDLINE (Ovid)

1. early ambulation/
2. Physical Therapy Modalities or "Physical Therapy (Specialty)"/
3. rehabilitation/ or "activities of daily living"/ or recovery of function/
4. movement/ or locomotion/ or walking/ or motor activity/
5. exercise movement techniques/ or exercise/ or exercise therapy/
6. 2 or 3 or 4 or 5
7. time factors/ or time/
8. 6 and 7
9. ((early or early\$ or accelerat\$ or immediate or fast-track or timing or rapid) adj10 (mobil\$ or ambulat\$ or rehab\$ or physiotherapy or physical therapy or physical activity or movement or sitting or standing or walking or semi-recumb\$ or out of bed)).tw.
10. (stroke unit\$ or mobility protocol).tw.
11. 1 or 8 or 9 or 10
12. cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or cerebrovascular accident/ or exp brain infarction/ or exp hypoxia-ischemia, brain/ or exp intracranial arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or exp vasospasm, intracranial/ or exp vertebral artery dissection/
13. (stroke or poststroke or post-stroke or cva or cerebral vascular or cerebrovascular).tw.
14. ((cerebral or cerebellar or brainstem or vertebrobasilar) adj5 (infarct\$ or ischaemi\$ or ischemi\$ or thrombo\$ or emboli\$ or apoplexy)).tw.
15. ((cerebral or brain or subarachnoid) adj5 (haemorrhage or hemorrhage or haematoma or hematoma or bleed\$)).tw.
16. hemiplegia/ or exp paresis/
17. (hemipleg\$ or hemipar\$ or paresis or paretic).tw.
18. or/12-17
19. 11 and 18
20. limit 19 to human
21. randomized controlled trial.pt.
22. randomized controlled trials/
23. controlled clinical trial.pt.
24. controlled clinical trials/
25. random allocation/
26. double-blind method/
27. single-blind method/
28. clinical trial.pt.
29. clinical trials/
30. (clin\$ adj5 trial\$).tw.
31. ((singl\$ or doubl\$ or tripl\$ or trebl\$) adj5 (blind\$ or mask\$)).tw.
32. (random\$ or quasi-random\$ or quasi random\$).tw.
33. research design/
34. meta analysis.pt.
35. meta-analysis/
36. control groups/
37. ((control or intervention) adj5 group\$).tw.
38. (metaanalysis or meta-analysis or meta analysis or systematic review).tw.
39. program evaluation/
40. or/21-39
41. 20 and 40

WHAT'S NEW

Last assessed as up-to-date: 4 May 2008.

Date	Event	Description
5 May 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Julie Bernhardt drafted the protocol and participated in all steps of the review. Janice Collier and Lynn Legg refined the protocol and contributed to the planned bibliographic searches. Matthew Thuy and Lynn Legg identified studies, assessed methodological quality and checked the extracted data. Matthew Thuy performed much of the planned bibliographic searches, obtained full-text articles and made contact with authors. All review authors commented on drafts of the manuscript.

DECLARATIONS OF INTEREST

Julie Bernhardt and Janice Collier are authors of the included trial ([AVERT II](#)). They did not participate in the quality assessment of this study and care was taken to ensure that review authors independent of these authors were responsible for decisions about trial inclusion. Matthew Thuy was funded by the Very Early Rehabilitation Research Program.

INDEX TERMS

Medical Subject Headings (MeSH)

*Early Ambulation; *Stroke Rehabilitation; Randomized Controlled Trials as Topic; Time Factors

MeSH check words

Humans