ABSTRACT

Purpose of review: Early rehabilitation is recommended in many guidelines, with limited evidence to guide practice. Brain neurobiology suggests early training, at the right dose, will aid recovery. In this review we highlight recent trials of early mobilisation, aphasia, dysphagia and upper limb treatment where intervention commenced within 7 days of stroke and discuss future research directions.

Recent findings: Trials in this early time window are few. While the seminal AVERT trial suggests a cautious approach is necessary immediately (<24 hours) after stroke, early mobility training and mobilisation appear well tolerated, with few reasons to delay initiating some rehabilitation within the first week. The results of large clinical trials of early aphasia therapy are on the horizon, and examples of targeted upper limb treatments with better patient selection are emerging.

Summary: Early rehabilitation trials are complex, particularly those that intervene across acute and rehabilitation care settings, but these trials are important if we are to optimise recovery potential in the critical window for repair. Concerted efforts to standardise 'early' recruitment, appropriately stratify participants, and implement longer term follow-up is needed. Trial standards are improving. New recommendations from a recent Stroke Recovery and Rehabilitation Roundtable will help drive new research.

Keywords: Stroke, rehabilitation, neurological recovery, mobility, thrombolysis

INTRODUCTION

Early commencement of rehabilitation after stroke is recommended in many clinical practice guidelines (1). Recommendations are typically general in nature. Rarely are the specific timing, dose or content of rehabilitation interventions defined, which reflects the current evidence base. In principal, there are few good reasons to delay rehabilitation. But to progress the field, we need better understanding of what interventions can or should be started early, in what dose and using what schedule in order to optimise patient recovery. In this review we define 'early rehabilitation' as interventions directed at improving post stroke impairments or disability that commence within the first 7 days post stroke. We chose the first 7 days for several reasons. With average length of acute hospital stay in many Western countries around 7 days, for many this period represents first (and for many patients only) access to multidisciplinary treatment in an organised stroke service. Around a third of stroke patients go on to receive some inpatient rehabilitation, although in lower income countries, post-acute stroke rehabilitation services are rare or non-existent. Secondly, recognising that understanding the neural substrates of recovery will help us develop better treatments underpinned by biology (2), pre-clinical research suggests that there is an early 'critical' or 'sensitive' period in which the brain is most responsive to improvements induced by motor training (3), with the first days and weeks important (4). Motor training started around 5 days post stroke is more effective than training started at day 14 or day 30 (5). Taken together, applying targeted treatments within an early sensitive period in a stimulating environment should provide the best opportunity of achieving true neurological recovery after stroke (3, 4).

In this review, we highlight recent early intervention trials in early mobility and exercise training, speech and language, swallowing and upper limb training. We searched PUBMED for full journal articles and searched the Cochrane Stroke Group trials register for trials published since 2015 in any of the areas outlined above. We excluded pharmaceutical trials.

Early mobility training, mobilisation and exercise

While the international, multicentre AVERT trial dominates the trial landscape, interest early onset mobility training and mobilisation has resulted in publication of a number of new randomised controlled trials (see Table 1) since our 2015 review (1) of the field. In the multicentre SEVEL trial, (6) an early sitting protocol, initiated within one calendar day after stroke onset, was compared to a late protocol commenced at day 3 for patients with ischemic stroke. Only the timing of first intervention was recorded, not subsequent interventions throughout hospitalisation. Primary outcome was modified Rankin Scale (mRS) at 3 months post stroke, with medical complications as key secondary outcomes. Patients were recruited from 11 French stroke centres and planned sample size was 366 patients. Unfortunately slow recruitment (largely due to poor trial infrastrcture) led investigators to close the trial early (total sample n=167; early sitting n=82, later n=85). There were no significant differences in mRS or complications at 3 months. Complication rates were low overall, and both interventions were well tolerated. A Brazilian study by Poletto and colleagues (7) aimed to test the safety and feasibility of a protocol commencing within 48 hours of stroke onset incorporating sitting out of bed plus 30 minutes of functional training per day led by a physiotherapist, 5 days a week compared with usual care (physical therapy generally performed in bed and only conducted when requested by staff). Planned recruitment was for 174 patients (82 per group), with mRS the primary outcome at 3 months post stroke, and

feasibility and safety endpoints that included the timing and duration of physical therapy. Once again, slow recruitment led investigators to close the study early, with late hospital arrival (>48 hours post stroke) cited as the primary reason for the high exclusion rate. Only 37 participants completed the trial (n=18 early, n=19 usual care). While the intervention was feasible with no safety concerns noted, there were no significant differences in any of the outcomes.

[INSERT TABLE 1 HERE]

Two further randomised controlled trials from India (8) and Italy (9) have also reported in the last 12 months. Chippalla and Sharma (8) largely adopted the phase II AVERT protocol (15), randomising patients to mobilisation out of bed within 24 hours of stroke onset (n=43), with 5-30 minutes of upright activities (as tolerated) per day or to usual care (n=43). The Barthel Index (BI) was used to assess functional status at 3 months with authors reporting significantly greater independence in the intervention group at 3 months compared to patients who received lower dose usual care. The investigators in the Italian trial (9), tested early versus delayed application of two different approaches to rehabilitation. Using a factorial design they compared early proprioceptive neuromuscular facilitation (PNF) or cognitive therapeutic exercise (CTE) commenced within 24 hours of admission, with delayed PNF and CTE groups, where treatment started 4 days later. A total of 340 patients were randomised and follow up occurred at 3 and 12 months. All groups improved over time, with no significant differences in mRS or BI between the early and delayed groups or between treatment approaches at 3 months.

Interventions tested in these trials ranged from simple out of bed sitting protocols, to more targeted, higher dose training. Many test the feasibility of delivering higher dose interventions within their stroke settings. A recent exercise study investigating the feasibility

of ‘intensive’ treadmill training within 2 days of onset of stroke symptoms, though small (n=25), is worth noting (11). Rarely is cardiovascular fitness a training target in the early time window. Thirty minutes of treadmill training, with bodyweight support as needed, twice daily for 5 consecutive days was the intervention target. This mild stroke cohort (median NIHSS 6, IQR 3-8) completed 88% of training sessions with non-serious adverse events (dizziness, leg pain) recorded in around 15% of training sessions. While the intervention was feasible and increased physical activity overall, few patients achieved the target exercise intensity of 50% heart rate reserve. Loss of cardiovascular fitness is presumed to be rapid after stroke. Larger trials of early exercise interventions to mediate this loss are expected.

Collectively, the randomised trials above add a further 630 patients from 4 countries to our planned 2009 Cochrane review update. AVERT will however dominate the meta-analysis, contributing 2,104 patients from 56 sites in 5 countries. Our main trial results for AVERT were reported in The Lancet early in 2015 (10), with our pre-specified dose-response analysis and process evaluation published more recently (16-18). To briefly recap, AVERT compared a frequent, higher dose of out of bed mobility based training protocol(on top of usual care) started within 24 hours of stroke onset and continued for 14 days or until discharge, to usual care alone. Primary outcome was mRS at 3 months. We found that the higher dose protocol resulted in lower odds of a favourable outcome at 3 months (mRS 0-2) compared with usual care, which also started at a median time of 22.4 hours post stroke. This finding surprised many. Importantly our results call into question the common therapeutic axiom that ‘more is better’, particularly in the very early time window after stroke (3, 10, 19). Further, our results highlight our need to better understand the biology of recovery and human response to training in the early post stroke period when the critical period is believed to exist. Our exploratory sub-group analyses of the primary outcome (10) found no significant treatment-

by-subgroup interactions, although patients with severe stroke (NIHSS > 16, n=291) and those with ICH (n=255) showed less favourable outcomes when treated with the higher intensity regimen. Interestingly, those treated with intravenous rtPA (n=503) were no different in their response to treatment. While further pre-specified analyses are ongoing, particularly around safety, later outcomes and cost (16, 20), our dose-response analysis results suggest that while higher amounts of training have a deleterious effect on outcome (mRS at 3 months, walking recovery, death), higher *frequency* of intervention is associated with more favourable outcome (17). These findings provide a new direction for future studies, suggesting both training thresholds and scheduling may be important in the very early period (19). Whether we should avoid any activity in the first day(s) post stroke is currently unknown. The favourable outcome and low complication rates experienced by patients in the usual care group in AVERT who also started some activity out of bed early suggests that a ban on out of bed activity is unwarranted. The current HeadPoST (21) cluster trial in which patients spend 24 hours after admission flat may provide further insights to guide practice.

Thrombolysis and early mobilisation

We included patients treated with rtPA (alteplase) in AVERT; it is standard of care, and protocols restricting patients to bed for 24 hours are not evidence-based. Recently, a detailed observational study (n=18) by Arnold et al (22) examined the safety profiles of ischemic stroke patients commencing out of bed mobilisation and rehabilitation between 13-23 hours post treatment with intravenous rtPA. No serious bleeding complications were found, although one patient experienced transient neurological changes with mobilisation, which resolved with rest. No long term outcomes were examined. At the other end of the spectrum,

a recent large (n=6153) retrospective study of those treated with intravenous rtPA by Momsaki et al (23) examined the association between starting rehabilitation (any physical or occupational therapy) within 3 days of admission and functional independence (mRS 0-2) at hospital discharge. Using a Japan-wide hospital database, and adjusting for age, sex, type of ischemic stroke, baseline mRS, comorbidities and process factors (admission day, unit size etc), the authors found significantly higher levels of independence in those receiving early rehabilitation and no differences in mortality or the incidence of haemorrhage. It remains unclear if rapid mobilisation or rehabilitation is desirable after rtPA treatment and whether successful recanalization following treatment has an important influence.

Early dysphagia and aphasia treatment

Unlike early mobilisation, which has seen a flurry of trial activity in the last 12 months, we found only one recent small trial of early dysphagia treatment with rTMS (24). In this 3-arm trial, 3Hz (n=15), 1 Hz (n=13) and sham rTMS (n=12) was applied to patients recruited a median of 6-9 days from stroke onset over 5 consecutive days. The primary outcome, Standardised Swallowing Assessment (SSA), was assessed by a blinded neurologist at 3 months. The authors found a significant improvement in SSA in both treatment groups that was retained to 3 months, but no change in the sham rTMS group. No harms were reported. The longer follow up period and retention of effect found here suggest it may be time for larger trials of rTMS for dysphagia treatment.

We identified 2 protocols for trials of early aphasia interventions (13, 14). The Rotterdam Aphasia Therapy Study-3 (RATS-3) (14) compares communication outcomes in people with first-ever acute stroke (n=150) following early intensive cognitive-linguistic therapy starting

before day 14 and those who received usual care aphasia therapy starting after day 30. This multicentre trial closed late in 2015 and results are under review. The Very Early Rehabilitation in SpEech (VERSE) trial is ongoing with full recruitment (n=246) expected in 2017 (13). The VERSE trial is testing whether two forms of daily, prescribed aphasia therapy for 20 sessions, beginning within 14 days of acute stroke, is more effective and cost saving than usual care at three months. Both trials begin aphasia intervention within the first week post-stroke. Intervention continues into sub acute recovery for four weeks, according to the ongoing therapeutic needs of stroke survivors. Exemplary collaboration between acute care, rehabilitation and community healthcare sites (and multiple ethics applications) are essential to achieve seamless clinical care and delivery of research outcomes. The challenge of interventions that span acute/rehabilitation/community care is a major barrier to early rehabilitation trials. The results of these trials are eagerly awaited.

Early upper limb rehabilitation

In the EXPLICIT-Stroke program trials, recruitment occurred an average of 8 days post stroke (12). Two interventions were tested; for patients with a favourable prognosis, a modified 3 week contraint induced movement therapy (mCIMT) program (n=29) was compared to usual care (n=29), while those with unfavourable prognosis were allocated to a 3 week EMG-NMS program (n=50) or usual care (n=51). The primary outcome for both trials was the ARAT score with final follow up at 26 weeks. The mCIMT program was more effective at improving function than usual care early, but effects were not sustained at 26 week. There was no benefit of EMG-NMS in those with poorer prognosis over usual care. Nested imaging and transcranial magnetic simulation (TMS) studies to examine brain recovery characteristics in 30 patients from each of the prognostic groups are planned (25).

In this review we have identified some of the challenges of rehabilitation research in the early time window. Rehabilitation trials are complex, often requiring input from multidisciplinary teams. Standardised, early recruitment is vital to improving the quality of our trials. How we stratify and select patients in recovery trials is not a trivial question. If we consider the benefits to be gained from careful, imaging based selection in many acute stroke trials, it is clear that we need to strive for more sophisticated approaches to patient selection. One example of an approach to determine the recovery potential of the upper limb based on remaining neurobiological characteristics is the PREP algorithm (26). An important distinction of this approach is that it is step down, pulling in brain imaging techniques (e.g., transcranial magnetic stimulation and magnetic resonance imaging) only when they have the potential to add information over and above what can be derived from clinical outcome measures. This approach has the potential to improve patient selection for upper limb intervention trials and be extended to other domains. At present however, our understanding of who recovers, who doesn't and why in response to treatment is incomplete and remains a priority.

CONCLUSION

Rehabilitation research has come a long way in recent years, but still has a long way to go. This year the first Stroke Recovery and Rehabilitation Roundtable was held with 60 world stroke experts. Our goal was to develop recommendations for standardisation and improved research practice in key areas; pre-clinical research, biomarkers, clinical trial outcomes, and intervention development and monitoring (2). Recommendations will be available early 2017. An important discussion point at the meeting was the need to start interventions earlier

(during the critical window), and to apply them at the right dose to improve the potential for neurological recovery and repair. It is exciting to see the benefit of new intra-arterial treatments, which improve not just global disability (mRS), but aphasia and other motor outcomes (27). Like acute stroke, we need to discover a game-changing treatment(s) that improves the potential for true recovery in the thousands of stroke survivors battling disability each year. Breakthrough interventions are likely to be multi-modal (3, 4). Such a discovery would kick start the next series of focused studies that will change the recovery landscape forever.

KEY POINTS

1. An early sensitive or critical period for recovery is likely in humans, we need to develop rehabilitation treatments that harness potential for recovery.
2. Interest in early mobility training and mobilisation evidenced by flurry of new trials in the first days post stroke
3. Challenges of conducting trials of early rehabilitation interventions are highlighted in this review
4. Several large early aphasia trials will be reporting in next 18 months

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LIST OF TABLES AND FIGURES

Table 1. Recent rehabilitation trials where the intervention was started within 7 days of stroke onset*

Trial	Randomised sample	Time between stroke and intervention	Intervention group	Comparison group/s	Primary Results
Mobilisation					
Herisson et al 2016 (6) SEVEL France	167	< 24 hours	*Early sitting:* seated out of bed within 24 hours *Dose:* ≥15min /day, as tolerated	*Progressive sitting*: positioned in bed at 30 degrees in first 24 hours, progressing to sitting out of bed by day 3 *Dose*: ≥15min for first sitting	*mRS score of 0-2 at 3 months:* Early sitting = 76.2% Progressive sitting = 77.3% *ns*
Poletto et al 2015 (7) Brazil	39	< 48 hours	*Intervention*: focused on sitting out of bed or standing, and physical therapy. *Dose*: 30min, 1/day, 5/week plus sitting out of bed whenever possible for first 14 days, or until discharge	*Control group*: routine hospital care, including conventional physical therapy *Dose*: Varied between patients, usually 15min sessions	*mRS score of 0-2 at 3 months:* no diff between groups, *Feasibility and safety:* no complications in either group
Chippalla and Sharma 2015 (8) India	86	< 24 hours	*Very Early Mobilisation (VEM)*: Usual care plus out of bed activities including sitting, standing and walking Dose: 5-30min, depending on tolerance, ≥2/day, ≤7 days	*Usual care*: routine stroke unit care *Dose*: 45 min/a day, ≤7 days or until discharge	*Independent on Barthel Index at 3 months*: Intervention = 85% Usual Care = 45% $p<0.01$

Morreale et al 2016 (9) Italy	340	< 24 hours	*Early rehabilitation*: daily out of bed activity with either (1) proprioceptive neuromuscular facilitation (PNF), or (2) Cognitive therapeutic exercise (CTE) *Dose*: 1 hour/day for first 4 days; followed by 2.25hours/day, daily for 14 weeks; followed by 1.5 hours/day, 5 days/week until final medical follow up (mean of 38 weeks)	*Usual care:* routine hospital care for first 4 days, followed by either (1) PNF or (2) CTE *Dose*: standard hospital care for first 4 days; from day 5, as per early rehabilitation groups	mRS at 3 months: No difference between groups *ns*
Bernhardt et al 2015 (10) AVERT Australia	2104	< 24 hours	*Early mobilization* (VEM): Emphasis on patient being upright and out of bed (sitting or standing). *Dose:* ≥2/day for first 14 days, or until discharge	*Usual care*: usual care provided by hospital *Dose:* as per usual care of individual sites	mRS of 0-2 at 3 months: VEM = 46% Usual Care = 50% OR=.73, *p*=.004
Exercise					
Strømmen et al 2016 (11) Denmark	25 included[#]		*Intervention*: walking on a treadmill, with body weight supported, target intensity of 50% heart rate reserve *Dose*: 30min, 2/day, ≤5 days, plus 2 sessions 30 days after inclusion	*N/A*	Number of sessions completed: 97% of intended training sessions were intiated 88% of sessions completed
Upper limb					
Kwakkel et al (12) EXPLICIT-Stroke Netherlands	159	Average of 8 days	*Upper limb intervention*: either (1) modified constraint induced therapy [mCIMT] or (2) electromyography-triggered neuromuscular stimulation [EMG-NMS]. *Dose*: 60min/day in 1-2 sessions, ≥3 weeks	*Usual care*: conventional upper limb therapy as provided by Physical Therapist *Dose:* 30min/day for 3 weeks	Action Research Arm Test at 5 weeks: mCIMT – usual care = 1.757, *p*=.01 EMG-NMS – usual care = -0.63, *ns*
Aphasia					

Godecke et al 2016 (13) VERSE Australia *ANZCTR Register: 2613000776707*	Target sample: 246	< 14 days	*VERSE Therapy*: usual care, plus a structured aphasia therapy program *Dose*: 45-60 min/session, 3-5 sessions/week, until total of 20 sessions	*Comparison groups*: either (1) Usual care along or (2) Usual care plus additional speech therapy as decided by treating therapist *Dose*: Additional therapy matched to intervention group	*NA – In progress*
Nouwens et al (14) RATS3 Netherlands *Dutch Trial Register: NTR3271*	Target sample: 150	< 2 weeks	*Early speech therapy*: Within two weeks of stroke cognitive-linguistic therapy including either (1) Phonological program or or (2) semantic program *Dose*: ≤7 hours/week	*Delayed speech therapy:* no therapy until four weeks post stroke *Dose:* Nil	*NA – Under review*

*For speech therapy trials, those starting therapy within two weeks of stroke onset were included

Single group study, no randomisation

OR = Odds ratio, ns = non-significant