Early mobilisation and rehabilitation in intensive care unit—ready for implementation?

Julie Bernhardt[1,2]

[1]Florey Institute of Neuroscience and Mental Health, University of Melbourne, Melbourne, Australia; [2]La Trobe University, Melbourne, Australia

Correspondence to: Julie Bernhardt. Florey Institute of Neuroscience and Mental Health, University of Melbourne, 245 Burgundy Street, Heidelberg, Melbourne, Australia. Email: j.bernhardt@florey.edu.au.

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The recent trial by Schaller and colleagues of early mobilisation in surgical patients managed in an intensive care unit (ICU) published in *The Lancet* (Lancet 2016;388:1377-88), represents an interesting addition to a growing number of ICU rehabilitation trials. Conducted in five hospitals in Austria, Germany and the USA between 2011 and 2015, this single-blind trial tested whether previously independent patients recently admitted to surgical ICU (SICU) and randomised to an early goal-directed mobilisation protocol, achieved a higher mobilisation level (the SICU optimal mobilisation score, SOMS), compared to patients who received institutional standard of care. The two key secondary outcomes were length of SICU stay and a modified functional independence measure of functional mobility at hospital discharge. The sample size of 200 patients (n=100 per group) was based on SOMS and length of stay data from previous studies. The study was conducted as planned, recruiting 104 patients to intervention and 96 to control. The groups appear well balanced. The intervention began within a day of enrolment, although the time from admission to SICU to start of treatment is unclear. The primary outcome in my mind reflects an important feasibility question, was the goal-directed protocol, which required strong interdisciplinary team coordination and communication, followed? If it was, we would expect to see higher levels of mobilisation. The intention-to-treat analysis showed just that, patients in the intervention group had significantly higher mean SOMS level than controls. The key secondary outcomes were analysed per-protocol rather than intention-to-treat, and were also found to be significantly different between intervention and controls in favour of the early mobilisation group. The investigators conclude that 'early' goal directed mobilisation improved mobilisation during SICU stay, shortened length of stay in the SICU and improved patients' functional mobility at hospital discharge'. That is, the treatment is feasible and has some short term patient benefit. So is the treatment ready for widespread implementation?

As the principal investigator of the large international AVERT trial in acute stroke patients which completed in 2015 (1), and a clinician researcher interested in rehabilitation over many years, I've had a keen interest in following the ICU trials of early rehabilitation. Most of these trials have focused on mobilisation or out of bed activity and training. The parallels between the two fields are significant. The early ICU trials have been generally small phase II trials in carefully selected populations showing feasibility and promising effects on length of stay, or functional outcomes at end of intervention. The early studies by Morris *et al.* (2008, n=330) (2) and Schweickert *et al.* (2009, n=104) (3) stimulated a flurry of new trials. These early findings were exciting, providing a possible pathway for an intervention that could be delivered early that may address problems of ICU acquired weakness, adverse events that may be related to bed rest, and

relearning in those with impaired function. These studies also stimulated changes to treatment approaches to allow for early rehabilitation (e.g., sedation protocols) and promoted significant discussion about how services could be delivered differently. The challenges and opportunities in the field were outlined in the review by Schweickert and Kress in 2011 (4). My takeaways from this review were that ICU-acquired weakness, a significant problem needing a solution, is more complex than weakness per se (which may be prevented or slowed by early onset rehabilitation), and that assessment of long term outcomes in ICU survivors who have undergone early rehabilitation approaches is an important area for future study.

Similar to this field, in acute stroke we have been working to determine whether the earlier start to rehabilitation is safe, effective in improving long term disability and whether it is cost effective. This latter point is important. Early rehabilitation approaches in acutely ill populations are not simple, they require at the very least a change in how staff interact with patients and manage their time. More commonly, they require multiple members of staff working together to achieve a mobilisation. In a fully implemented model, the staff requirements alone may represent a significant cost and the cost-benefit of the exercise is an important area for study. It is therefore surprising to see so few properly developed health economic evaluations sitting beside current trials of ICU-delivered interventions.

Early trials of mobilisation in acute stroke were small, single or multi-site trials. These included our own Phase II trial which reported in 2008. The results looked promising both in terms of functional outcome at 3 months (5) and potential cost-effectiveness (6). This prompted the AVERT Phase III trial which included over 2,000 patients, from 56 sites in five countries. The accumulation of evidence prior to the reporting of our Phase III trial, came from three randomised controlled trials (total n=159) and showed non-significant improvements in the odds of favourable functional outcome (Barthel Index), no difference in complication rates and less deaths in the control group, but this too was not significant (7). Since this 2014 systematic review, a further 4 trials (8) adding 632 patients have been completed.

We reported our large (n=2,104) AVERT trial in 2015 (1). We found, to many people's surprise, a clear signal of harm with significantly reduced odds of a favourable outcome (no or little disability on the modified Rankin Scale) at 3 months post stroke (primary outcome). We had more deaths in our early and intensive intervention group, although at 3 months this was not significant. The number of patients who died from a stroke-related event (stroke progression) was higher in the early group. Both groups achieved functional walking early with no difference between groups, compared to an exciting positive finding in phase II (9). Importantly we found, similar to our phase II trial, that the treatment was feasible and could be delivered as planned.

These findings bring a note of caution to the field of early stroke rehabilitation, and possibly to the field of ICU rehabilitation. We don't really understand the biology of recovery in the early phase after brain injury with stroke, and this may be a significant factor in explaining the very important finding of harm in AVERT. Showing that something is feasible, does not necessarily mean it works to reduce long term disability, a meaningful outcome for our patients. The lesson from AVERT is that promising interventions may, in well powered trials, turn out to be harmful.

In the paper by Schaller and colleagues, there were a higher number of in-hospital deaths. While this was not statistically significant, one wonders whether a larger trial may see a similar finding. A very recent systematic review by Tipping *et al*. [2016] (10) to some extent may allay concern about early deaths in ICU trials. In this review, 14 studies of varying quality, including 1,753 patients receiving a range of interventions were included. Notwithstanding the significant risk of bias in many of these trials, the pooled analysis for death by ICU discharge was not significantly different. The pooled analysis for mortality at hospital discharge, which included the current results, also found no significant differences in death between early rehabilitation and standard care.

Over the past 15 years I've witnessed and tracked the growing interest in the possibility that early, more intensive rehabilitation could be a breakthrough treatment in acutely ill stroke patients. The AVERT trial took 8 years to complete recruitment, and we found that usual care changed to an earlier start time, year by year (1). While the dose of the intervention delivered did not shift significantly towards the early, intensive training over the course of the trial, the problem of practice creep is not insignificant. We studied clinical opinion at the beginning and near the end of the trial in over 400 clinicians. We found that while the evidence base for early rehabilitation did not change significantly, opinion, and potentially practice, did (11,12). These finding speak to the conundrum that we often face—it is often incredibly hard to get uptake of best evidence into practice, but it can be quite easy to get uptake of low or no

evidence based treatments into practice.

Similar to early rehabilitation in stroke, the signs that practice is creeping to an earlier, more intensive model of care are present in the ICU literature. Not only have consensus recommendations been published [e.g., (13)], but teaching courses are also available to those interested. Given our experience in acute stroke, I for one would like to see a large multi-site ICU trial with evaluation of long term functional outcome. The high drop out at follow up in the study by Schaller and colleagues (42% follow up—84 of 200 patients) (14) is concerning, but argued as not unexpected in this population. Finding methods of follow up through data linkage or registry data looks appealing if direct access to patients in this group proves so challenging. The importance of long-term patient-centered outcomes cannot be under-estimated and represents a logical direction for future trials (15). Given the speed at which adoption may already be taking place in response to these trials, the time for a large definitive trial of ICU rehabilitation is right now.

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None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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