Critique of A Very Early Rehabilitation Trial (AVERT)

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Based on a large multicenter/intercontinental patient population, the A Very Early Rehabilitation Trial (AVERT) suggests that early intensive mobilization procedures negatively affect 3-month outcome in severely affected stroke victims and in patients with intracerebral hemorrhage. This unexpected finding is interpreted in view of the limitations of the trial. It is argued that these results should not lead to prolonging immobilization and inactivity after stroke and to a cessation of clinical research that aims at integrating rehabilitative intervention into acute stroke care.

The AVERT trial is the largest randomized multicenter trial conducted in stroke rehabilitation to date. It compares very early mobilization within 24 hours after symptom onset with usual care in patients with ischemic or hemorrhagic stroke without significant coexisting comorbidity or premorbid disability.

The authors are to be complimented to have achieved this high quality collection of data across 5 countries in 3 continents (Australia/New Zealand, Europe, and Asia). Rehabilitation interventions are difficult to test in multicenter trials because they often lack standardization and involve a great deal of human effort on the side of the therapist and the patient. This complexity is even higher in the acute phase after stroke where time is short for meeting all acute care requirements, that is, treating the acute event, finding its cause, and preventing complications. The AVERT investigators invested substantial effort to ensure comparability of the intervention across the centers, to meet preestablished criteria for treatment quality, and blinding of investigators involved in assessments. The trial is pragmatic in the sense that the early mobilization protocol selected was simple and relatively inexpensive, hence, had the potential for a quick adoption beyond the trial. In addition, the protocol was supported by preliminary data of a phase 2 trial conducted by the same group.

The trial compares a group of 1042 patients mobilized after 18.5 hours (median; IQR, 12.8–22.3) versus 1036 patients mobilized after 22.4 hours (16.5–29.3).

The results are unexpected—as the authors admit—in that they lead to rejection of their hypothesis that very early mobilization is superior to usual care. The findings suggest that early rehabilitation may be worse than usual care fueling an old debate. Some argue that early activity increases brain injury. Others claim that early rehabilitation makes use of a limited time window of heightened plasticity after stroke. A favorable outcome (primary outcome=modified Rankin Scale score 0–2) was achieved in 46% of patients in the early and in 50% of patients in the late mobilization group (P=0.004 adjusted for baseline NIHSS and age, P=0.068 unadjusted analysis).

Deliberation of the findings has to take a few arguments into account: the modified Rankin Scale, if convolved into 2 groups (≤2 and >2), is a rather broad assessment of stroke outcome. Likely, a more gradual scale, such as the Extended Barthel Index, would have been preferable. No significant ordinal shift was seen in modified Rankin Scale strata between groups; if modified Rankin Scale score=3 rather than 2 would have been chosen as the primary end point, the differences between groups would probably have been insignificant. This diminishes the strength of the finding.

However, significance has been found although methodologically both groups were not treated much differently: the time difference to first mobilization between the groups was only 4 hours, and 92% of patients in the early group versus 59% in the control group were mobilized within the first 24 hours. During the trial, the interval between stroke onset and mobilization decreased in the usual care group (median of 28 minutes per year), suggesting that usual care practices were influenced and moved toward earlier mobilization. Also, patients with very severe stroke were excluded (patients not responding to voice), hence, the sample avoided those with very large stroke or hemorrhages in whom early mobilization may have been especially dangerous and technically unfeasible. These issues can be expected to reduce any between-group difference, and therefore emphasize the validity of the significant difference that was detected nevertheless.

The generalizability of the finding (external validity of the trial) can be regarded as good despite the fact that only 6% of subjects screened were actually recruited. The main reason for exclusion was late arrival to the hospital, representing one of the greatest obstacles to successful stroke treatment in general.

The superiority of later and less intense mobilization found in AVERT may prompt stroke physicians the reverse the tendency of integrating rehabilitation into acute stroke care. Patients may be kept immobile and inactive for...
prolonged period of time, which may be tempting because of a reduction of workload on busy wards. This is dangerous. Delayed mobilization is not only associated with complications. Muscle wasting and disuse-related neural adaptations will create a significant problem when rehabilitation is eventually started at a later stage. One also has to realize that patients can be kept active without necessarily taking them out of bed. Several devices and therapy methods exist for this purpose.

This danger of falling into the opposite extreme of immobilization and inactivity now raises the question whether the AVERT intervention was ready for testing in a large trial thereby accepting the possibility of a negative outcome. Were therapy protocols and patient selection optimized to enter the scrutiny of a trial? Changes in blood pressure observed with verticalization after stroke are a frequent problem and need special procedures and technology to be prevented.\(^6\) In addition, mobilization may have even been delivered too late in AVERT considering that the negative effect of early intense mobilization was not observed in the 374 patients mobilized within 12 hours. This is not a critique of AVERT, which provides an important and valuable data set and results. It is a pledge not to stop here and neglect further clinical research on early mobilization and activation.

In conclusion for clinical practice, AVERT provides a signal to suggest that very early mobilization within 24 hours after stroke has to be considered with caution and should be avoided in those who are severely affected or had intracerebral hemorrhage. The cause of bad outcome after early and intense mobilization may be stroke progression, which was the adverse event with the largest between-group differences in survivors and nonsurvivors alike.

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References

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