Randomized Controlled Trial of Early Rehabilitation After Intracerebral Hemorrhage Stroke
Difference in Outcomes Within 6 Months of Stroke

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Background and Purpose—Mechanisms, acute management, and outcomes for patients who experience intracerebral hemorrhage may differ from patients with ischemic stroke. Studies of very early rehabilitation have been mainly undertaken in patients with ischemic stroke, and it is unknown if benefits apply to those with intracerebral hemorrhage. We hypothesized that early rehabilitation, within 48 hours of stroke, would improve survival and functional outcomes in patients with intracerebral hemorrhage.

Methods—This was a multicenter, randomized controlled study, with blinded assessment of outcome at 3 and 6 months. Eligible patients were randomized to receive standard care or standard care plus early rehabilitation. Primary outcome includes survival. Secondary outcomes includes health-related quality of life using the 36-item Short Form Questionnaire, function measured with the modified Barthel Index, and anxiety measured with the Zung Self-Rated Anxiety Scale.

Results—Two hundred forty-three of 326 patients were randomized (mean age, 59 years; 56% men). At 6 months, patients receiving standard care were more likely to have died (adjusted hazard ratio, 4.44; 95% confidence interval [CI], 1.24–15.87); for morbidity outcomes, a 6-point difference in the Physical Component Summary score of the 36-item Short Form Questionnaire (95% CI, 4.2–8.7), a 7-point difference for the Mental Component Summary score (95% CI, 4.5–9.5), a 13-point difference in Modified Barthel Index scores (95% CI, 6.8–18.3), and a 6-point difference in Self-Rating Anxiety Scale scores (95% CI, 4.4–8.3) was reported in favor of the intervention groups.

Conclusions—For the first time, we have shown that commencing rehabilitation within 48 hours of intracerebral hemorrhage improves survival and functional outcomes at 6 months after stroke in hospitalized patients in China.


Key Words: cerebral hemorrhage ■ clinical trial, randomized ■ outcome assessment (health care) ■ rehabilitation

At least ≥30% of strokes in China are intracerebral hemorrhages (ICH) when compared with ≤15% in Western countries, with a noticeable south–north gradient.1–4 In absolute terms, this equates to large numbers of cases in China, and interventions to reduce the effects of ICH are important to determine. This is because ICH is generally more severe than ischemic stroke5 and is associated with poorer functional outcome and higher case-fatality.6 Evidence suggests that very early physical rehabilitation (VER) of stroke survivors may result in better motor recovery, reduced mental, functional and neurological disability, and improved quality of life.7–11 However, previous studies have included only small proportions of people with ICH,5,10 and further research in large phase III studies for all stroke subtypes is still needed.12 Patients who have experienced ICH may differ to those with ischemic stroke in regards to risk factors, mechanisms of

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stroke, acute care interventions received, and outcomes. For example, they are less likely to be managed on a stroke unit and are less likely to receive early allied health interventions, independent of stroke severity. Clinical guidelines for the management of ICH recommend close monitoring and stringent blood pressure control in the early period after ICH. This may cause reluctance to implement early active treatments in these patients, despite the guidelines also recommending that rehabilitation commence as early as possible. Among clinicians, there is still debate about when mobilization or rehabilitation should commence. However, there is a general consensus that patients with ICH should be mobilized later than those with ischemic stroke, despite a lack of evidence to support this view. Consequently, data on the safety and effectiveness of early rehabilitation after ICH are needed.

We aimed to compare VER with standard care in patients with ICH. We hypothesized that VER within 48 hours of ICH onset would result in reduced mortality, morbidity, and better quality of life outcomes when compared with standard care at 3 and 6 months after stroke.

Materials and Methods

Study Design

This was a prospective, multicenter, randomized controlled study, with 2 parallel groups followed up for 6 months with blinded assessment of outcomes. The trial took place in 3 hospitals: the First, Second, and Third Affiliated Hospitals of the Medical college of Xi’an Jiaotong University in Shaanxi Province, China, from April 2010 to May 2013. The trial was registered with the Chinese Clinical Trial Registry. (Clinical Trial Registration NO.ChiCTR-TRC-13004039). Written informed consent was obtained from all participants before randomization. Patients were assured of their right to refuse to participate or to withdraw from the trial at any time. On completion of the study, patients were presented with a gift (valued at $8 USD).

Patient Eligibility

Patients presenting <48 hours after ICH to the neurology ward or rehabilitation units of participating hospitals were recruited to the study. The inclusion criteria were (1) patients with a first time ICH confirmed by MRI or computed tomography; (2) no contraindications to being mobilized within 48 hours of stroke onset (based on the medical teams clinical judgment and exclusion criteria 3); and (3) a Fugl-Meyer stroke deficit score between 27 and 90 (thereby excluding those with severe or minor motor impairments). Exclusion criteria were (1) participants with mild deficits as described above; (2) patients who were unable to complete the baseline survey because of serious aphasia, language difficulties, or cognitive deficits; (3) patient with other medical conditions, such as severe heart failure, acute coronary syndrome, lower-limb disorders, which prevented early mobilization; and (4) patients who were unable to provide informed consent.

Recruitment Process and Randomization

Once eligibility was determined and consent was obtained, participants were informed that they would be randomized to 1 of 2 different styles of rehabilitation: VER plus standard care or standard care. Group allocation was computer generated, using blocked randomization procedures. Details of group allocations were placed into opaque, sealed envelopes, which were strictly held by research staff. The hospital staff were contacted by telephone or emailed the allocation sequence.

Intervention

Both groups received standard care, which was performed on a neurology ward or stroke rehabilitation unit until they were discharged from hospital (average length of stay 28.39; SD, 6.21 days). In China, standard rehabilitation care is performed by the patient’s relatives under the guidance of medical staff and usually involves (1) exercises of daily living, stretching exercises, and neuromuscular electric stimulation and (2) functional training in which the patients are instructed to do repetitive and systematic practice of tasks, such as sitting, grasping, and pointing. Rehabilitation is usually commenced 1 week after stroke admission. In this study, all rehabilitation therapies were provided in a nonspecified order to imitate what would occur in normal activities of daily living or clinical practice, and therapy was performed ≥16x per month for 60 minutes each session.

All participants received standard care, but participants in the VER group commenced rehabilitation as soon as practical after randomization but within 48 hours of ICH onset. In contrast, the standard care group commenced rehabilitation after 7 days. Within the first week of admission standard rehabilitation care for ICH involves bed rest or sitting in a chair. There is no showering or active rehabilitation with the main focus being medical management. To avoid contamination, patients enrolled in the trial were encouraged by staff not to replicate the therapy behaviors of other patients.

Baseline Assessments

After randomization, the baseline assessment of demographic characteristics and medical history was undertaken by nursing staff. The data collected included (1) sociodemographic data, such as age, sex, occupation, and education; (2) stroke details such as stroke site, age at onset, stroke severity on the National Institutes of Health Stroke Scale assessment; (3) medical history and lifestyle risk factors for stroke, such as alcohol intake, drinking, sleeping time, and physical activities; and (4) details of laboratory examinations, such as blood pressure, blood glucose, high-density lipoprotein and low-density lipoprotein. We also collected data on clinical comorbidities, such as hypertension, diabetes mellitus, and cardiovascular diseases.

Primary Outcome

The primary outcome was death. The cause of death was obtained from death certificates and direct contact with patient families by a researcher who was unaware of group allocation (ie, blinded). The end point for the primary outcome was 6 months after stroke.

Secondary Outcomes

Secondary outcome measures were evaluated by blinded research staff at 3 and 6 months after ICH for both intervention and control groups. Participants were provided with paper copies of the questionnaires when discharged from hospital. Participants were asked to return the questionnaires at 3 and 6 months. If they were at home and the questionnaire had not been returned, participants were contacted by the research staff and the questionnaires completed via telephone interview. If the participant was still in hospital, a face-to-face interview was performed.

The following questionnaires were administered:

- Short Form-36 (SF-36): This is a health-related quality of life measure containing 36 questions, which are combined into 8 subscales and a physical component summary score and mental component summary score. Scores range from 0 to 100 and higher scores indicate a better quality of life;

- Modified Barthel Index: This is a functional measure used to measure performance in activities of daily living. Scores range from 0 to 100, with higher scores indicating better independence in activities of daily living;

- Zung Self-Rated Anxiety Scale: This is used to assess patients’ anxiety levels. Higher scores indicate greater anxiety with a score of ≥60 indicating marked to severe anxiety levels

Recurrent stroke: Information on whether patients had experienced a second stroke attack were obtained from the hospital register.

Sample Size

Sample size estimation was based on the number required to detect a difference in our primary outcome of death, as well as our secondary differences in our secondary outcome of stroke mortality at 3 and 6 months.
outcome of disability. We estimated that we needed a minimum sample of \( \geq 170 \) patients. This sample size provided 80% power (at the 5% level) to detect a 30% reduction in mortality based on the predicted 30-day mortality rate of 50% for ICH in China.\(^2\) A sample size of 120 per group was the final target for this trial to also provide 80% power to detect a 20% difference in the number of participants with severe dependency in activities of daily living (≤70% points on the Barthel Index) at follow-up.

**Statistical Analyses**

Intention-to-treat analyses were used for all comparisons of outcome. Categorical variables were compared using the \( \chi^2 \) test. The \( t \) test was used to compare continuous variables that were approximately normally distributed and the Wilcoxon Mann–Whitney Rank-Sum test was used for continuous variables that were not normally distributed. The primary outcome of death was assessed using survival analyses. Survival curves were calculated using the Kaplan–Meier method, and the difference between curves was generated using the log-rank test. Survival analyses were confirmed by multivariable analyses adjusted for (1) confounders known to be associated with outcomes: these were hospital, age, sex, and baseline stroke severity (Modified Barthel Index score), heart failure, and diabetes mellitus; and (2) baseline factors with a difference between groups of \( P < 0.1 \): these were valvular heart disease and annual income. Backward stepwise regression was used to identify variables that had the strongest association with outcome for inclusion in the final model.

Statistical significance was set at \( P < 0.05 \) (2 sided), and all analyses were conducted using SAS version 9.0 (SAS Institute, Cary, NC) and SPSS for Windows version 13.0 (SPSS Inc, Chicago, IL).

**Results**

There were 436 patients with ICH admitted to the 3 affiliated teaching hospitals during the study recruitment period (April 2010 to May 2013). Among these, 326 were considered eligible for the study. Figure 1 provides a study flow diagram and outlines reasons for exclusion. A total of 243 subjects were included in the study. We recruited 103 patients from the first affiliate hospital, 71 patients from the second affiliate hospital, and 69 patients from the third affiliate hospital; there were 122 participants in the VER group and 121 in the standard care group. One participant in VER group withdrew before the 3-month interview because of disability and arthritis pain.

There were no statistically significant differences between the VER and standard care groups for baseline characteristic (Table 1). Average length of hospital stay was 10 days less in the intervention group, 24 days (SD, 11.2 days) in the VER group, and 34 days (SD, 15.1 days) in the standard care group (\( P < 0.001 \)). In-hospital complications were experienced by 73 patients (60.3%) in the standard care group and 64 (53.3%) in the VER group (\( P = 0.318 \)).

The number of participants who reported experiencing ≤2 adverse event during the 6 months after ICH were significantly greater for the standard care group when compared with that for the VER group (n=90 [83%] versus n=37 [31%];

### Table 1. Baseline Demographics, Clinical History, Lifestyle, and Functional Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Very Early Rehabilitation (n=122)</th>
<th>Standard Care (n=121)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>58.5 (12.3)</td>
<td>59.1 (15.5)</td>
<td>0.62</td>
</tr>
<tr>
<td>Men</td>
<td>67 (54.9)</td>
<td>70 (57.9)</td>
<td>0.65</td>
</tr>
<tr>
<td>Stroke risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>76 (62.3)</td>
<td>78 (64.5)</td>
<td>0.76</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>37 (30.3)</td>
<td>33 (27.3)</td>
<td>0.60</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>57 (46.7)</td>
<td>46 (38.0)</td>
<td>0.17</td>
</tr>
<tr>
<td>Orthopedic problems</td>
<td>27 (22.1)</td>
<td>27 (22.3)</td>
<td>0.97</td>
</tr>
<tr>
<td>Family history of stroke</td>
<td>70 (57.3)</td>
<td>78 (64.5)</td>
<td>0.26</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>30 (24.6)</td>
<td>28 (23.1)</td>
<td>0.79</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>14 (11.5)</td>
<td>25 (20.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>Heart failure</td>
<td>32 (26.2)</td>
<td>22 (18.2)</td>
<td>0.13</td>
</tr>
<tr>
<td>Stroke severity measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>National Institutes of Health Stroke Scale, mean (SD)</td>
<td>9.97 (1.31)</td>
<td>9.98 (1.43)</td>
<td>0.98</td>
</tr>
<tr>
<td>Mild (1–7)</td>
<td>2 (1.6)</td>
<td>2 (1.7)</td>
<td>0.83</td>
</tr>
<tr>
<td>Moderate (8–16)</td>
<td>120 (98.4)</td>
<td>119 (98.3)</td>
<td></td>
</tr>
<tr>
<td>Severe (&gt;16)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Modified Barthel Index, mean (SD)</td>
<td>62.3 (32.9)</td>
<td>61.6 (32.3)</td>
<td>0.83</td>
</tr>
<tr>
<td>Clinical data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, median (Q1, Q3)</td>
<td>156 (120, 169)</td>
<td>154 (111, 166)</td>
<td>0.21</td>
</tr>
<tr>
<td>Diastolic BP, median (Q1, Q3)</td>
<td>97 (70, 105)</td>
<td>97 (68, 109)</td>
<td>0.35</td>
</tr>
<tr>
<td>Blood sugar, median (Q1, Q3)</td>
<td>4.5 (3.8, 9.9)</td>
<td>5.1 (4.2, 5.2)</td>
<td>0.14</td>
</tr>
<tr>
<td>Triglyceride, median (Q1, Q3)</td>
<td>3.9 (3.2, 5.7)</td>
<td>3.8 (3.2, 5.9)</td>
<td>0.43</td>
</tr>
<tr>
<td>Total cholesterol, mean (SD)</td>
<td>4.4 (1.5)</td>
<td>4.3 (1.5)</td>
<td>0.50</td>
</tr>
<tr>
<td>High-density lipoprotein, mean (SD)</td>
<td>1.4 (0.5)</td>
<td>1.3 (0.5)</td>
<td>0.20</td>
</tr>
<tr>
<td>Low-density lipoprotein, mean (SD)</td>
<td>3.1 (1.3)</td>
<td>3.1 (1.3)</td>
<td>0.52</td>
</tr>
<tr>
<td>Apolipoprotein A, mean (SD)</td>
<td>1.6 (0.6)</td>
<td>1.5 (0.6)</td>
<td>0.10</td>
</tr>
<tr>
<td>Apolipoprotein B, mean (SD)</td>
<td>0.9 (0.3)</td>
<td>0.9 (0.3)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Values are n and (%) unless otherwise indicated. BP indicates blood pressure.
Adverse events included any medical problem, such as early neurological deterioration, falls, epilepsy, infection, pressure sores, or psychological problems. However, there was no significant difference between groups in the number of participants who experienced a second stroke during the study period.

Few deaths were reported for the intervention group during the first 3 months after stroke (VER, 1 death; standard care, 10 deaths). However, the majority were reported for the standard care group. By 6 months, there were a total of 3 deaths in the intervention group (1 because of a second stroke, 1 because of heart failure, and 1 because of diabetes mellitus) and 12 deaths in the standard care group (5 because of a second stroke, 4 because of heart failure, 3 because of diabetes mellitus; Figure 2). Patients receiving standard treatment were less likely to be alive at 6 months after stroke when compared with those in the VER group (unadjusted hazard ratio, 4.25; 95% confidence interval [CI], 1.20 to 15.07) and this was confirmed in the multivariable analysis (Table 2).

No significant differences were found for short-term improvements (0–3 months) in secondary outcome measures. However, in the 3- to 6-month period after stroke, there was a statistically significant difference between groups for all outcomes in favor of the intervention group. This was because of both an apparent deterioration in the standard care group and improvements in the VER group. At 6 months after ICH, there was a 6-point difference between the intervention and the control group for the Physical Component Summary score (95% CI, 4.2 to 8.7), a 7-point difference between groups for the Mental Component Summary score (95% CI, 4.5 to 9.5), a 13-point difference between groups for the Barthel Index (95% CI, 6.8 to 18.3), and a 6-point difference in Self-Rating Anxiety Scale scores (95% CI, −8.3 to −4.4; Table 3). The differences between the 2 groups were clinically meaningful for all of the SF-36 subscales, the SF-36 summary scores (minimal clinically important difference, 5), and the Barthel Index (minimal clinically important difference, 2).22,23

**Discussion**

This is the first randomized controlled trial in a large sample of Chinese patients to compare the effects of VER with standard care on long-term outcomes in patients with ICH. The most important finding was that patients with ICH who were randomized to VER were much more likely to be alive at 6 months than those who received standard care alone. Patients who received VER also had a shorter length of hospital stay and reported significantly greater quality of life, independence with activities of daily living, and improved mental health outcomes at 6 months after stroke when compared with those randomized to standard care. Our results provide evidence that VER is beneficial for patients with ICH. Although the overall mortality rate was lower than that estimated in our power calculations, the effect size was well above the anticipated reduction of 30% in the intervention group.

Although the existing evidence remains limited, our results are similar to those reported in recent phase II or pilot studies performed in general stroke populations.3,10,24 In the A Very Early Rehabilitation Trial (AVERT) phase II trial (71 participants) those who received very early and intensive mobilization demonstrated significant improvements in secondary outcomes, such as disability at 12 months but not at 3 or 6 months.9 Other smaller pilot studies, such as the Very Early Rehabilitation or Intensive Telemetry After Stroke (VERTAS) trial in the Unit Kingdom and the very early mobilization trials in Norway and Sweden,10,24,25 also showed early mobilization to be safe and feasible. Participant numbers in these 2 studies were small, and patients were only followed up for 3 months. As demonstrated with our trial, and the AVERT Phase II trial, longer follow-up periods (≥6 months) may be needed to demonstrate the full benefits of VER.

In our study, the differences between groups at 6 months were because of a combination of functional deterioration in the standard care group and improvements in the VER group. China is a developing country with an evolving healthcare system. There are few trained and skilled health practitioners for treating stroke, and there are no primary care medical practitioners in the community (ie, all health care is accessed through the hospitals).26 Consequently, stroke survivors are discharged home with little or no support, follow-up, secondary prevention strategies, or health maintenance.26 Family members look after the stroke survivor and perform ongoing rehabilitation and care.

The shorter length of stay and early commencement of rehabilitation in our intervention group may have meant that family members were more likely to continue to encourage the patient to be active once they returned home when compared with those in the standard care group. Those in the standard care group may have taken on a more dependent role, resulting in adverse long-term health consequences. This may have also been partly because of this participant group being aware that they were not allocated to the early rehabilitation treatment as outlined in the participant information form creating

**Table 2. Survival Analysis Results at 6 Months**

<table>
<thead>
<tr>
<th>Very Early Rehabilitation, n/N (%)</th>
<th>Standard Care, n/N (%)</th>
<th>HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>118/122 (97)</td>
<td>108/121 (89)</td>
<td></td>
</tr>
</tbody>
</table>

CI indicates confidence interval; and HR, hazard ratio.

*Adjusted for valvular heart disease and age.
some responder bias. Additional research is needed to determine the long-term implications of VER within the context of the posidischarge setting.

Implications for Clinical Practice

Our trial demonstrated that it is safe to commence rehabilitation within 48 hours after ICH. The exact mechanism by which VER improves outcomes is not known. The larger mortality rate of the standard care group in the first 3 months after ICH may be because of reduced complications in the VER group (such as pneumonia or pulmonary embolism). This is similar to results from the VERITAS study, and the A VERT study in which fewer adverse events were reported for the intervention group at 5 days and 3 months, respectively.8,10

Table 3. Secondary Outcomes for the SF-36, Barthel Index, and Self-Rated Anxiety Scale at 3 and 6 Months After Intracerebral Hemorrhage

<table>
<thead>
<tr>
<th></th>
<th>Very Early Rehabilitation, Mean (SD; n=120)</th>
<th>Standard Care, Mean (SD; n=111)</th>
<th>Mean Difference</th>
<th>95% CI for Difference</th>
<th>Very Early Rehabilitation, Mean (SD; n=118)</th>
<th>Standard Care, Mean (SD; n=109)</th>
<th>Mean Difference</th>
<th>95% CI for Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36 Subscales</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Physical function</td>
<td>56.0 (24.7)</td>
<td>54.0 (17.5)</td>
<td>1.9</td>
<td>-3.6, 7.5</td>
<td>60.8 (25.6)</td>
<td>48.3 (24.2)</td>
<td>12.5</td>
<td>5.8, 19.2</td>
</tr>
<tr>
<td>Role physical</td>
<td>47.1 (32.8)</td>
<td>44.8 (30.7)</td>
<td>2.3</td>
<td>-6.0, 10.5</td>
<td>53.8 (33.0)</td>
<td>43.8 (33.2)</td>
<td>9.8</td>
<td>1.1, 18.5</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>68.4 (21.7)</td>
<td>69.6 (17.5)</td>
<td>-1.2</td>
<td>-6.4, 3.9</td>
<td>74.0 (18.2)</td>
<td>57.3 (21.2)</td>
<td>16.7</td>
<td>11.5, 21.8</td>
</tr>
<tr>
<td>General health</td>
<td>53.7 (14.6)</td>
<td>47.9 (13.4)</td>
<td>5.8</td>
<td>2.1, 9.4</td>
<td>63.7 (14.5)</td>
<td>38.3 (23.2)</td>
<td>25.5</td>
<td>20.4, 30.5</td>
</tr>
<tr>
<td>Vitality</td>
<td>55.9 (16.5)</td>
<td>53.6 (14.4)</td>
<td>2.3</td>
<td>-1.7, 6.3</td>
<td>63.9 (16.2)</td>
<td>46.3 (22.8)</td>
<td>17.6</td>
<td>12.5, 22.8</td>
</tr>
<tr>
<td>Social function</td>
<td>65.2 (21.9)</td>
<td>62.8 (24.5)</td>
<td>2.4</td>
<td>-3.6, 8.4</td>
<td>70.7 (20.7)</td>
<td>54.7 (26.1)</td>
<td>15.9</td>
<td>9.8, 22.1</td>
</tr>
<tr>
<td>Role emotional</td>
<td>58.9 (34.0)</td>
<td>61.4 (32.8)</td>
<td>-2.5</td>
<td>-11.2, 6.1</td>
<td>64.4 (32.7)</td>
<td>53.8 (35.4)</td>
<td>10.6</td>
<td>1.6, 19.5</td>
</tr>
<tr>
<td>Mental health</td>
<td>58.8 (14.9)</td>
<td>56.7 (14.7)</td>
<td>2.1</td>
<td>-1.7, 6.0</td>
<td>64.5 (15.3)</td>
<td>48.9 (22.4)</td>
<td>15.6</td>
<td>10.6, 20.6</td>
</tr>
<tr>
<td>Physical Component Summary</td>
<td>41.2 (7.8)</td>
<td>40.1 (6.0)</td>
<td>1.1</td>
<td>-0.7, 2.9</td>
<td>43.8 (7.9)</td>
<td>37.4 (9.0)*</td>
<td>6.4</td>
<td>4.2, 8.7</td>
</tr>
<tr>
<td>Mental Component Summary</td>
<td>44.5 (7.1)</td>
<td>44.0 (7.7)</td>
<td>0.5</td>
<td>-1.4, 2.4</td>
<td>47.3 (7.8)</td>
<td>40.3 (11.1)*</td>
<td>7.1</td>
<td>4.6, 9.6</td>
</tr>
<tr>
<td>Barthel Index</td>
<td>68.3 (22.0)</td>
<td>67.6 (14.3)</td>
<td>0.7</td>
<td>-4.1, 5.6</td>
<td>73.8 (23.2)</td>
<td>61.3 (20.4)</td>
<td>12.5</td>
<td>6.8, 18.3</td>
</tr>
<tr>
<td>Self-Rating Anxiety Scale</td>
<td>51.8 (4.9)</td>
<td>51.8 (5.8)</td>
<td>0</td>
<td>-1.4, 1.3</td>
<td>48.9 (4.8)</td>
<td>55.2 (9.3)</td>
<td>-6.4</td>
<td>-8.3, -4.4</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; and SF-36, Short Form-36.

* n=1 missing data.

Limitations

Our inclusion criteria were broader than that used in previous studies performed in general stroke populations,8,24 such as no upper or age limit, increasing the generalizability of our results. However, there are some limitations to our study. Death rates in our trial were low when compared with case-fatality rates reported in epidemiological studies.1 However, our results are consistent with recent data from the nationwide China National Stroke Registry, whereby 22.5% of patients with ICH died at 6 months.28 Our low death numbers may have been because of selection bias based on (1) our exclusion criteria such that severe cases were excluded; (2) differences in socioeconomic status (participants had above average earnings and socioeconomic status); and (3) the characteristics of the hospitals involved in our trial. The 3 hospitals in our study were large teaching hospitals that are difficult for the general public to access because of both demand on services and the higher costs borne by patients. There may also have been many patients with severe ICH who died at home and so were not admitted to hospital.

Another limitation is that we did not collect baseline data on important predictors of death in patients with ICH, such as hematoma volume and details of hematoma site. It is possible that, by chance, these markers of ICH severity were unbalanced between our groups in favor of the VER group. We used alternate measures of stroke severity at baseline to account for this possibility in our multivariable modeling. Although the time of commencement of rehabilitation was specified, we do not know whether the dose of rehabilitation was the same for each group. This is because rehabilitation was performed by the patient’s family, which meant that it was not possible to record the exact amount and type of rehabilitation received by patients. Also, although we measured the number of adverse events during the study period, we did not record the details of these events.

Inclusion into the study was, in part, subject to clinical judgment. Although this should not have biased the results, it may affect the generalizability of the study because clinicians may
have different subjective criteria. Also, patients were recruited from hospitals in only 1 city in Shaanxi Province, China. Therefore, we do not know to what extent our results can be generalized to other areas in China or the feasibility of implementing our model of VER in hospitals in other regions. The differences in standard care and postdischarge management between China and other countries may also affect the generalizability of the results. However, given the magnitude of the differences between the intervention and the control group in this study VER is likely to be beneficial for patients with ICH when compared with most other standard care models.

Conclusions
Commencement of rehabilitation within 48 hours of ICH significantly reduced hospital length of stay and improved long-term survival and morbidity outcomes when compared with standard practices in China of commencing rehabilitation 7 days after ICH. The feasibility of VER as a treatment option for patients with ICH has also been shown. The large benefits of VER for patients with ICH demonstrated by our study highlights the need for further research in this area. Larger trials across multiple settings and countries specific to this group are needed.

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Disclosures
None.

References
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뇌내출혈 이후 조기 재활치료에 관한 무작위배정 임상시험
뇌졸중 발생 이후 6개월 이내의 결과

Randomized Controlled Trial of Early Rehabilitation After Intracerebral Hemorrhage Stroke
Difference in Outcomes Within 6 Months of Stroke

Ning Liu, MPH; Dominique A. Cadilhac, PhD; Nadine E. Andrew, PhD; Lingxia Zeng, PhD; Zongfang Li, PhD; Jin Li, PhD; Yan Li, MM; Xuewen Yu, PhD; Baibing Mi, MM; Zhe Li, ME; Honghai Xu, MPH; Yangjing Chen, MM; Juan Wang, BM; Wanxia Yao, PhD; Kuo Li, MM; Feng Yan, MM; Jue Wang, PhD

(Stroke. 2014;45:3502-3507.)

Key Words: cerebral hemorrhage □ clinical trial, randomized □ outcome assessment (health care) □ rehabilitation

배경과 목적
뇌내출혈의 기전, 급성기 치료 및 예후는 허혈뇌졸중 환자와 비교할 때 다를 수 있다. 조기 치료의 효과에 대한 연구는 주로 허혈뇌졸중 환자에 대하여 수행되었으며, 뇌내출혈 환자에 적용하는 이점이 있음에 대해서는 아직 알려진 바가 없다. 여기서는 뇌졸중 발생 이후 48시간 이내에 시작되며 조기 재활치료는 뇌내출혈 환자의 생존 및 기능적 예후에 긍정적인 영향을 미친다고 가정하였다.

방법
본 연구는 다기관 무작위배정 대조 임상시험으로, 논가설법을 적용하여 발생 3개월 및 6개월 시점에 결과를 측정하였다. 무작위 배정된 임상시험 대상자들은 일반적인 치료 혹은 일반적인 치료 및 조기 재활치료를 받았다. 일차 결과 변수는 생존이었다. 이차 결과 변수로 건강 관련 삶의 질은 36개 항목 축약본으로 측정한 SF-36(item Short Form Questionnaire)를 사용하였으며, 기능적 회복은 수정바텔지수(modified Barthel Index), 불안감은 Zung 자가측정불안척도(Zung Self-Rated Anxiety Scale)를 사용하였다.

결과
326명 가운데 243명이 무작위배정 되었으며, 평균 연령은 59세이고 남성이 56%이었다. 6개월 시점에서 일반적인 치료를 받은 군의 환자들은 사망 가능성이 더 높았다(보정 위험비 4.44; 95% CI, 1.24~15.87). 6개월 시점에서 36개 항목 축약본 가운데, 신체활동척도는 6점 차이가 났고(95% CI, 4.2~8.7) 정신활동척도 요약점수는 7점 차이가 있었고(95% CI, 4.5~9.5), 수정바텔지수 점수는 13점 차이가 있었으며(95% CI, 6.8~18.3), 자가측정불안척도는 6점 차이가 있었다(95% CI, 4.4~8.3). 이러한 차이는 모두 조기 재활군에서 유리한 방향으로 측정되었다.

결론
본 연구에서 최초로 뇌내출혈 환자에서 발생 38시간 이내에 시작되는 조기 재활치료는 6개월 시점 생존 및 기능적 회복을 향상시킴을 중국의 입원 환자를 대상으로 증명하였다.

Figure 2. Kaplan–Meier cumulative survival plot for all cause mortality in very early rehabilitation (VER) and standard care (SC) during 183-day poststroke follow-up.