Stereotactic Treatment of Intracerebral Hematoma by Means of a Plasminogen Activator
A Multicenter Randomized Controlled Trial (SICHPA)
O.P.M. Teernstra, MD; S.M.A.A. Evers, PhD; J. Lodder, MD; P. Leffers, MSc; C.L. Franke, MD; G. Blaauw, MD

Background and Purpose—Treatment of intracerebral hematoma (ICH) is controversial. An advantage of neurosurgical intervention over conservative treatment of ICH has not been established. Recent reports suggest a favorable effect of stereotactic blood clot removal after liquefaction by means of a plasminogen activator. The SICHPA trial was aimed at investigating the efficacy of this treatment.

Methods—A stereotactically placed catheter was used to instill urokinase to liquefy and drain the ICH in 6-hour intervals over 48 hours. From 1996 to 1999, 13 centers entered 71 patients into the study. Patients were randomized into a surgical group (n=36) and a nonsurgical group (n=35). Admission criteria were the following: age >45 years, spontaneous supratentorial ICH, Glasgow Eye Motor score ranging from 2 to 10, ICH volume >10 cm³, and treatment within 72 hours. The primary end point was death at 6 months. As secondary end points, ICH volume reduction and overall outcome measured by the modified Rankin scale were chosen. The trial was prematurely stopped as a result of slow patient accrual.

Results—Seventy patients were analyzed. Overall mortality at day 180 after stroke was 57%; this included 20 of 36 patients (56%) in the surgical group and 20 of 34 patients (59%) in the nonsurgical group. A significant ICH volume reduction was achieved by the intervention (10% to 20%, P<0.05). Logistic regression analysis indicated the possibility of efficacy for surgical treatment (odds ratio, 0.23; 95% confidence interval, 0.05 to 1.20; P=0.08). The odds ratio of mortality combined with modified Rankin scale score 5 at 180 days was also not statistically significant (odds ratio, 0.52; 95% confidence interval, 1.2 to 2.3; P=0.38).

Conclusions—Stereotactic aspiration can be performed safely and in a relatively uniform manner; it leads to a modest reduction of 18 mL of hematoma reduction over 7 days when compared with control, which has a 7-mL reduction, and therefore may improve prognosis. (Stroke. 2003;34:968-974.)

Key Words: intracerebral hemorrhage ■ randomized controlled trials ■ stereotactic aspiration ■ surgical treatment ■ thrombolytic therapy
Patients and Methods

Patient Selection

Between March 1996 and May 1999, patients with a primary supratentorial intracerebral hematoma, including those on anticoagulants, were enrolled in the trial. Inclusion criteria were based on a Dutch study on prognosis in ICH.30 The criteria were designed to select a relatively uniform group with an expected mortality of 88% (when applied to the study population of Franke et al30) to maximize the chance of detecting a treatment effect. Before enrollment all patients had CT scanning for ICH localization and volume estimation. Patients had to be 45 years of age or older and have an ICH volume exceeding 10 mL and a Glasgow Eye Motor score between 1 and 10 (the verbal score was left out as it is unrevealing in dominant hemisphere lesions), at least one pupil reactive to light, and a normal coagulative status (corrected if necessary). Furthermore, surgery within 72 hours after ICH onset had to be possible. The study was approved in advance by the institutional review committees of all participating centers. Before inclusion, written informed consent had to be obtained from the patient or closest kin. Most participating centers referred the ICH patient directly to a neurological unit where the attending neurosurgeon handled the inclusion procedure. Otherwise, the attending neurologist consulted the neurosurgeon on eligibility for potential drainage. An independent external agency was contacted by phone for verification of inclusion criteria and treatment allocation. Patient data were forwarded to the trial office by fax. Eight separate treatment random allocation lists were used on the basis of prestratification on GCS (<9 vs ≥10). In each list, block sizes of two and four in random order were used.

Data Collection

At prespecified intervals during 180 days of follow-up, attending physicians and nursing staff filled out Clinical Record Forms (Table 1). These were then sent to the trial office, where the data were entered into a database. On admission, the following baseline patient characteristics were recorded: history of "stroke" (a history of transient ischemic attack and/or stroke), history of hypertension, diabetes,31 "cardiovascular history" (ischemic heart disease, heart failure, or cardiac arrhythmias), and history of "hemorrhagic diathesis" (easy bruising, frequent nosebleeds, epistaxis, etc32). Use of anticoagulants (aspirin, warfarins, and heparin33) on admission was recorded. Laboratory tests were performed to ascertain "abnormal hemostatic parameters" (low platelet count [<50×10^9/L] and/or activated partial thromboplastin time >50 seconds and/or partial thromboplastin time >11 seconds). Also GCS, pupil size, and reactivity and blood pressure were recorded. The ICH volume was estimated using a validated practical rule (ABC/2, where A=biggest diameter, B=radius at 90 degrees from A, and C=number of slices×slice thickness; the presence of intraventricular hemorrhage [IVH] was not included in the equation34). This method was checked by comparing its results with results from seven scans, the volumes of which were calculated on the CT scanner itself. The ABC/2 measurements were done twice for all of the CT scans by the same individual.

To test the hypothesis that stereotactic treatment of ICH by means of a plasminogen activator (SICHPA) improves survival and functional outcome, the present study was carried out as a randomized multicenter trial.

Outcome Measures and Statistical Analysis

The number of patients needed in each trial arm was estimated at 75 (α=0.05 and β=0.10), assuming a mortality reduction at 6 months from 88% to 53% in the surgical group. Although the analysis was performed on the basis of the "intention-to-treat" principle, an additional protocol analysis was carried out to test for discrepancies. Statistical significance is expressed as P<0.05 and was always measured two-tailed. The primary end point was death at 6 months. As secondary end points ICH volume reduction

<table>
<thead>
<tr>
<th>TABLE 1. Patient Evaluation During Follow-Up</th>
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<tbody>
<tr>
<td>Test</td>
</tr>
<tr>
<td>----------------------------</td>
</tr>
<tr>
<td>CT scanning</td>
</tr>
<tr>
<td>Glasgow Coma Scale</td>
</tr>
<tr>
<td>Scandinavian Stroke Scale</td>
</tr>
<tr>
<td>Barthe Index</td>
</tr>
<tr>
<td>Modified Rankin Score</td>
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</table>

Downloaded from http://stroke.ahajournals.org/ by guest on October 30, 2017
and overall outcome measured by the mRS were chosen. Differences between both groups in treatment modalities, complications, and ICH volumes on days 1, 3, and 7 were compared with a Mann Whitney U test. Because the trial protocol allowed for treatment up to 72 hours after the stroke, we also checked for imbalances between treatment groups in timing of randomization, surgery, and CT scanning. Functional outcome in mRS scores from 0 to 5 plus death at day 180 after stroke were compared using a Mann-Whitney U test.

Survival was examined with Kaplan-Meier curves and Cox regression analysis (with the same variables entered as in the binary logistic analysis). The effect of stereotactic aspiration on mortality and morality combined with mRS score 5 at 180 days was analyzed using binary logistic regression analysis to account for imbalance in prognostic variables.36 The regression analysis omitted seven patients with missing data, therefore decreasing the number of patients in this analysis to 63 of 70. All variables were entered dichotomized according to their median values. The protocolized binary logistic regression model included, besides the effect parameter and the “center of inclusion” variable (a prestratification variable), only variables supposed to have a substantial influence on the outcome parameter (age >70 years, right-sided location of ICH, GCS score <10 points, ICH volume >59 cm3, abnormal hemostatic parameters, and history of cardiac disease).

**Results**

After 3 years of patient enrollment, the trial was stopped. Seventy-one patients had been randomized, 36 to the surgical group and 35 to the nonsurgical group. One patient was excluded from the study because of an arteriovenous malformation. There were nine protocol violations, as follows: one patient had been randomized for stereotactic drainage but had craniotomy instead (alive at 180 days); craniotomy was performed in one patient in the nonsurgical group (alive at 180 days); one patient in the surgical group died during preoperative CT scanning; four patients received no stereotactic drainage, two of them as a result of early neurological recovery (one died at the 45th day, and the other survived 180 days), a third because of fast neurological deterioration resulting in death, and the fourth because of suspected amyloid angiopathy (alive at 180 days). One patient died after three drainages (out of a total of nine drainages). One patient received seven drainages before the catheter broke down (alive at 180 days). Retrospectively the intensive care unit (ICU) length of stay was analyzed in the UNCL, which included 48% of the patients. There was a significant difference in the ICU stay in the UNCL between the conservatively treated group (1.8 days, SD 7.1 days) and the surgical group (3.9 days, SD 6.1 days; P=0.007). This difference is due to standard ICU care after the stereotactic cranial surgery. To not only account for differences in ICU care, we compared all patients in both groups for different medical supportive care modalities on the whole. Supportive medical care was similar with the exception that patients in the surgical group on average more often received low molecular weight heparin and mechanical ventilation (Table 2). The latter is likely related to the stereotactic procedure. There were no statistically significant imbalances between the conservatively treated and stereotactically treated groups with regard to mean time to randomization (12.5 and 12.5 hours), time to first CT scan (9.8 and 13.2 hours), time to second CT scan (3.1 and 3.0 days), and time to third CT scan (7.0 and 7.8 days). In one third of the surgical patients (UNCL), the time elapsed from the moment of stroke to actual surgery was retrieved and, with a mean 12 hours (SD 19 hours), this was within protocol limits (72 hours).

Table 3 shows the baseline characteristics of the two treatment groups. Patients in the surgical group more often had a history of cardiovascular disease. They also had worse neurological scores on admission as reflected in the GCS and SSS scores. On average, the ICH volume was smaller in the nonsurgical group, whereas deep hematomas and presence of intraventricular blood were more frequent in this group.

The ABC2 method was compared with seven volumes measured by the CT scanner; the mean difference was 3 mL (SD 6 mL), which was considered to be acceptable. A total of 158 ICH volumes were measured twice, and the intraobserver variability expressed as k was 0.8.

Protocol analysis showed that the patients in the conservatively treated group had a mean ICH volume of 51.8 mL (SD 32 mL) on day 1, 52.2 mL (SD 28.6 mL) on day 3, and 42.7 mL (SD 24.5 mL) on day 7. Patients in the stereotactically

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**TABLE 2. Treatment Modalities and Complications**

<table>
<thead>
<tr>
<th>Complications</th>
<th>Nonsurgical*</th>
<th>Surgical*</th>
<th>Significance†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic (stroke)</td>
<td>5 (23.6)</td>
<td>0</td>
<td>0.23</td>
</tr>
<tr>
<td>Convulsions</td>
<td>7.7 (27.2)</td>
<td>6.3 (24.6)</td>
<td>0.83</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Cardiological problems</td>
<td>0</td>
<td>10 (30.5)</td>
<td>0.11</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>42.9 (5.4)</td>
<td>42.4 (50.2)</td>
<td>0.97</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>40 (50)</td>
<td>28.1 (45.7)</td>
<td>0.35</td>
</tr>
<tr>
<td>Septic shock</td>
<td>24 (43.6)</td>
<td>20 (40.7)</td>
<td>0.72</td>
</tr>
<tr>
<td>Decubitus</td>
<td>4.2 (20.4)</td>
<td>3.5 (18.6)</td>
<td>0.89</td>
</tr>
<tr>
<td>Rebleeding</td>
<td>0</td>
<td>21.9 (42)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

*Figures represent mean percentage (standard deviation percentage). †Statistical significance (P value) calculated by Mann-Whitney U test.
treated group had a mean ICH volume of 65.4 mL (SD 28.1 mL) on day 1, 47.5 mL (SD 30 mL) on day 3, and 44.4 mL (SD 30.7 mL) on day 7. The absolute mean volume reductions for both groups are depicted in Figure 1. The percentages of ICH volume reduction in the conservatively treated and stereotactic groups were compared with a Mann-Whitney U test. This comparison showed significant differences between days 1 and 3 (8% and 18% respectively [P = 0.012]) and between days 1 and 7 (3% and 10% respectively [P = 0.015]). An example of a successful drainage is shown in Figure 2.

Overall mortality at day 180 after stroke was 57%; this included 20 of 34 patients (59%) in the nonsurgical group and 20 of 36 (56%) in the surgical group. There was one missing value in the analysis of functional outcome (mRS), leaving n = 69 in the Mann-Whitney U test. There were no significant differences between treatment groups (P = 0.7) (Figure 2). Kaplan-Meier analysis demonstrated similar survival times between the groups (P = 0.9, Breslow test). Cox regression failed to demonstrate a statistical difference between the groups (P = 0.6) (Figure 3).

Apart from the effect parameter “stereotactic treatment” and the variable “center of inclusion” (subvariables for each of the four neurosurgical centers), variables that were entered

![Figure 1. Hematoma volume reduction. Black line indicates stereotactic aspiration; grey line, conservative.](image1)

![Figure 2. Example of successful stereotactic drainage. Black line indicates stereotactic aspiration; grey line, conservative. Left (day 1) on admission; middle (day 2), just before drain removal; right (day 7), fifth day after drain removal.](image2)

### TABLE 3. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Nonsurgical*</th>
<th>Surgical</th>
<th>Significance†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>34 (49%)</td>
<td>36 (51%)</td>
<td></td>
</tr>
<tr>
<td><strong>Male sex</strong></td>
<td>19 (56%)</td>
<td>21 (58%)</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>Mean age, y‡</strong></td>
<td>69 (71, 49–89)</td>
<td>67 (68, 47–84)</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>Clinical history</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>9 (27%)</td>
<td>8 (22%)</td>
<td>0.63</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>16 (47%)</td>
<td>17 (47%)</td>
<td>0.82</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>4 (12%)</td>
<td>3 (8%)</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Cardiovascular disease</strong></td>
<td>7 (21%)</td>
<td>12 (33%)</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>Abnormal hemostasis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anticoagulant use</strong></td>
<td>14 (41%)</td>
<td>9 (25%)</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>Clinical signs</strong></td>
<td>2 (6%)</td>
<td>7 (19%)</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Abnormal lab tests</strong></td>
<td>2 (6%)</td>
<td>5 (14%)</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Clinical condition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>21 (62%)</td>
<td>22 (63%)</td>
<td>0.93</td>
</tr>
<tr>
<td><strong>GCS score (EMV)</strong></td>
<td>10 (9, 6–14)</td>
<td>9.5 (9.5, 4–15)</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>Scand. Stroke Scale score§</strong></td>
<td>16 (14, 0–41)</td>
<td>13 (8, 0–50)</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Imaging</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lobar ICH</strong></td>
<td>14 (41%)</td>
<td>24 (67%)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Right sided ICH</strong></td>
<td>14 (41%)</td>
<td>14 (42%)</td>
<td>0.97</td>
</tr>
<tr>
<td><strong>Intraventricular blood</strong></td>
<td>13 (38%)</td>
<td>10 (27%)</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>ICH volume, mL</strong></td>
<td>52 (49, 11–132)</td>
<td>66 (73, 11–128)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Unless mentioned otherwise, figures represent mean (percentage).†Statistical significance (P value) calculated by Mann-Whitney U test.‡Figures represent mean (median, range).§Minimum score is 0 and maximum 70 points.
into the binary logistic analysis were the following: age (>70 years), right-sided location of ICH, GCS score (<10 points), ICH volume (>59 cm³), abnormal hemostatic parameters, and history of cardiac disease.

There was a positive effect of the stereotactic treatment in reducing mortality at 180 days with an odds ratio (OR) of 0.23, but this was not statistically significant (95% confidence interval [CI], 0.05 to 1.20; \( P = 0.08 \)) (Figure 4). Other factors in the model that had a significant effect were the following: right-sided location of ICH (OR, 0.10; CI, 0.02 to 0.58; \( P = 0.01 \)), GCS score (<10 points) (OR, 8.24; CI, 1.50 to 45.23; \( P = 0.02 \)), and ICH volume (>59 cm³) (OR, 9.63; CI, 1.40 to 66.48; \( P = 0.02 \)). Because of its imbalanced distribution between the groups, the variable “lobar ICH” was separately tested with this model eventually left out because it did not contribute to the model fit and had only a slight impact on the effect parameter (OR, 0.84; CI, 0.13 to 5.56; \( P = 0.86 \)). Mortality combined with severe handicap (mRS score 5) at 180 days yielded an OR of 0.52, which was a nonsignificant reduction (CI, 1.2 to 2.3; \( P = 0.38 \)). Other factors in this regression model that turned out to be statistically significant were age (>70 years) (OR, 4.8; CI, 1.04 to 22.24; \( P = 0.05 \)) and ICH volume (>59 cm³) (OR, 7.07; CI, 1.24 to 40.19; \( P = 0.03 \)). Both models were also run without the eight protocol violation cases, showing no marked changes in results (OR for stereotactic treatment, 0.26 at \( P = 0.11 \) and 0.35 at \( P = 0.23 \)). When in seven cases missing values were replaced by the mean of the particular variable, the ORs for stereotactic treatment changed to 0.47 at \( P = 0.30 \) and 0.57 at \( P = 0.45 \), respectively.

Comorbidity figures were similar between the surgical and conservative treatment groups (Table 2). The clinical diagnosis of rebleeding was recorded in seven patients in the surgical group and none in the conservatively treated group. To obtain a more uniform and systematic measure for rebleeding, we investigated all patients with hematoma enlargement, coinciding with neurological deterioration. Hematoma enlargement, defined as a >10% volume increase at any time between CT scanning on days 1, 3, and 7, occurred in 60% (SD, 50%) of nonsurgical and 38% (SD, 50%) of surgical patients (\( P = 0.14 \)). The 10% threshold was chosen also to include patients with slight ICH enlargements. Hematoma enlargement combined with neurological deterioration (defined as a >10% drop in SSS score at any time between days 1, 3, and 7) or death within the first 7 days occurred in 17% (SD 39%) of nonsurgical and 35% (SD 49%) of surgical patients (\( P = 0.18 \)).

**Discussion**

Although small, the SICHPA trial is up to now the largest trial on the efficacy of stereotactic treatment of primary intracerebral hematoma with the use of plasminogen activator. Our study showed that stereotactic aspiration can be performed safely and in a relatively uniform manner. Besides that, stereotactic aspiration leads to an absolute reduction of 18 mL of hematoma volume over 7 days when compared with control, which has a 7-mL reduction. Overall the study resulted in a relative reduction of 34% in the hematoma volume. Mortality in the intervention group de-

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**Figure 3.** mRS score at day 180 including death. Black line indicates stereotactic aspiration; grey line, conservative. \( N = 69 \) (one missing value); a score of 6 refers to patients who died before 180th day after stroke. There was a nonsignificant reduction in morbidity and mortality (OR, 0.52; CI, 1.2 to 2.3; \( P = 0.38 \)).

**Figure 4.** Kaplan-Meier survival curve. Black line indicates stereotactic aspiration; grey line, conservative. Survival is similar for both groups (\( P = 0.9 \), Breslow test).
creased from the predicted 88% to 56% and to 59% in the conservatively treated group. No statistically significant difference in mortality and morbidity at 180 days was found. The complication rate was similar between groups.

The reduction in mortality in the conservative group is difficult to explain. One reason might be a Hawthorne effect. All patients and centers in our study were monitored both by the trial coordinators and the monitoring committee at regular intervals, which might have caused an overall increase in supportive care in the trial. Another possible explanation could be the presence of an aspecific selection bias causing our patients to have a more favorable prognosis compared with those in the Franke et al study.

Compared with spontaneous resolution, stereotactic drainage combined with urokinase-induced clot lysis significantly reduced ICH volume. Our data show that ICH volume reduction, which is assumed to be associated with lower mortality, is practically achievable by this method. However, there may not be a simple relationship between ICH volume reduction, chance at rebleeding, and consequent (functional) outcome; rebleeding more often occurred in the surgical group, and fewer surgical patients had hematoma enlargement, but those who had hematoma enlargement more often had an unfavorable outcome than conservatively treated patients with hematoma enlargement. Post hoc analysis showed a significant association between a 25% or more volume reduction and chances for a more favorable outcome (O.P.M. Teernstra, MD, et al, unpublished data, 2002). As ultra-early surgery leads to a higher rate of rebleeding, timing of surgery could be an important part of its effectiveness; this factor, however, was not included in our trial design.

The imbalance in prognostically important variables between groups is an unfortunate result of the small number of patients enrolled. The trial was prematurely stopped for the following four reasons. First, patient acquisition had been projected on the basis of an earlier Dutch epidemiological study, but these incidence estimates might have been too optimistic. Secondly, the so-called “gray area of uncertainty” (whether to operate or not) that was discussed and agreed on in advance with participating neurosurgeons appeared to be much smaller in reality. Thirdly, an intention-to-treat interim analysis showed a slight detrimental effect of the experimental procedure. The probability of achieving a statistically significant difference between groups by including more patients was deemed unlikely. This preplanned interim analysis carried out for safety reasons did not account for an imbalance in prognostic variables between groups. Finally, we were unable to secure sufficient funding to continue the trial.

Recently, Becker et al pointed out that the most important variable predicting poor outcome in ICH patients is the level of provided medical support. Perception of futility of aggressive therapy leads to early withdrawal of medical support, which is less likely in ICH patients who are surgically treated. Mayer and Kossoff reported that, in a neurocritical care service over a 3-year period, among 74 non–brain-dead patients, 32 (43%) were terminally extubated. Although in the present study both groups received the same level of supportive care, in no instance was early withdrawal of supportive care reported to the monitoring committee. Although not formally reported, there might have been a tendency to withdraw supportive care less easily in the intervention group, and therefore it is possible that the study was influenced by this potential bias.

The present trial shows that stereotactic aspiration of ICH using urokinase effectively reduces ICH volume. The method used in our trial, however, was less successful in the magnitude and timing of volume reduction compared with other small trials. Better potential benefits might be achieved by a greater reduction in hematoma volume over a shorter period of time. Because there is no uniform procedure in stereotactic aspiration, a Phase II study should be initiated in which insight should be gained into the optimal dosage and time span for which urokinase should administered. However, it remains unproven whether this leads to a reduction in mortality compared with conservative treatment alone. Additionally, if the Phase II trial indicates favorable results regarding volume reduction, a large-scale Phase III clinical trial should subsequently investigate whether ICH volume reduction definitely improves survival as well as functional outcome. To optimize patient accrual rate in a future trial, inclusion should focus on patients in whom open craniotomy is not preferred by most neurosurgeons, such as those with a deep ICH and lowered consciousness. To avoid heterogeneity of data, uniform standards of care should be defined and apply to all patients in such a trial.

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References


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