Practice patterns for neurosurgical utilization and outcome in acute intracerebral hemorrhage: INTERACT 1 and 2 studies

Abstract

Background: The prognosis in acute spontaneous intracerebral hemorrhage (ICH) is related to hematoma volume, where >30 mL is commonly used to define large ICH as a threshold for neurosurgical decompression but without clear supporting evidence.

Objectives: We aimed to determine the factors associated with large ICH and neurosurgical intervention among participants of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trials (INTERACT).

Methods: We performed pooled analysis of the pilot INTERACT1 (n = 404) and main INTERACT2 (n = 2839) studies of ICH patients (< 6 hrs of onset) with elevated systolic blood pressure (SBP, 150-220 mmHg) who were randomized to intensive (target SBP < 140 mmHg) or contemporaneous guideline-recommended (target SBP < 180 mmHg) management. Neurosurgical intervention data were collected at 7 days post-randomization. Multivariable logistic regression was used to determine associations.

Results: There were 372 (13%) patients with large ICH volume (>30 ml), which was associated with non-residing in China, non-diabetic status, severe neurological deficit (National Institutes of Health stroke scale [NIHSS] score ≥15), lobar location, intraventricular hemorrhage (IVH) extension, raised leucocyte count, and hyponatremia. Significant predictors of those patients who underwent surgery (n = 226, 226 of 3233 patients overall; 83 of 372 patients with large ICH) were younger age, severe neurological deficit (lower Glasgow coma scale score, and NIHSS score ≥15), baseline ICH volume >30 mL, and IVH.

Conclusions: Early identification of severe ICH, based on age and clinical and imaging parameters, may facilitate neurosurgery and intensive monitoring of patients.

Short title: Practice patterns for neurosurgical utilization in ICH

Key Words: Clinical trial, INTERACT, intracerebral hemorrhage, neurosurgery,
Introduction

Acute spontaneous intracerebral hemorrhage (ICH) is the most lethal and disabling type of stroke, resulting in high case fatality and significant disability. However, aside from well organized stroke unit care, there has been no established definitive treatment. Surgical decompression for ICH, in particular remains controversial as the randomized evidence is conflicting. Although the totality of the evidence, summarized in a Cochrane review of conventional surgical craniotomy compared with conservative treatment in 2059 ICH participants from 10 trials reported benefits (an odds ratio [OR] of 0.71; 95% confidence interval [CI] 0.58-0.88) in favor of craniotomy, individual trials, such as the Surgical Trial in Intracerebral Hemorrhage (STICH) and STICH II studies, failed to demonstrate clear superiority of early surgery versus conservative management overall or in superficial cortical hematomas, respectively. Similarly, minimally invasive surgery (MIS) was shown to be superior to conservative medical treatment or conventional craniotomy in a meta-analysis of 1955 patients from 12 randomized controlled trials, but is rarely used in clinical practice outside of China.

Surgical practice for ICH varies between and within countries, in part because of clinician training and experience, and in part because of variable acceptance of the evidence. The aim of this study was to define the factors associated with neurosurgical intervention in ICH among participants of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trials (INTERACT 1 and 2). Review of this large international database may provide a better understanding of the characteristics of patients undergoing neurosurgical intervention in relation to patterns of clinical practice in different regions.

Methods

Study design and participants
The INTERACT1 and 2 studies were international, multicenter, open, blinded endpoint, randomized controlled trials, the details of which are outlined elsewhere. In brief, 404 and 2839 patients, respectively, with spontaneous ICH within 6 hours of onset and elevated systolic blood pressure (SBP, 150-220 mmHg) were randomly assigned to receive intensive (target SBP <140 mmHg within 1 hour) or contemporaneous guideline-recommended (target SBP <180 mmHg) BP lowering therapy. Study protocols were approved by the appropriate ethics committee at each participating site, and written informed consent was obtained from patients or an appropriate surrogate.

Procedures

Demographic and clinical characteristics were recorded at the time of enrolment. Stroke severity was measured with the Glasgow coma scale (GCS) and National Institutes of Health stroke scale (NIHSS) at baseline (time of randomization). Computerized tomographic (CT) scans were performed according to standardized techniques at baseline, and centrally analyzed without any identifying information. ICH volumes were calculated with computer-assisted multi-slice planimetric and voxel threshold techniques in MIStar software version 3.2 (Apollo Medical Imaging Technology, Melbourne, Australia). Manual measurements were applied to calculate hematoma volumes in a small number of CT scans that were stored as digital images or plain films. Hematoma volume of >30 mL was defined as ‘large’ as it is widely used to define a threshold for decompressive surgery. Surgery was defined as any of open craniotomy, endoscopic surgery, stereotactic aspiration with thrombolytic instillation and repeated aspiration, or decompressive surgery; as reported according to standard criteria for a serious adverse event (SAE) or as a management factor recorded on the study case record form at 7 days (or hospital discharge, if sooner). If multiple SAEs were reported, only the first was included in the analyses. Outcomes of interest for these analyses were death or major disability, death, and major disability, as defined by scores 3–6, 6, and 3–5, respectively, on the modified Rankin scale (mRS), assessed by an independent observer blind to treatment allocation, at 90 days post-
**Statistical analysis**

Factors associated with large hematoma volume (>30 ml) and neurosurgical intervention were identified in logistic regression models. Associations of surgery and clinical outcomes were also estimated by logistic regression models, with adjustment for confounders. We also performed stratified analysis by baseline ICH volume into two groups: ≤30 vs. >30 ml. The association was compared between the two groups by adding an interaction term to the model. A standard level of significance was set at a P value of <.05. Data are reported with OR and 95% CI. All analyses were undertaken with SAS software (version 9.3, SAS Institute, Cary, North Carolina, USA).

**Results**

Among a total of 3243 participants across the two studies, 2959 (91.2%) had available data on baseline hematoma volume and 3233 patients (99.7%) were included in the analysis of factors associated with neurosurgical intervention. There were relatively small numbers of participants with cerebellar (103, 3.5%) and brainstem (92, 3.1%) ICH.

Table 1 shows for 372 (12.6%) patients with large hematoma volume (>30 ml), the associated variables were older age, non-residing in China, no history of diabetes mellitus, severe neurological impairment (NIHSS >15), lobar location, presence of intraventricular hemorrhage (IVH), raised leucocyte count, and hyponatremia.

Table 2 shows the independent associations for neurosurgical intervention were younger age, residing in China, severe neurological deficit (NIHSS ≥15), large baseline hematoma volume, and IVH.

A total of 83 (22.3%) patients with large hematomas had neurosurgery, and they were more likely to be young, residing in China, with severe reduction in level of consciousness (See Table, Supplemental Digital Content 1, which illustrates comparison of non-surgery versus
surgery among patients with hematoma >30 ml). However, among the 2587 patients with ICH ≤30 ml, there were still 131 (5%) patients who underwent surgery; these patients were younger, had lower GCS score, higher NIHSS score, larger baseline ICH, and IVH, as compared to those who did not undergo surgery. (See Table, Supplemental Digital Content 2, which illustrates comparison of non-surgery versus surgery among patients with hematoma ≤30 ml).

There were 1,694 patients who were either dead or disabled at 90 days. Surgery was associated with an increased risk of death or major disability at 90 days (86% for surgery vs. 51% for no surgery; adjusted OR 5.13, 95% CI 3.22–8.16; p < .001) (Table 3). Similar associations were observed for death (adjusted OR 1.91, 95% CI 1.28–2.85; p = 0.002) or major disability (adjusted OR 4.37, 95% CI 2.71–7.07; p < .001). Table 4 shows that among patients with hematoma ≤ 30 mL, surgery was found to increase the risk of death or major disability (adjusted OR 12.00, 95% CI 6.10–23.5; p < .001), death (adjusted OR 2.72, 95% CI 1.62–4.57; p < .001) and major disability (adjusted OR 10.11, 95% CI 5.11–20.02; p < .001) at 90 days. Conversely, for those with hematoma >30 mL, surgery no longer significantly increased the risk of poor outcomes (all P interaction < .05).

**Discussion**

This study derived from an international clinical trial database has shown that being young, residing in China, having either reduced consciousness or severe neurological deficit, a large hematoma volume and the presence of IVH, are the key determinants of the need for neurosurgery after the onset of acute spontaneous ICH. Despite having such intervention, these patients retain a poor prognosis.

Our results are consistent with guideline recommendations5, 16 and other studies of neurosurgical intervention in ICH.10 The recently updated American Heart Association (AHA) / American Stroke Association (ASA) guidelines recommend that patients with ICH located in the cerebellum who are deteriorating neurologically or have brainstem
compression and/or hydrocephalus from ventricular obstruction should have urgent surgical removal of the hemorrhage (Class I, level B). Conversely, the European Stroke Organization guidelines only recommend early surgery for patients with a GCS score in the range of 9-12. A survey indicates that British neurosurgeons are less likely to be uncertain of intervening if patients are deteriorating, if the neurological deficit is minor, and if the hematoma has a lobar location. Similarly, analysis of the screening logs from the STICH network of 3893 ICH patients in 42 centers showed that neurosurgeons are less likely to express clinical uncertainty about whether to operate in older patients, those with normal or minor drowsiness defined by high GCS scores, and in those where the hematoma is located in the right hemisphere, or basal ganglionic / thalamic regions. Also from this network, Gregson et al showed there are significant country differences in craniotomy rates, reflecting either variable clinician uncertainty or health care practices. A unique finding from our study was the presence of IVH being an indication for surgery to reduce intracranial pressure. However, we could not identify hematoma location as being associated with neurosurgery, and this may reflect consideration of the STICH trials showing no clear support for removal of deep or cortically located hematomas.

Our finding showed that neurosurgical intervention did not improve functional outcome, whether expressed by the combined or separate components of death or major disability at 90 days. In subgroup analyses, patients with small hematomas who underwent surgery had a poor outcome whereas not such association was evident in patients with large hematomas who had surgery. As surgery is often done in poor prognosis, deteriorating patients, these results provide some support for the criteria of 30ml threshold of large hemorrhage, as being appropriate for consideration of surgery. However, the results should be interpreted with caution. The majority of patients (87%) in our study had small baseline hematomas (volume ≤30 ml), which may not usually be appropriate candidates for surgery, whilst those who were considered suitable for early surgery may have been excluded. Surgery was therefore undertaken in carefully selected patients with clinical
deterioration, which may be another source of election bias. The threshold of >30 ml requires further investigation because of the low proportion of patients with large hematomas and receiving surgery within the present analysis.

A strength of this study was the inclusion of a broad range of patients across a wide range of health care settings as part of two large international multicenter clinical trials. However, there are several limitations that should be emphasized. First, of selection bias related to a clinical trial population, with inclusion criteria of ICH patients with initial hypertension and mild-to-moderate severe ICH without a plan for early neurosurgery. Furthermore, this is post-hoc, with incomplete adjustment for all potential confounding variables related to indication. With only days from randomization to surgery (See Table, Supplemental Digital Content 3, which illustrates days from randomization to surgery) available, an absence of data on the exact timing from ICH onset to surgery is another source of bias.9,15,18

In summary, our international clinical trial analysis indicates that neurosurgeons tend to perform interventions on those who are young, residing in China, with severe neurological deficit defined by level of consciousness or neurological impairment, with a large hematoma and often with IVH. Early identification of severe ICH based on age and clinical and imaging parameters may facilitate the use of neurosurgery and more intensive monitoring of patients with this serious condition.

References


**Supplemental Content Legends:**

Supplemental table 1. Comparison of non-surgery versus surgery among patients with hematoma > 30 mL
Supplemental table 2. Comparison of non-surgery versus surgery among patients with hematoma $\leq 30$ mL

Supplemental table 3. Days from randomization to surgery