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Eligibility for the Surgical Trial in Intracerebral Hemorrhage II Study in a Population-Based Cohort

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Abstract

Introduction—No proven treatments exist for intracerebral hemorrhage (ICH). Carefully selected patients may benefit from surgery, and an international multicenter trial is ongoing. We sought to determine how many patients in a population-based ICH cohort would have been eligible for surgery using the Surgical Trial in Intracerebral Hemorrhage II (STICH II) criteria.

Methods—We identified all patients aged ≥ 18 years residing in the five-county Greater Cincinnati region who were hospitalized with first-ever nontraumatic ICH in 2005. STICH II trial criteria were used to determine eligibility for treatment and reasons for exclusion.

Results—During 2005, 286 ICH patients were identified (103 lobar, 126 deep cerebral, 23 brainstem, 28 cerebellar, and 6 IVH). Non-lobar hemorrhages are not eligible for STICH II. Among patients with lobar hemorrhage, 22 had no exclusions. The most common (not mutually exclusive) reasons for exclusion were volume $< 10\text{cc}$ or $> 100\text{cc}$ ($n=46$) and presence of IVH ($n=27$). No significant age, gender, or racial differences existed between eligible and ineligible patients with lobar ICH. Only one (4.5%) of the 22 STICH II eligible patients in our population had surgery, compared with 8 of 81 (9.9%) ineligible lobar ICH patients ($p=0.43$). Mortality at 180 days in STICH II eligible patients was 36% versus 49% for ineligible lobar ICH patients ($p=0.19$).

Conclusions—In this population-based ICH cohort, 7.7% (22 of 286) of ICH patients would have qualified for STICH II enrollment. Other treatment options need to be explored for most ICH patients.

Keywords

acute stroke; intracerebral hemorrhage; neurosurgery; surgery

Introduction

Spontaneous intracerebral hemorrhage (ICH) occurs in about 67,000 persons annually in the United States.¹ The 30-day mortality for ICH is 40–50%.² There are no proven medical or

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surgical treatments for ICH as determined by large phase III randomized trials. Surgical evacuation of the hematoma may be beneficial not only by decreasing mass effect and relieving increased pressure, but also perhaps by attenuating adverse inflammatory responses to the hematoma.³ Previous population-based studies and small randomized trials of surgery suggest that some patients may benefit from surgery following ICH.^{4–6}

In 2005, the first large phase III international randomized surgical trial, the Surgical Trial in Intracerebral Hemorrhage (STICH) was published.⁷ The STICH trial randomized 1033 patients with ICH to conservative medical management versus hematoma evacuation within 24 hours of randomization. The primary outcome measure was the Glasgow outcome scale (GOS) score at 6 months. No overall benefit from surgery was found when compared with initial conservative, medical management (26% versus 24% favorable outcome, $p=0.41$).⁷ However, in a subgroup analysis STICH patients with a hematoma within a centimeter of the cortical surface showed a benefit for early surgery, and a significant interaction was found between treatment assignment and depth of ICH.⁷ It therefore remains possible that a subset of patients with lobar ICH may benefit from early surgical treatment. The current American Heart Association (AHA) guidelines for management of ICH reflect this possibility with Class II recommendations for surgery as deemed necessary by care providers in patients with superficial lobar ICH.²

The STICH investigators have begun the Surgical Trial in Intracerebral Hemorrhage II (STICH II) study “to evaluate the role of early surgery in superficial supratentorial lobar haematomas without intraventricular haemorrhage.”⁸ STICH II is the largest ongoing randomized phase III clinical trial in ICH, with a planned enrollment of 600 patients. If the trial shows a benefit for surgery over initial medical management, this would become the only proven treatment for a carefully selected group of ICH patients. We sought to determine the impact such results might have on practice by estimating the number and characteristics of patients in a population-based ICH cohort who would meet the STICH II inclusion criteria.

Methods

This report analyzes data from a group of patients with ICH identified as part of the Genetic and Environmental Risk Factors for Hemorrhagic Stroke (GERFHS) study. The methodology of the GERFHS study has been previously described.⁹ Briefly, we attempted to identify all persons ≥ 18 years of age from the five-county Greater Cincinnati/Northern Kentucky (GCNK) area who were hospitalized with first-ever ICH between 1/01/05 and 12/31/05. Cases were identified by retrospective review of primary and secondary ICD-9 codes 430–438.9. Study nurses also maintained active surveillance (“hot pursuit”) at several hospitals that treat most ICH in the area by reviewing neurosurgery logs and patient rosters several times each week. All potential cases were abstracted by study nurses and confirmed by study physicians. Patients living outside the five counties, determined by zip code of residence, were excluded. Other exclusion criteria were previous ICH, traumatic ICH, hemorrhagic cerebral infarction, hemorrhage associated with brain tumor or encephalitis, and thrombolytic treatment of ischemic stroke. Patient demographics and clinical information were recorded by chart review. For all patients, the first available computed tomography (CT) or magnetic resonance (MR) scan was reviewed.

All hemorrhage volumes were measured by one of two reviewers (M.L.F or H.T.). The intraclass correlation for hemorrhage volume was tested for 31 scans and found to be 0.97 for the difference between the two reviewers. There was perfect agreement for the presence or absence of IVH when 31 scans were compared between reviewers. Hemorrhage volumes, presence of intraventricular hemorrhage (IVH), presence of hydrocephalus, hematoma location, hematoma distance from the cortical surface, and deep extension of hematoma were

recorded. Hemorrhage volumes were measured using the abc/2 method.¹⁰ Presence of IVH was defined as any amount of visible IVH per STICH II criteria.⁸ IVH was not included in volume calculations.

The STICH II criteria are presented in Table 1. For ease of interpretation all criteria are expressed as exclusion criteria (for instance, instead of using hematoma distance < 1 cm from the cortical surface as an inclusion criterion, hematoma distance > 1 cm from the cortical surface is considered an exclusion criterion). We considered hydrocephalus an exclusion criterion only if it was felt to be secondary to the hemorrhage; patients were not excluded for ex vacuo hydrocephalus due to cerebral atrophy. The STICH II criteria also require rapid correction of coagulopathy and ability to tolerate surgery within 12 hours of randomization. We were unable to make these determinations from our retrospective assessment. We assumed that all patients met these criteria. Finally, we approximated the exclusion criterion “severe pre-existing physical or mental disability” by using a baseline modified Rankin Scale (mRS) score > 3, which entails a minimum of moderately severe disability, inability to ambulate, and inability to attend to bodily needs without assistance.¹¹

Patient mortality was assessed by querying GERFHS study records and the Social Security Death Index. Separate survival curves for STICH II eligible and ineligible lobar ICH patients from our population were created using actuarial methods. A log-rank test was used to compare mortality between eligible and ineligible lobar ICH patients. For other comparisons between groups, a t-test was used for age, a chi-square test for gender, and Fisher’s exact test for race. GCS was considered an ordinal variable and was compared using Wilcoxon two sample test. ICH volumes were log transformed to approximate normality and compared using a t-test.

Results

During 2005, 286 ICH patients were identified (103 lobar, 126 deep cerebral, 23 brainstem, 28 cerebellar and 6 IVH). The 183 patients with non-lobar hemorrhages would not have been eligible for STICH II. Of the 103 lobar cases, 22 (21.4% of lobar cases, 7.7% of all ICH cases) would have met STICH II eligibility criteria, although this number included seven patients on warfarin who were assumed to meet the study criterion requiring correction of coagulopathy prior to surgery. A total of 23 out of 103 (22%) lobar ICH patients were on warfarin. For the 81 patients with lobar ICH who would have been excluded from STICH II, the most common (not mutually exclusive) reasons for exclusion were volume < 10cc or > 100cc (n=46) and presence of IVH (n=27). Counts for all exclusion categories are shown in Table 1.

A comparison of baseline characteristics between STICH II eligible and ineligible lobar ICH patients is presented in Table 2. No significant age, gender, or racial differences existed between the groups. Among all patients (including non-lobar ICH), 26 (9.1%) had surgery. One of 22 (4.5%) STICH II eligible lobar ICH patients had surgery in our population compared with 8 of 81 (9.9%) ineligible lobar ICH patients (p=0.43). Survival curves are presented in the Figure. Among lobar ICH patients, STICH II eligible patients had a 30-day mortality of 13.6% compared with 37% for ineligible patients (p=0.05); 180-day mortality for eligible patients was 36% compared with 49% for ineligible lobar ICH patients (p=0.19). STICH II eligible lobar ICH patients showed a trend towards lower 180-day mortality (p=0.09) than non-lobar ICH patients, while ineligible lobar ICH patients showed similar mortality to non-lobar patients (p=0.40) (Figure).

Discussion

In this population-based ICH cohort, only 7.7% of patients qualified for the STICH II study. With an estimated 67,000 patients with ICH in the United States annually,¹ approximately

5,000 ICH patients may be STICH II eligible. It is important to note that for STICH II, as for STICH I, eligible patients are only enrolled in cases of clinical equipoise for surgery versus medical management. Patients judged to be at imminent risk of herniation and death are often operated upon and would not be enrolled in these trials. Only 1 out of 22 (4.5%) STICH II eligible patients were operated upon in our community compared with 25 of 264 (9.5%) of ineligible lobar and non-lobar ICH patients. If surgery were performed on all STICH II eligible patients, the frequency of surgery for all ICH patients would have increased from 9.1% to 16% in our population. The most common reasons for STICH II exclusion among lobar ICH patients in our cohort were volume < 10cc or > 100cc and presence of IVH. Mortality at 30-days was lower in eligible lobar ICH patients compared with ineligible patients ($p=0.05$), likely because of exclusion of known predictors of poor outcome such as IVH and massive (> 100cc) hemorrhages. The STICH II trial is powered to show a 12% absolute increase in favorable outcomes at 6 months in surgically treated patients compared to medically treated patients.⁸ With an expected increase in favorable outcome rate from 37% with medical management to 49% with surgery,⁸ our data suggest this magnitude of benefit would prevent death and severe disability in approximately 600 patients annually in the United States. Our findings indicate that most ICH patients would not be operated upon by STICH II criteria and that other treatment options need to be aggressively sought for the majority of ICH patients.

Potential areas of investigation include better determination of patients who may benefit from early hemostatic therapy, surgery, or a combination of these approaches. Recombinant activated factor VII (rFVIIa) is a hemostatic agent that reduces early hemorrhage growth when administered to subjects with hyper-acute ICH.¹² Clinical outcomes were improved among patients treated with rFVIIa in a phase IIb study but not in a phase III trial.^{12,13} Inclusion of patients with known predictors of poor outcome such as large hemorrhages, presence of IVH and older age may have limited assessment of potential benefit of rFVIIa in the phase III trial.¹³ Two recent reports have identified the “spot sign” on early neuroimaging as predictive of hemorrhage growth.^{14,15} Early CT angiography to determine the presence or absence of a spot sign may better define patients at risk for hemorrhage growth who thus may benefit from rFVIIa therapy. Patients with a negative spot sign on early CT angiography may be less likely to have bleeding complications associated with early surgery⁵ and may warrant further study for potential surgical benefit. Small studies have reported improved outcomes in patients who had stereotactically evacuated hemorrhages^{16,17} and the Minimally Invasive Surgery Plus rtPA for Intracerebral Hemorrhage Evacuation (MISTIE) study is ongoing.¹⁸ Since early surgery has been associated with increased bleeding,⁵ hemorrhage stabilization must be attained prior to surgery in the MISTIE trial. A future trial may consider administration of rFVIIa to achieve hemorrhage stabilization prior to stereotactic evacuation of the hemorrhage. Unfortunately, any of these potential studies are years from directly impacting clinical care of ICH patients.

Our study has several limitations. Given its retrospective nature, we were unable to reliably assess some of the STICH II criteria. We could not determine how many patients may have been unable to tolerate surgery within 12 hours of randomization. We also did not specifically assess difficulties correcting coagulopathy before surgery. With an estimated 20% of spontaneous ICH now associated with anticoagulants¹⁹ and 22% of lobar ICH patients on warfarin in our study, we may have overestimated the proportion of ICH patients eligible for STICH II in our population. Finally, our urban population was representative of the United States’ population in 1993–94,¹ but with increasing Hispanic race/ethnicity in the 2000 United States census,²⁰ the 2005 data on our primarily biracial population presented in this study may not be representative of the United States’ population. Nonetheless, our population-based findings provide guidance with respect to the potential impact of the STICH II trial and of future studies on the subject.

Summary

ICH remains a devastating disease with high mortality and morbidity. STICH II has a planned enrollment time of 30 months and is the only ongoing ICH trial that may have an immediate impact on clinical practice. If STICH II favors surgery, our study demonstrates that a low proportion of ICH patients will be eligible for surgery based on the inclusion/exclusion criteria. Thus, other innovative clinical trials to find effective treatments for ICH are warranted.

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Figure.
Survival Curves for STICH II Eligible and Ineligible Lobar, and Non-Lobar ICH Patients

Table 1

Application of STICH II Criteria to GERFHS Study Lobar ICH Patients from 2005

Exclusion Criterion*	Number (%)
>1cm from cortex	18 (17.5)
Volume <10cc >100cc Total	27 (26.2) 19(18.4) 46 (44.7)
ICH from structural causes (aneurysm, AVM, cavernoma)	12 (11.7)
Presence of IVH	27 (26.2)
Hydrocephalus	17 (16.5)
Deep extension	20 (19.4)
Baseline mRS > 3	11 (10.7)
Motor score on GCS<5 or Eye score on GCS<2	19 (18.4)
Onset to CT scan > 48hrs	14 (13.6)
Total Excluded Lobar ICH Patients	81 (78.6)

STICH = Surgical Trial in Intracerebral Hemorrhage

GERFHS = Genetic and Environmental Risk Factors for Hemorrhagic Stroke

*
Exclusion criteria are not mutually exclusive

Table 2

Comparison of STICH II Eligible and Ineligible Lobar ICH Patients from the GERFHS Study, 2005

	Lobar Eligible	Lobar Ineligible	p value
N	22	81	
Age, mean (SD)	70.8 (16.4)	67.3 (16.8)	0.39
White Race (%)	18 (81.8)	70 (86.4)	0.73
Male Gender (%)	9 (40.9)	36 (44.4)	0.77
GCS, median (range)	14 (10–15)	13 (3–15)	0.09
ICH volume, mean $\pm$ SD	28.5 $\pm$ 1.8	19.3 $\pm$ 7.2	0.12
30-day mortality (%)	3 (13.6)	30 (37.0)	0.05
180-day mortality (%)	8 (36.4)	40 (49.4)	0.19

STICH = Surgical Trial in Intracerebral Hemorrhage

GERFHS = Genetic and Environmental Risk Factors for Hemorrhagic Stroke