Surgery in Intracerebral Hemorrhage
The Uncertainty Continues

H.M. Fernandes, FRCS; B. Gregson, PhD; S. Siddique, FRCS; A.D. Mendelow, PhD

Background and Purpose—Primary intracerebral hemorrhage (ICH) accounts for 10% to 20% of stroke but carries the highest rates of mortality and morbidity of all stroke subtypes. Current treatment, however, is varied and haphazard. The most recent Cochrane systematic review refers to 4 prospective, randomized controlled trials. We present a further meta-analysis to include 3 new trials. In addition, we review the trials of Chen et al and McKissock et al and discuss aspects of their quality that, we believe, prevent their inclusion in modern day meta-analysis.

Methods—Literature databases and articles were searched from 1966 to October 1999. Using the end points of death and dependency, the results of the 7 identified randomized trials were expressed as odds ratios. All available data were then analyzed with meta-analysis techniques. Analysis of relevant subsets of trials was also carried out.

Results—Meta-analysis of all 7 trials shows a trend toward a higher chance of death and dependency after surgery (OR 1.20; 95% CI 0.83 to 1.74). Meta-analysis was also carried out after exclusion of the Chen and McKissock trials for reasons discussed in the text. This meta-analysis suggests a benefit from surgery, with a reduction in the chances of death and dependency after surgical treatment by a factor of 0.63 (OR 0.63; 95% CI 0.35 to 1.14).

Conclusions—When meta-analysis is restricted to modern-day, post-CT, well-constructed, balanced trials, a trend for surgery to reduce the chances of death and dependency is found. Perhaps, then, in the modern era of CT, good neuroanesthesia, intensive care, and the operating microscope, surgery has a role in the treatment of supratentorial intracerebral hemorrhage. The results of a large, multicenter, randomized controlled trial are urgently needed, and the ongoing International Surgical Trial of Intracerebral Hemorrhage should fulfill this objective. (Stroke. 2000;31:2511-2516.)

Key Words: intracerebral hemorrhage | meta-analysis | surgery

Stroke remains a major cause of mortality and disability worldwide. Primary intracerebral hemorrhage (ICH; ie, ICH unrelated to aneurysm, arteriovenous malformation, trauma, or tumor) accounts for 10% to 20% of these episodes, but of all stroke subtypes carries the highest mortality and morbidity rate. It is also the most common type of stroke in the younger patient (aged ≤50 years). Despite this, there is no clear indication from the literature of the optimal treatment of these patients, surgical or otherwise. Current clinical practice seems varied and haphazard. Proper evaluation of the role of surgery following spontaneous ICH should be undertaken in the format of a prospective randomized controlled trial. Indeed, several investigators have emphasized the need for this as a matter of urgency. There are currently 7 published randomized trials that have studied the surgical evacuation of spontaneous ICH. The first, carried out in 1961 by McKissock et al, shows no benefit from surgical evacuation of hematoma and has had a strong influence on neurosurgical practice, even to the present day. This is the largest trial carried out to date. Trials by Juvela et al in 1989 and Batjer et al in 1990 were too small to be conclusive. A single trial by Auer et al published in 1989 found a significant benefit from endoscopic evacuation of ICH. The only trial to conclude that surgery is beneficial, it included 100 patients, 50 randomized to surgery. The results of 2 further small trials have subsequently been published. Our search of the literature also identified a trial of Chinese origin published by Chen et al in 1992. This has been identified by others but to date has not been included in any meta-analysis. A further randomized trial, recently finished in the Netherlands, evaluates the role of thrombolytic evacuation of ICH (Dr G. Blauw, unpublished data, 1999). Meta-analyses of the first 4 trials are available. We present a further meta-analysis to include the 3 new trials and discuss previously unrecognized information that may render previous meta-analyses invalid.

Subjects and Methods
MEDLINE and OVID databases were searched from 1966 to October 1999, using the medical subject heading terms “intracerebral hemorrhage,” “brain hemorrhage,” and “intracerebral hemorrhage and surgery.” Reference lists of all the articles identified were examined, and relevant cited references were similarly reviewed.
Although many nonrandomized studies were identified, they have been previously reviewed.6 Those previously identified randomized controlled trials were selected alongside 3 newly identified references. The inclusion/exclusion criteria of all 7 trials were studied alongside the diagnostic modalities used, the method of randomization, treatment methods, and the method of obtaining and classifying outcome. Using the end points of death and dependency, the results of the 7 identified trials were expressed as odds ratios with their associated 95% confidence intervals. All available data were then combined to be analyzed as a whole by using the well-established meta-analysis methods.17,18 Further analyses of relevant subsets of the identified trials were also carried out when it became clear on careful inspection of trial data that they may not be particularly homogenous.

### Results

An elegant description of the relevant details of the previously meta-analyzed trials is already available6 and will not be repeated here. All identified trials, however, are presented in Table 1. The first randomized controlled trial carried out by McKissock et al in 1961, however, deserves special mention. In this study, 180 patients from a series of 303 patients in 2 central London hospitals were randomized. Clinical examination, lumbar puncture, and cerebral angiography established the diagnosis of ICH (this trial was carried out in the era preceding CT), but patients were excluded from the trial if they had rapidly improving signs or if an aneurysm, arteriovenous malformation, or occluded cerebral vessel was demonstrated on angiography. In addition, patients were excluded where the hemorrhage was infratentorial or when the diagnosis was uncertain and a tumor or abscess could not be excluded. It is obvious, however, that without the diagnostic ability of CT, despite the best efforts of the authors,
patients without a spontaneous ICH could have been random-ized into the trial. Misdiagnosis was, in fact, recognized in 4 patients in the surgical group. Two patients were found to have negative ventriculograms, and in another 2 the ICH was actually found to be cerebellar in origin. Known errors were also made in 5 of the medically treated patients. In 1 an aneurysm was found at postmortem examination, in 2 a delayed air study was negative, another patient was shown to have massive infarction, and in the fifth a tumor was found to be the cause of hemorrhage. Overall this gives a known diagnostic error rate of 5%. Of further interest, and not previously discussed, is the postrandomization selection of patients for surgical treatment. Patients, once randomized, underwent craniotomy and evacuated of hematoma as soon as the hematoma could be localized. Localization, it is said in the article, was possible in 60% of cases; in others, ventriculography was performed, and craniotomy was carried out if the lesion was accessible. In cases in which the hematoma was confined to the basal ganglia and thalamus, craniotomy was not performed (but such patients, nevertheless, quite correctly remained in the operative group). It is not clear from the article what proportion of the patients randomized to surgery actually received the allocated treatment, but this trial was clearly primarily a study of the surgical treatment of lobar hemorrhage. Perhaps a significant proportion of patients randomized to surgery did not actually receive their allocated treatment. While this may have been a reasonable process in the 1960s, it does bring to question the validity of the inclusion of these data in modern day meta-analysis for other than the pre-CT diagnostic problems. Overall, however, the results of this trial show a significant trend toward a higher chance of death or dependency with surgery (OR 2.00; 95% CI 1.04 to 3.86). The next 3 trials, those of Auer et al, Juvela et al, and Batjer et al, are all carried out in the CT era and include patients with basal ganglia and thalamic hematomas that are surgically treated. ORs are shown in the Table.

An additional trial from the United States has recently been published. Morgenstern et al randomized 35 patients between surgery (craniotomy) and best medical treatment in a single center out of a group of 76 eligible patients. Patients were eligible if they presented within 3 hours of ictus (surgery was carried out within 12 hours of ictus) with an ICH, as shown on CT scan, of >9 mL that was lobar or deep in location and extended outside the thalamus. The Glasgow Coma Scale (GCS) score had to be between 5 and 15. Patients with a hematoma volume 10 to 19 mL and a GCS of 15 and better-than-antigravity strength on the affected side were excluded, as were patients with extensive intraventricular hemorrhage. Randomization was performed with the sealed envelope technique. In addition to the randomization treatment, all patients who presented with a GCS 9 or below underwent placement of an intracranial pressure (ICP) monitor and were treated with ventricular drainage, osmotic agents, hyperventilation, and paralytic to maintain the ICP below 21 cm H₂O. Follow-up was performed at 30 days and at 6 months (mortality and Barthel score). No mention is made of how this information was obtained and whether it was obtained in a blinded fashion. Randomization groups were balanced for ICH volume and GCS. The surgical group was significantly more likely to have presented earlier after ictus and had fewer lobar hematomas. Mortality was lower in the surgical group (6%) than the medical group (24%) at 1 month but similar between groups at 6 months. Barthel Index scores were similar for the survivors. The results of this trial show a trend toward a lower chance of death or dependency with surgery, although the 95% CI does cross unity (OR 0.46; 95% CI 0.11 to 1.88).

A randomized trial published in 1992 in the Acta Academicae Medicinae Shanghai, a Chinese journal, was identified. Translation from the native Chinese was necessary. From the translation we learn that Chen et al recruited 127 patients with a spontaneous intracerebral hemorrhage as diagnosed by CT scan between 1986 and 1990. Patients were excluded if they required an emergency operation for herniation or showed “bad compliance” with the study. No further information is available on the latter part of this statement. Medical patients received therapy to control hypertension and decrease ICP. Patients assigned to surgery underwent stereotaxically guided hematoma clearance, craniectomy, or ventricular drainage. Patients were followed up at 1 and 3 months and graded on a 5-point scale: dead, poor, fair, good, and excellent. No indication is given of how this information was obtained. Sixty-four patients were randomized to surgery and 63 to medical treatment. The groups appear similar in terms of sex, age, and history of hypertension but differ significantly in level of consciousness (P<0.001), the size of the hematoma (P<0.001), and the presence of hemiplegia (P<0.01). Cerebellar hematomas, in addition, have been included. At 1 month the medical group is reported to have a statistically significantly higher rate of excellent outcomes (P<0.05), but no differences between the groups are reported at 3 months. The results of this trial show a trend toward a higher chance of death or dependency (assuming that “poor” and “fair” indicate dependency) with surgery, although the 95% CI again crosses unity (OR 1.66; 95% CI 0.82 to 3.34).

A further randomized trial has recently been published. In this feasibility study, 20 patients were randomized in a 24-month period, 9 to surgical intervention and 11 to medical treatment. Patients were eligible if they presented within 24 hours with a hematoma at least 10 mL in volume, had a GCS over 4, were at least 18 years of age, and had a neurological deficit secondary to their hemorrhage. Randomization was carried out with sealed opaque envelopes. Surgical technique was guided by that most appropriate to the hematoma and included craniotomy and stereotaxic aspiration. Medical treatment included mannitol, ventricular drainage, intubation if necessary, and hyperventilation if the ICP remained >20 mm Hg despite these other methods. Outcome was measured both at the time of discharge and at 3 months, with the Glasgow Outcome Scale (GOS) score as the major end point. Other measures included the modified Rankin scale, mortality, the Barthel Index, and the National Institute of Health Stroke Severity (NIHSS) index. A nurse coordinator not involved in the treatment of patients performed the outcome evaluation. The surgical and medical groups were comparable with respect to baseline characteristics, GCS, median time from ictus to randomization, and ICH volume. There was no difference in mortality between the groups at 3

Fernandes et al Surgery in Intracerebral Hemorrhage 2513
months (surgical group 22%, medical 27%). Similarly, there was no significant difference in mortality at 3 months. Analysis, however, of the other outcome measures showed a nonsignificant trend toward a better outcome in the surgical group versus the medical treatment group for median GOS, Barthel Index, and Rankin scale scores and a significant difference in the NIHSS (4 versus 14, \( P = 0.04 \)). The ORs of this trial indicate a tendency toward better outcome with surgery, although the 95% CIs are wide (OR 0.48; 95% CI 0.09 to 2.69).

Systematic Overview
Previous meta-analyses of pooled results of the first 4 trials totaling a group of 349 patients (173 patients randomized to surgical treatment) indicate a nonsignificant increase in the odds of death and dependency at 6 months for patients treated surgically (OR 1.23; 95% CI 0.77 to 1.98). A further previous meta-analysis looking at the end point of death only found a statistically significant beneficial effect for surgery for analysis of trials from the CT era only (to exclude the study of McKissock et al). The odds of death were reduced with surgery by a factor of one half (OR 0.50; 95% CI 0.38 to 1.44). With the data from the 3 new trials, we chose to perform a meta-analysis in several different ways, based on the quality and content of the various trials. Some difficulty in comparing data from these 7 trials arises because the investigators have used different measures to assess outcome and it is not clear whether they provide equivalent assessments of the patients disability. We have defined the following categories as disabled: in McKissock et al, the total disability group, ie, “patients incapable of taking care of themselves”; in Auer et al, those “conscious patients totally dependent on others for activities of the day”; in Batjer et al, those “dependent at home or in an institution”; in Chen et al, those with a “fair” or “poor” outcome; in Morgenstern et al, those with a Barthel score of \( \leq 60 \); and in Juvela et al and Zuccarello et al, those with a GOS value of “severely disabled.”

Meta-analysis of all 7 trials to include that of McKissock et al again shows a trend toward a higher chance of death and dependency after surgery (OR 1.20; 95% CI 0.83 to 1.74; Figure 1). We have included patients randomized to a third treatment arm of best medical management plus ICP monitoring by Batjer et al within this analysis. They have been excluded from the control group in meta-analysis by previous authors, but this was recently amended in a revision of
the Cochrane Stroke Systematic Review. Analysis of all trials excluding the McKissock trial, however, showed no real influence of either treatment, surgical or medical, with an OR of 0.94 (95% CI 0.60 to 1.47; Figure 2).

Meta-analysis was also carried out of the 5 trials from the post-CT era to exclude the trial available from China. The trial of Chen et al presents some methodological difficulty, given that we are relying on a translation of the published paper, with no information from the unit directly. This translation suggests some marked differences in the characteristics of operated and nonoperated patients and the inclusion of cerebellar hematomas alongside supratentorial bleeds. Surgical treatment may also have included ventricular drainage for hydrocephalus only. The results of this meta-analysis actually suggest some benefit from surgery, with a reduction in the chances of death and dependency after surgical treatment by a factor of 0.63 (OR 0.63; 95% CI 0.35 to 1.14; Figure 3).

Discussion

Correct meta-analysis requires the possession of all the relevant studies. Invariably, a simple literature search is not enough, and on the basis of this we have been able to identify 1 previously unrecognized trial. In addition, as further studies are completed, formal repetition of the meta-analysis is imperative if we are to maintain our knowledge and offer our patients validated and proven treatments as soon as they are available.

Further study of the McKissock trial has identified flaws that differentiate it from the high standards of modern-day trial practice. We believe that these flaws should exclude it from modern-day systematic reviews. This is by no means a condemnation of the trial, which in its era was elegant, forward thinking, and well constructed, but a realization that as the diagnosis and treatment of any condition changes in time so does the relevance of studies carried out before that era. Thus, the meta-analysis reported here is carried out with and without the McKissock trial. Criticism can also be levied at the Chen trial.

Although previous studies have evaluated the surgical effects of open craniotomy and endoscopy separately, we do not feel that this is a useful or relevant separation. From information collected from neurosurgeons in the United Kingdom, it would appear that many surgeons use differing methods of evacuation but endoscopic surgery per se is not common. Although eventually it may be important to study the relevant benefits of differing surgical methods, we feel that the overriding question at present is, Does surgery help? Perhaps if this can be shown, further work to establish what type of surgery is best will be more relevant.

We find it interesting that when meta-analysis is restricted to modern-day, post-CT, well-constructed, balanced trials, a trend for surgery to reduce the chances of death and dependency is found. This finding is in concurrence with a previous meta-analysis from which McKissock’s trial was excluded which found a trend toward improved mortality (OR 0.50; 95% CI 0.28 to 0.92) and death and dependency (OR 0.72; 95% CI 0.38 to 1.44) with surgery. This meta-analysis pooled data from the studies of Juvela et al, Auer et al, and Batjer et al only.

Perhaps, then, in the modern era of CT, good neuroanesthesia, intensive care, and the operating microscope, surgery is beginning to find a therapeutic role in the treatment of supratentorial intracerebral hemorrhage. Further trials, however, are badly and urgently needed. We are therefore pleased to report the ongoing International Surgical Trial in Intracerebral Haemorrhage (ISTICH), a multicenter, randomized controlled trial designed to evaluate the role of surgery after spontaneous supratentorial ICH. This trial is coordinated from our center in Newcastle-on-Tyne but involves 86 centers worldwide and at the time of writing had randomized 400 patients. We are encouraging new centers.

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References


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