Update on management of intracerebral hemorrhage

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Intracerebral hemorrhage (ICH) is a lingering cause of significant mortality and morbidity rates in contemporary society. Despite its established burden, considerably less investigative attention has been devoted to the study of ICH than other forms of stroke. Only a limited number of clinical studies have been performed to examine the surgical (both craniotomy and minimally invasive) and medical management of patients with ICH. No consistently efficacious strategies have been identified through such investigations. Limitations in study design and execution have universally impaired the interpretation and impact of available data. Management of ICH unfortunately remains heterogeneous across institutions, and it continues to suffer from the lack of proven medical and surgical effectiveness. Urgently needed are further prospective randomized controlled trials in which investigators consider the shortcomings of previous endeavors in the management of ICH. In the present article the authors review the current management practices of ICH, discuss the controlled trials, and highlight recent trials and future avenues of further study.

KEY WORDS • intracerebral hemorrhage • medical management • surgical management • clinical trial

The management of ICH remains an enigma. Despite its relatively high incidence (15–35 per 100,000 persons)^{2,8,9} and its poor associated outcomes (30–40% 30-day mortality rate),^{2,9,10,12,14} neither medical nor surgical intervention has been shown consistently to improve survival or QOL significantly. Limited success in establishing efficacious therapies is due, in part, to the limited quantity and quality of clinical studies. This paucity of quality data has left current management recommendations largely based on theory and clinicians attempting to modify factors that have been associated with poor outcomes. In this report, we review the current management of ICH, discuss related controlled trials, and highlight recent trials and new theories that await investigation in ICH management.

Considerable attention has been directed toward identifying predictive factors of poor outcome. The potentially modifiable factors have been of particular interest in developing treatments for ICH, despite the fact that these factors have only been associated with rather than proven

to cause poor outcomes. Several factors that have been associated with poor outcome include volume of the hematoma, neurological status (GCS score⁴¹) on admission, intraventricular extension of the clot and/or hydrocephalus, subarachnoid extension, anticoagulation agents, and relative edema.^{6,7,12,13,15,18,28,38,40} Of these, the most tangible factor on which to base therapeutic intervention is the volume of the hematoma. A reduction in hematoma volume theoretically decreases mass effect, lessens ICP, and limits the potential stimulus for edema formation and cell death.^{1,43–45} Raised ICP is also treated when appropriate. Although not clearly established as an independent predictor of poor outcome, it is postulated to have direct adverse effects on cerebral tissue but also interacts with other prognostic factors. For example, raised ICP impairs the resolution of vasogenic edema following experimental ICH.²⁰ Hence, theoretical therapeutic targets emerge from the analysis of potentially modifiable predictors of poor outcome. As will be discussed, however, it is not clear whether post hoc modification of these factors is beneficial.

The methods for managing ICH are broadly divided into two categories: medical and surgical interventions. Medical management includes cardiopulmonary optimization and blood pressure control, ICP reduction (using,

Abbreviations used in this paper: GCS = Glasgow Coma Scale; ICH = intracerebral hemorrhage; ICP = intracranial pressure; QOL = quality of life.

for example, patient positioning, hyperosmolar fluids, hyperventilation, and barbiturate coma), general medical management (including careful glucose management³⁹), and reversing coagulation defects. Surgical management has included craniotomy, stereotactic clot lysis and/or aspiration, endoscopic lysis and/or aspiration, ventriculostomy, and decompressive craniectomies or combinations thereof. Unfortunately, the division between “medical” and “surgical” management is artificial, grouping diverse methodologies together, each of which has a distinct profile of risks and benefits, making it difficult to assess the advantage of any single intervention.

This difficulty is highlighted by a randomized trial conducted by Chen and colleagues¹¹ in which surgery (craniotomy, stereotactic clot evacuation, craniectomy, and ventricular drainage) was compared with medical management. Although after 1 month the patients in the medical treatment group had experienced relatively superior outcomes, this difference was not maintained at 3 months. The grouping of all surgical techniques into one category adds several uncontrolled factors into the assessment, thereby reducing the study’s power to identify a difference, if present, and consequently making the results difficult to interpret. Therefore, in this review we subdivide surgical management by type of intervention and discuss the controlled trials involving each of these techniques separately.

CURRENT MANAGEMENT OF ICH

Despite the lack of evidence suggesting the appropriateness of specific therapies, most neurosurgeons agree on initial medical management. Most importantly, initial management should address the ABCs (airway, breathing, and circulation). In addition, reversible causes of active bleeding should be corrected, including coagulopathies and platelet disorders, by administration of fresh-frozen plasma, vitamin K, and platelets. Because of the critical nature of ICH at presentation, patients are generally admitted to a neurological intensive care unit to undergo blood pressure control measures and close monitoring for neurological deterioration.

Blood pressure control is of paramount importance in patients with ICH. Uncontrolled hypertension is a leading cause of ICH and continued elevated blood pressure after the hemorrhagic event is associated with poorer outcomes.^{16,33,35,37} Despite this association, it is not always clear whether high blood pressures observed immediately after ICH are the cause or result of ICH (an increase in ICP may provoke an increase in blood pressure to maintain cerebral perfusion). Consequently, there is some concern regarding excessive blood pressure reduction in the setting of ICH.^{26,36} Numerous authors have shown, however, that the cerebral vasculature tolerates blood pressure reduction well (by using autoregulation) and does not put the brain at increased risk of ischemia.^{34,36} At our institution, systolic values of less than 160 mm Hg are the aim for modest reductions in blood pressure, and we always tailor the therapy to each patient. The intravenous antihypertensive agents labetalol and nicardipine are preferred for titrating blood pressures; nitroprusside may cause increased cerebral pressure (by acting directly on the cerebral vasculature) and is therefore not often used.

In addition to blood pressure control, neurological status must be monitored closely for signs of deterioration that might indicate possible hematoma expansion. In comatose patients in whom neurological status is severely impaired at baseline (GCS score < 9), ICP monitoring, with the aid of either a fiberoptic intraparenchymal monitor or ventriculostomy, may be considered. The advantage of the ventriculostomy is that it can also be used as a therapeutic means of reducing ICP. Other ICP reduction strategies include keeping the head-of-bed elevated at 30° with the patient’s neck in a neutral position to maximize venous outflow; minimizing the patient’s agitation (including the use of sedatives as needed); hyperventilation (which reduces cerebral blood flow, but should only be used as a temporary measure); hyperosmolar therapies (including mannitol and hypertonic saline, to reduce intracranial water content); and, rarely, barbiturate-induced comas. The administration of corticosteroid agents in patients with ICH remains controversial. Our preference has been to use them in certain circumstances—specifically when there is evidence of large amounts of vasogenic edema and mass effect.

After using these parameters to optimize medical management, further intervention is determined by the clinician. At our institution, all clinical, pathological, and radiological data are considered in conjunction with frank discussion involving a patient’s family; we highlight management options, potential risks and benefits, and realistic expectations. The decision to intervene further is individualized by considering the aforementioned factors in addition to the patient’s preictal wishes, if known. Significant consideration for surgical intervention is given in cases involving younger patients (that is, those < 60 years of age) with superficial hemorrhages (particularly in the non-dominant hemisphere) in whom neurological status deteriorates after an initially good presentation. The unequivocal surgery and guidelines for intervention are unclear because the results reported in the majority of randomized trials have been inconclusive. We briefly review these trials and discuss the questions that future studies will need to address.

RANDOMIZED TRIALS

Craniotomy in ICH Treatment

The most widely used surgical intervention in ICH is craniotomy and evacuation of the gross clot. This is a relatively invasive procedure associated with additional risks by subjecting patients to surgery, potential brain manipulation, and anesthesia. McKissock, et al.,³⁰ published the first investigation of the possible benefits of surgery over the best available medical management. They studied 180 patients (89 assigned to surgery and 91 to medical management) in the pre-computerized tomography scanning era, relying on clinical examination, lumbar puncture, and angiography to establish the diagnosis. They found that surgery was associated with an increased chance of death or dependence, relative to the best medical management (odds ratio 2; 95% confidence interval 1.04–3.86). Although their study had several identifiable shortcomings and faults (for example, extended time to surgery and non-radiographic assessment of ICH), it set the stage for a

series of other studies, all of which failed to demonstrate an advantage of craniotomy over medical treatment.

Juvela and colleagues²² also studied spontaneous supratentorial ICHs, randomly assigning 26 patients each to craniotomy and medical management groups. Their series differed from that reported by McKissock, et al.,³⁰ in two important ways: 1) computerized tomography scanning was performed to confirm ICH; and 2) only patients with severe neurological deficits or depressed level of consciousness were entered into the study. Despite these differences in study design, the authors did not find a significant difference in outcomes. In the surgery-treated group, 46% died and 50% were dependent, whereas in the medical group 38% died and 42% became dependent. Although this study was intended to be a randomized controlled study, status in the two groups was significantly different at baseline, with respect to admission GCS score, size of hematoma, and frequency of intraventricular hemorrhage (all factors that have been shown to be independent predictors of prognosis), making further interpretation difficult.

In another study, in which they specifically examined putaminal ICH, Batjer and colleagues⁴ randomly assigned patients to one of three groups: best medical management (nine patients), ICP monitoring (four patients), and craniotomy (eight patients). Inclusion criteria mandated that the hematoma be greater than 3 cm in largest diameter. Similar to the previous two studies, these authors found no statistically significant difference in mortality and morbidity (dependence) across groups. These results, however, are limited because the number of patients enrolled was prohibitively small, which significantly reduces its power to detect differences. The study was terminated because, according to the authors, "... it became obvious that outcome in each treatment group was unacceptably poor."

Morgenstern and colleagues³² also compared craniotomy with best medical management in a randomized study of ICH. Their inclusion criteria necessitated that the ICH be nontraumatic, greater than 9 ml in volume, be associated with significant neurological impairment, and have occurred fewer than 12 hours before surgery. The investigators included 34 patients (which may have also been too few to detect small differences). Unlike prior studies, however, the authors required that craniotomy be performed within 12 hours of symptom onset. Despite these differences, the 1- and 6-month mortality rates were 6 and 24% in the surgery group and 17 and 24% in the medical group, respectively (not statistically significant). Using Kaplan-Meier methods, however, the authors were able to identify nonsignificant trends toward improved survival in the surgery-treated group. No significant intergroup differences in morbidity rates were reported either. The lack of significant intergroup differences may have been due to the small number of individuals enrolled in the study, as discussed by the authors. Unfortunately, once again, the two groups were not well matched, especially with respect to ICH location, making the results difficult to interpret.

Most recently, Tan and colleagues⁴⁰ studied basal ganglia ICH in a randomized fashion. Unlike previous studies, the authors matched the two groups with respect to initial hematoma volume and GCS scores (the two major predictors of ICH outcomes) and used a blinded observer

to measure outcomes. The authors did not, however, require that surgery be undertaken in a timely manner; in some cases, patients underwent surgery 48 hours after symptom onset. Despite these controls, the authors still found no difference in outcomes between the groups at 3, 6, or 12 months, as measured using the modified Barthel Index. These data suggest that craniotomy and gross clot evacuation may not offer a significant advantage over medical management, at least in cases in which surgery was not performed in a timely manner. The importance of timing of surgery will be further discussed.

No randomized study to date has demonstrated the superiority of medical management or craniotomy/hematoma evacuation. The unanimity of these studies is a compelling argument against craniotomy and clot removal. Although reducing clot size and thereby reducing ICP and removing the irritating intraparenchymal hematoma should theoretically benefit the patient, no investigators of randomized controlled studies have been able to demonstrate this benefit. Failure to show this benefit may arise from several possibilities, including delayed and untimely clot evacuation, the risks and added stress of surgery outweighing the theoretical benefits of clot evacuation, or a true lack of benefit of clot removal once a hematoma has already expanded within the parenchyma.

Although these studies are randomized, shortcomings limit their reliability. Most importantly, most studies suffered from heterogeneity between comparison groups and small numbers of individuals. Another limitation of most of these studies is that all supratentorial ICHs were considered a single disease entity. Although both putaminal and lobar ICHs represent blood within the brain parenchyma, it is conceivable and probable that the management of these hemorrhages is different, because of differences in origin, surgical accessibility, and functionality of the regions themselves. The grouping of distinct ICHs may have, in part, limited the power of some of these studies to detect differences. Ideally, each lesion/ICH location should be studied separately to determine the best management option since each represents a distinct disease process. These limitations argue for better-designed and controlled studies with larger populations, such as the ongoing Surgical Treatment of Intracerebral Hemorrhage trial,³² in which the aim is to randomize 1000 patients.

Although not randomized, a study by Kanaya and Kuroda²³ perhaps highlights the benefit and power of assessing a large number of patients with a single disease process (putaminal hemorrhages). The investigators retrospectively studied 7010 patients with putaminal hemorrhages; 3375 underwent surgery and 3635 underwent medical management. The authors found that patients who were alert and oriented, those with ICH limited to outside or within the internal capsule, and those with a hematoma volume of less than 10 ml were significantly less likely to die when treated medically and also experienced significantly better functional outcomes ($p < 0.001$ in all cases). Conversely, they found that in stuporous and comatose patients, in those with ICHs involving both the anterior and posterior limbs of the internal capsule or extending to the thalamus or subthalamus, and in those with a hematoma volume greater than 30 ml, surgery was associated with a decreased mortality rate ($p < 0.001$),

although functional outcomes were not significantly better. Although retrospective studies are plagued by selection bias (surgery-treated patients in this study were generally sicker), this study strongly suggested that better outcomes can be achieved in specific populations by applying specific management strategies.

Endoscopic Aspiration of ICH

Many neurosurgeons would argue that the failure to prove the supremacy of craniotomy/clot removal over medical management is due to the added stress of the craniotomy and brain manipulation and/or violation. Alternative surgical strategies have therefore been developed to evacuate clots without craniotomy. Endoscopic aspiration of the cerebral hematoma offers such an alternative.

Only one randomized study has been published in which authors compared endoscopic aspiration with medical management. Auer and colleagues³ reported on 100 patients, 50 of whom underwent burr hole, neuroendoscopic navigation, and aspiration of hematoma. Only patients harboring a supratentorial hematoma of greater than 10 ml were studied, excluding those with an identifiable vascular cause of hemorrhage (for example tumor, arteriovenous malformation, aneurysms). At 6 months, the mortality rate (42%) in the surgically-treated group was significantly lower than in the medically treated group (70%) ($p < 0.01$). Specifically, in patients with large-sized hematomas (> 50 ml), the mortality rate was found to be lower in the surgery-treated group despite the absence of significant change in QOL. In patients with smaller-sized hematomas (< 50 ml), quality of life was improved in the surgical group, but the mortality rate was unchanged. Notably, the benefit of surgery with respect to QOL was limited to patients with lobar hematomas and those younger than 60 years of age.

This aforementioned trial represents the only randomized trial to date to report a statistically significant benefit of one management option over another. This benefit may in fact be due to the reduced stress provided by this less invasive surgical procedure, with the persistent benefit of reducing clot volume. Their subanalysis indicating that the benefit was only seen in lobar hematomas emphasized a possible need to classify ICHs by locations of hematoma.

Stereotactic Aspiration and Clot Lysis

If the benefit reported in the endoscopic aspiration trial was indeed due to the minimally invasive nature of the intervention, then we may postulate a benefit of stereotactic aspiration as well. Teernstra and colleagues⁴² recently published the first randomized controlled study in which stereotactic aspiration with clot lysis was compared with medical management (the Stereotactic Treatment of Intracerebral Hematoma by Means of a Plasminogen Activator trial). In a multicenter trial the authors studied 71 patients, assigning 36 to surgical intervention within 72 hours and 35 to medical management. All patients were older than 45 years of age, harbored spontaneous supratentorial hemorrhages of greater than 10 ml, and had Glasgow Eye Motor scores between 2 and 10. Although the surgery-treated group harbored a statistically significant

reduced hematoma volume, there was no intergroup difference with respect to the primary end point of death at 6 months (56 and 59% in the surgery and medical treatment groups, respectively). The authors suggest that the reduced volume may suggest improved prognosis, but the data in the study does not support this conclusion.

The lack of benefit of stereotactic aspiration despite the documented benefit of endoscopic aspiration³ may have been masked by the 22% rebleeding rate in the surgical group, presumably at least partially associated with the use of urokinase.⁴² Moreover, the baseline profile data of the groups were dissimilar; in the surgical treatment group hematoma volumes were significantly larger than those in the medically managed patients, thereby introducing confounding variables. The results of these studies should be interpreted carefully. There may still be an advantage to minimally invasive intervention to reduce clot size. This advantage may have been masked by the deleterious effects of urokinase, calling into question the safety and benefit of clot lysis in ICH management; rebleeding rates were significantly higher in the surgery-treated group compared with the medical treatment group and historical controls from other clinical trials of ICH.

HEMOSTATIC THERAPY: FUTURE?

The goal of all surgical interventions to date is to reduce clot volume after the hematoma has already expanded. The lack of surgery-related benefit may suggest that clot evacuation after hematoma expansion is not beneficial. Recently, attention has been turned toward hemostatic therapy or therapies focusing on stimulation of the coagulation pathways. It has been a longstanding tenet of ICH management that reversible causes of bleeding need be attended immediately to control hematoma expansion. Hemostatic therapy, however, is intended to stimulate clotting in individuals in whom the coagulation cascade is otherwise normal, to modify the evolution of the hematoma.²⁹

In particular, much attention has been given to factor VIIa, which promotes local hemostasis at sites of vascular injury in patients with and without coagulopathies.^{17,19} No randomized trial has been reported in which this therapy was applied in patients with ICH. The possibility is exciting, however, because it is the first therapy to offer a truly new approach to treating ICH. Instead of merely removing the clot, hematoma expansion is actively inhibited. Although it is an extremely attractive theory, it should be emphasized that it offers only a theoretical advantage because hematoma volume and outcomes are associated, but not causatively related.

UNRESOLVED ISSUES IN ICH MANAGEMENT

The aforementioned studies provide no consensus regarding the superiority of any particular treatment. Further studies will have to be conducted to identify which interventions, if any, can improve outcomes. In addition to this, there are other issues regarding ICH management that remain unresolved in particular, deciding the most appropriate timing for intervention and which individuals will benefit most from intervention.

Timing of Intervention

In the case of spontaneous ICH, earlier interventions would intuitively appear superior. This presumption, however, has already been proven incorrect in relation to other neurovascular disease processes. In particular, in the case of aneurysms, despite evidence that the greatest risk of rerupture is in the first 48 hours after the initial event, the timing-of-surgery trials have indicated that earlier surgery was not necessarily associated with improved outcomes.²⁵ For a combination of reasons, however, early surgery has been adopted as the preferred contemporary management plan.

The benefit of early surgery in ICH was suggested by Morgenstern and colleagues³² in 1998, when they reported improved neurological function (although not significant) in patients treated within 12 hours of ICH. Kaneko and colleagues²⁴ also demonstrated superior outcomes (relative to epidemiological data) when they reported a 6-month 7% mortality rate in a series of patients with 100 putaminal ICHs treated surgically within 7 hours of ictus. Lee and colleagues²⁷ also showed a significant difference between patients surgically treated within 24 hours of ICH and those who underwent surgery later. Finally, Zucarello and colleagues⁴⁶ showed a trend toward improved outcomes (not significant) in the only randomized study in which there was an attempt to address this question. Despite the apparent advantage of early intervention, Morgenstern and colleagues³¹ showed that ultraearly surgery (that is, < 4 hours after ICH) is associated with increased rehemorrhage and mortality rates. The ideal timing of ICH intervention may therefore depend on characterizing the rehemorrhage rates of ICH at hourly intervals after initial ictus, among other factors. The ideal timing of surgery or interventions remains to be elucidated in a systematic study.⁴⁶

Who Benefits From Intervention?

The authors of at least one randomized study³ and other nonrandomized studies²³ have shown that patients of different ages respond differently to various therapies. The question therefore remains, should people of all ages be treated equally and with the same interventions? Further studies with adequate patient enrollment will have to be conducted to address the impact of age on recommended interventions in ICH.

CONCLUSIONS

Clearly, the appropriate management of ICH is undecided. To identify and deliver the best care, randomized prospective trials must be conducted. In such studies investigators need to separate ICH by location, match baseline characteristics of compared groups (especially presenting hematoma volume and GCS score), investigate the utility of one surgical intervention at a time (instead of grouping all surgical interventions together), and establish a large enough sample size to allow adequate power to detect potential differences. To date, analysis of the data indicates that no particular intervention is clearly superior. A review of the randomized studies available, however, indicates that perhaps less invasive surgical options that

are able to reduce clot burden safely may prove beneficial for patient outcomes. This may be particularly true in young patients in whom there are signs of neurological deterioration within the first 24 hours of ICH.

Although reducing hematoma volume remains the mainstay of most interventions and is a worthwhile avenue in such investigations, future interventions will undoubtedly address underlying mechanisms of brain injury in ICH. This interest in identifying biochemical mechanisms of injury is mirrored in the recent increase in publications regarding the underlying cellular and molecular mechanisms underlying secondary injury in ICH.^{5,21} In the meantime, the onus remains on the clinician to make the best possible judgment in the management of patients harboring ICHs.

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