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Minimally invasive therapy for intracerebral hematomas

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Intracerebral hemorrhage (ICH) occurs in approximately 40,000 new cases every year and has an incidence rate of 15 cases per 100,000 population [1], accounting for 15% of all strokes. The estimated mortality rate from ICH at 30 days is 35% to 52%, with half of the fatalities occurring within the first 2 days of the ictus [2,3]. To date, no treatment has been proven effective in primary supratentorial ICH, and the controversy between surgical and nonsurgical management as the treatment of choice continues. This is mainly the result of the paucity of randomized prospective clinical trials and of the adoption of therapeutic strategies based on clinical series with multiple biases. Nevertheless, more than 7000 surgical procedures per year are performed in the United States alone [4].

The failure of clinical trials to demonstrate benefit from open surgical evacuation of ICH compared with medical therapy has led to the search for alternative methods for clot removal, all of which rely on the growing experience in the field of minimally invasive surgical techniques. The results of small series using minimally invasive approaches seem to show promise for more effective treatment of ICH. The rationale behind a minimally invasive approach to ICH treatment and the experience with the different techniques, along with our own at the University of Cincinnati, are reviewed in this article.

Rationale for minimally invasive therapy

The goals of surgical evacuation of ICH are to reduce mass effect with subsequent control of intracranial hypertension and to reduce tissue damage in the areas surrounding the clot caused by secondary damage. If the first goal is achieved easily, the second is more difficult, because open surgical procedures are frequently associated with additional brain tissue injury. The benefit of surgical over medical therapy of ICH has never been established, and the criteria for surgical intervention have not been clearly identified [2].

Minimally invasive techniques have recently become attractive. Some of the features of ICHs that make them candidates for minimally invasive approaches have been summarized by Kaufman [5] as follows: (1) they can be easily diagnosed by readily available methods, such as CT or MRI; (2) they are suitable for stereotactic localization; (3) their physical properties make them susceptible to aspiration, which can be further facilitated by the administration of fibrinolytic agents or mechanical devices; and (4) their removal can be accomplished without a high risk of rebleeding

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under circumstances in which bleeding can be detected and treated.

The advantages of minimally invasive techniques over conventional craniotomy include the following: (1) operative time is shortened, which is especially valuable for treatment of ICH in elderly patients with other comorbidities; (2) the procedures may be performed under local anesthesia; (3) minimal surgical invasion may be associated with a lower surgery-related morbidity; (4) these procedures enable the surgeon to reach lesions, such as deeply seated hematomas, that are inaccessible by conventional surgery; and (5) such procedures enable the surgeon to control the amount of clot evacuation and eventual complications (catheter misplacement, rebleeding) in real time with the use of intraoperative ultrasound, CT, or MRI.

Minimally invasive surgical techniques also enable early evacuation of ICH. The concept of early removal of ICH is supported by findings that recurrent or continued bleeding commonly occurs within the first few hours after spontaneous ICH. This bleeding leads to an increase in hemorrhage volume with clinical deterioration and a worse outcome [6–8]. In an ICH porcine model, hematoma removal at 3 hours markedly reduced mass effect and perihematoma edema at 24 hours [9]. A report of early surgery (<7 hours) in 100 nonrandomized cases demonstrated lower mortality (7%) and improved functional outcome in the surgical group compared with medically treated patients (39%) [10]. A recently reported Surgical Treatment for Intracerebral Hemorrhage randomized trial of standard craniotomy within 12 hours of symptom onset versus optimal medical treatment in ICH patients showed decreased mortality in the surgical group compared with the medically treated group [11]. At our institution, during a feasibility study of the early surgical evacuation of acute ICH, a trend toward decreased morbidity 3 months after surgical intervention was found [12]. The potential benefits of early removal are being elucidated in an ongoing multicenter clinical trial [13].

Potential disadvantages include reduced surgical exposure; inability to treat a structural lesion, such as an arteriovenous malformation or aneurysm; rebleeding related to the use of fibrinolytics; and infection related to a prolonged indwelling catheter in the hematoma cavity. The rates of complications associated with minimally invasive therapies for ICH evacuation are low overall, varying with the different procedures, and are discussed separately for each surgical technique.

Surgical procedures

Simple aspiration

Simple aspiration was advocated as a potential treatment in the 1950s; however, the results were discouraging. In one report from 1951, 9 of 15 patients treated with simple aspiration had a significant hematoma remnant at surgery or autopsy [14]. The results generated no interest, and the technique was abandoned.

A number of reports from Japan reported rates of aspiration ranging from 29% to 85% of hematoma volume using simple aspiration under CT guidance. Kaufman [5] pointed out the difficulty in interpreting these studies, based on the scanty information about the techniques and devices used during those studies.

Mechanical devices

The two major difficulties encountered initially with the aspiration of ICH were targeting of the lesion and difficulty in achieving aspiration because of heterogeneity in consistency of the clot [15]. With the development of stereotactic techniques, targeting was no longer a problem, and efforts were directed to achieve a higher amount of hematoma aspiration.

Within a few hours of the onset of an ICH, the clot consists of approximately 20% liquid blood and 80% denser clot by volume [16,17]. These physical attributes make simple aspiration difficult. A variety of instruments and pharmacologic agents have been developed to fragment and liquefy these consolidated clots as well as to increase the volumetric yield of aspiration.

In 1978, Backlund and von Holst [18] described a new instrument for stereotactic evacuation of hematomas, which consisted of a 4-mm cannula encasing an Archimedes screw. Suction was applied to aspirate the clot into the cannula while the rotating screw morcellated the hematoma. Using this technique, Broseta et al [19] were able to evacuate ICHs almost completely in 13 of 16 patients in their series. Nevertheless, 81% of these patients died. After these pioneering reports were published, several modifications to the device were described [16,20,21].

Other innovative devices included a specially designed ultrasonic aspirator [22], a modified nucleotome [5,23], and a double-track aspiration system [24,25]. Aspiration under ultrasound guidance to provide real-time evacuation guidance has also been described, but this procedure requires a craniotomy with a bony window at least 2.5 cm × 4 cm [26]. Although some of these approaches showed interesting results, they have not become popular.

Endoscopy

In 1989, Auer et al [27] reported the results of a randomized clinical trial of 100 patients subjected to ultrasound-guided endoscopic evacuation with laser coagulation within 48 hours for ICHs with a volume greater than 10 cm^3 versus medical therapy alone. There was a decreased mortality rate at 6 months in the surgical group (42% versus 70% in the medical therapy group). A trend toward better outcomes in the surgical group was also observed, and endoscopic evacuation of smaller hematomas led to significantly better quality of life in patients treated surgically compared with those treated medically. Surgical benefit was limited to patients with lobar hematomas and to patients younger than 60 years of age. There are no follow-up studies in the literature from this or other groups regarding the use of this technique, however.

Fibrinolysis

A different approach to maximize the effectiveness of hematoma aspiration involves the instillation of fibrinolytic agents into the clot cavity. Using various protocols, a catheter is placed by stereotactic means into the clot cavity, and the fibrinolytic agent is instilled at the patient's bedside several times for several days. The most commonly used thrombolytic agent has been urokinase, which is administered at a dose of 5000 or 6000 IU twice daily via a catheter in the hematoma cavity with subsequent drainage and aspiration. Based on animal studies, urokinase promotes lysis of the hematoma without damaging the surrounding brain [17]. The efficacy of this treatment modality on outcome was demonstrated by Niizuma et al [28], who reported that 81% of 175 patients with putaminal hemorrhage resumed useful lives. A number of nonrandomized studies using this approach reported aspiration rates ranging from 30% to 90% [3,26,27,29]. The rebleeding rate was 0% to 10%, with a mean of 4% in 392 cases [3,26–30]. Recurrent bleeding is the most worrisome potential risk of administering thrombolytic agents into an ICH cavity; however, these rates of recurrence are acceptable when compared with those of conventional hematoma evacuation [7]. In 1999, we published a report on a series of patients with spontaneous ICH randomized to undergo surgical treatment or to receive optimal medical treatment. The principal eligibility criteria were randomization within 24 hours of symptom onset, an ICH volume greater than 10 cm^3, and a Glasgow Coma Scale score greater than 4. Nine of 20 patients enrolled underwent surgery within 3 hours of randomization, and 11 patients received optimal medical therapy. There was no difference in the 3-month mortality rate (27% medical versus 22% surgical), but the secondary 3-month outcome measures showed a nonsignificant trend toward a better outcome in the surgical group than in the medical treatment group for the median Glasgow Outcome Score, Barthel Index, and Rankin Scale. A significant difference was seen in the 3-month National Institutes of Health Stroke Scale score (4 in the surgical group versus 14 in the medical group; $P = 0.04$). The median time from onset of symptoms to surgery was 8 hours and 35 minutes, and the median time from admission to surgery was 4 hours and 3 minutes.

Of the 9 patients treated by surgery within 3 hours of randomization, 5 were treated with open craniotomy and hematoma evacuation and 4 were treated with stereotactic aspiration and thrombolysis with urokinase. In the patients who underwent stereotactic aspiration and thrombolysis, 3 of 4 had a 3-month Rankin score of 1 (normal or minimal deficit) and the fourth patient had a 3-month Rankin score of 2. By comparison, no patient in the medically treated group had a 3-month Rankin score of 1, and only 2 of 11 patients had a Rankin score of 2. Similarly, no patient in the open craniotomy group had a 3-month Rankin score of 1, and only 1 of 5 patients had a 3-month Rankin score of 2. A limitation of this comparison is that the treatment groups differed in the initial volume of ICH. Our study demonstrated that early surgical evacuation for acute ICH was feasible, and the trend toward a lower 3-month morbidity rate with surgical intervention in patients with ICH warranted further investigation of very early and minimally invasive hematoma removal [12].

The goal of a recently terminated European trial was to evaluate the efficacy of stereotactic evacuation of ICH with instillation of urokinase. Seventy-one patients were randomized to two groups (stereotactic evacuation and medical management). Primary endpoints were death or degree of functional handicap at 6 months. A significant reduction in mortality (40%) was found in the surgical group. No statistically significant difference in functional outcome scores was detected at different treatment intervals. Unfortunately, this trial was discontinued because of slow patient accrual [31]. In 1999, urokinase became unavailable in the United States because of reports of the potential for viral contamination of urokinase during drug production.

Another fibrinolytic agent that has been widely used in the treatment of ischemic stroke is tissue plasminogen activator (t-PA). The first clinical use of t-PA in hemorrhagic stroke was for lysing intraventricular hemorrhage (IVH). Rohde et al [32] reported that IVH disappeared earlier (1–3 days) with t-PA than with urokinase (5–8 days). Compared with ventriculostomy alone, IVH treated with the addition of t-PA decreased the mortality rate from 60% to 90% to a mere 5% [32]. Other similar studies have indicated that the use of intraventricular t-PA may improve the prognosis in patients with large IVHs [33,34]. To date, the literature describes 75 patients treated with intraventricular fibrinolytics with a low incidence of complications, usually consisting of infections and hemorrhage [15,33–35].

More recently, t-PA has been used in the treatment of ICH. Lippitz et al [36] and Schaller et al [37] have reported that daily administration of t-PA into the hematoma cavity beginning 12 to 24 hours after stereotactic placement of a catheter resulted in an average 85% reduction in hematoma volume by 2 to 4 days after onset. Lippitz et al [36] used a standard dose of 3 mg of t-PA dissolved in 3 mL of 0.9% sodium chloride; depending on the volume of residual hematoma after the first injection, t-PA administration was repeated every 24 hours for 1 to 3 days. Schaller et al [37] calculated the dose of t-PA relative to the maximum diameter of the hematoma; every 1 cm of hematoma diameter required 1 mg of t-PA. Repeated doses of t-PA were administered every 24 hours for an additional 48 hours if hematoma remained. No systemic adverse effects, including intracranial bleeding or rebleeding, were reported. Recently, using a porcine model of ICH, Wagner et al [9] reported that hematoma aspiration after fibrinolysis with t-PA resulted in greater than 70% removal of the clot and marked reduction of perihematoma edema. Using these results, we have initiated a prospective dose-escalation pilot study consisting of ICH aspiration through a stereotactically placed catheter aided by t-PA thrombolysis started within 12 hours of the onset of symptoms in patients with primary supratentorial ICH. We use stereotactic CT, which provides three-dimensional coordinates, to precisely locate the ICH for catheter placement. After placement of the catheter, we aspirate the ICH, and t-PA is administered to dissolve the remaining hematoma. Aspiration is repeated after 24 hours, and a follow-up CT scan is performed. If a significant amount of hematoma remains, the procedure is repeated for up to 3 days or until the hematoma is reduced to less than 15 cm^3. Seven patients are to be entered for the low-dose and high-dose tiers. So far, four patients have been enrolled in this study, and no complications have been observed after instillation of t-PA in the hematoma cavity (Fig. 1).

Application of less invasive techniques for stereotactic location of intracranial lesions, such as

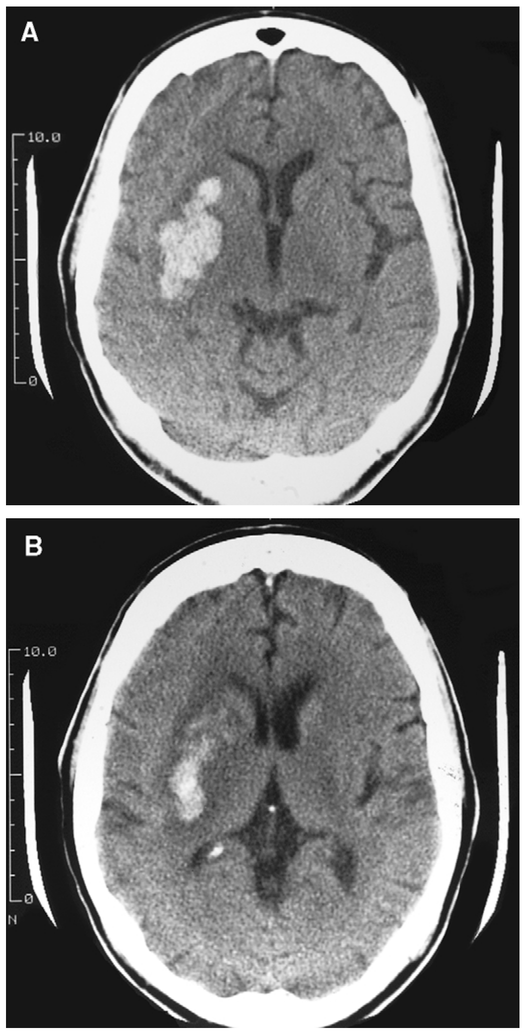

Fig. 1. Aspiration of intracerebral hemorrhage with instillation of tissue plasmogen activator (t-PA). (A) Initial CT scan. (B) CT scan after one instillation of t-PA at a rate of 1 mg/10 cm^3 of clot. (C) CT scan after 30 days.

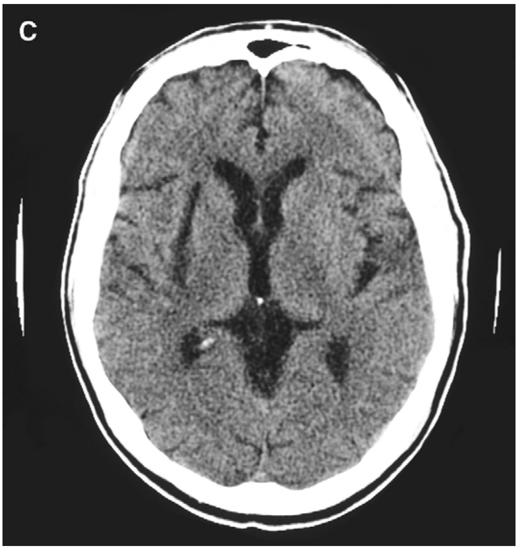

Fig. 1 (*continued*)

frameless stereotaxis and intraoperative MRI, makes the possibility of always treating patients in a less invasive fashion even more attractive.

Tyler and Mandybur [38] reported on 10 patients harboring intracerebral hematomas who were treated by frameless stereotactic means without fiducial markers; using an intraoperative MRI scanner, these patients underwent surgery within 1 to 34 days after hemorrhage. Aspiration was successful in all cases in removing 70% to 90% of each clot. Intrahematoma t-PA infusion was used in two cases, with subsequent 80% to 90% clot removal. There were no complications or rehemorrhages. All patients showed some form of improvement, including either improved blood pressure control, speech, or cognitive abilities. The authors concluded that using an intraoperative MRI scanner to perform frameless stereotactic aspiration of acute/subacute intracerebral hematoma without fiducial markers is a safe and potentially effective means of treating ICH [38]. Bernays et al [39] reported complete evacuation in 62% of their cases and subtotal evacuation in 31% of their cases in their series of 13 patients with ICH treated with a specially designed artifact-free aspiration cannula using intraoperative MRI. No rebleeding was demonstrated, and neurologic function improved in 11 of the 12 patients eligible for assessment. The authors demonstrated the feasibility of an excellent degree of clot evacuation using near-real-time guidance and a positive trend regarding neurologic outcome with this technique [39].

Summary

The efficacy of surgical treatment of ICH remains unproven and controversial [40]. Although open surgery does not appear to improve the patient's outcome [2], less invasive methods of hematoma evacuation seem to show promising results in improving patient outcome and survival. To date, the only two clinical trials that have demonstrated benefit from surgical treatment over medical therapy for ICH have used minimally invasive techniques [27,38]. Randomized controlled clinical trials comparing minimally invasive surgical techniques versus best medical treatment are needed to determine the best management of ICH.

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