Intracranial vascular surgery

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Purpose of review

To review the recent literature on intracranial vascular surgery, to summarize the main findings, and to discuss the impact of these findings on clinical practice.

Recent findings

Three areas of vascular neurosurgery literature have recently generated significant interest, controversy and heated debate: (1) The International Study of Unruptured Intracranial Aneurysms studied the natural history and treatment options of unruptured aneurysms, and reported surprisingly low aneurysm rupture rates for small asymptomatic aneurysms. The study also reported favorable morbidity rates for endovascular treatment compared with surgical treatment of unruptured aneurysms. (2) The International Subarachnoid Aneurysm Trial compared endovascular and surgical treatments for ruptured intracranial aneurysms. The study concluded that the outcome in terms of survival free of disability at one year was significantly better with endovascular coiling. (3) The Intraoperative Hypothermia for Aneurysm Surgery Trial compared intraoperative hypothermia and normothermia for potential neuroprotection during neurovascular procedures. Preliminary results suggest no difference between the treatments.

Summary

The International Study of Unruptured Intracranial Aneurysms and the International Subarachnoid Aneurysm Trial have provided data on the natural history of unruptured intracranial aneurysms and on the morbidity and mortality of surgical and endovascular treatments for intracranial aneurysms. Although morbidity rates of endovascular therapy compare favorably with those of surgery, long-term data on the efficacy of endovascular coiling of aneurysms are needed to assess the overall risk–benefit ratio of these therapies.

Keywords

endovascular coiling, intracranial aneurysm, microsurgical repair

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Abbreviations

IHAST	Intraoperative Hypothermia for Aneurysm Surgery Trial
ISAT	International Subarachnoid Aneurysm Trial
ISUIA	International Study of Unruptured Intracranial Aneurysms
SAH	subarachnoid hemorrhage

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Introduction

The clinical practice of vascular neurosurgery is changing as a result of a better understanding of the natural history of unruptured intracranial aneurysms, the ongoing development and improvement of endovascular techniques to treat intracranial aneurysms, and new data on different treatment options for intracranial aneurysms. This review will concentrate on three areas of vascular neurosurgery literature that have recently generated significant interest, controversy and heated debate: (1) The International Study of Unruptured Intracranial Aneurysms (ISUIA) studied the natural history and treatment of unruptured aneurysms [1,2•]. (2) The International Subarachnoid Aneurysm Trial (ISAT) compared endovascular and surgical treatments for ruptured intracranial aneurysms [3]. (3) The Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) compared intraoperative hypothermia and normothermia for potential neuroprotection during neurovascular procedures.

Natural history of unruptured intracranial aneurysms

Up to 10 years ago the treatment of an unruptured intracranial aneurysm was reasonably straightforward: intraoperative clipping of the aneurysm or conservative therapy. For years this treatment option seemed to be well supported by both the knowledge of the devastating outcome of subarachnoid hemorrhage (SAH) as well as the high success of surgical aneurysm clipping to protect the patient from rupture of the aneurysm. However, recent publications have challenged previous clinical practice by providing novel data on the natural history of unruptured intracranial aneurysms and on morbidity and mortality rates of both endovascular and surgical treatments for unruptured aneurysms [1,2•,3].

The frequency of unruptured intracranial aneurysms has been estimated to be 0.2–9.9%. These rates are somewhat higher in certain populations (Finland, Japan), and in some families. The incidence of aneurysmal SAH has been estimated to be six to eight per 100 000 individuals, and the rupture rate of unruptured intracranial aneurysms has been estimated to be 1–2% per year. However, the recent ISUIA reported that the rupture rate of previously unruptured aneurysms varies from as low as 0.05% per year to 6% per year depending on the size and location of the aneurysm [1]. In the largest retrospective study of patients with unruptured aneurysms, 1449 patients were followed for 2023 patient-years at 53

participating centers. Patients were divided into two groups: (1) patients with asymptomatic aneurysms with no previous SAH ($n = 727$); and (2) patients with multiple aneurysms who had a SAH from one of the aneurysms that had subsequently been repaired successfully ($n = 722$).

The 1449 patients in the retrospective ISUIA study had a total of 1937 aneurysms. The study reported an approximately 11 times higher rate of aneurysmal rupture in patients with previous SAH compared with patients with asymptomatic aneurysms. They also reported an exceedingly low likelihood of rupture (0.05% per year) in patients with an aneurysm that was less than 10 mm in diameter. The highest rupture rates (6% during the first year) were reported in aneurysms that were over 25 mm in diameter. Aneurysm size and location were independent predictors of rupture, with basilar tip, vertebrobasilar, posterior cerebral artery and posterior communicating artery aneurysms having higher rates of rupture.

In a prospective study, the ISUIA study group (61 centers) assessed 4060 patients with aneurysms [2•]. A total of 1692 of those patients did not have aneurysm repair, and were followed up for 6544 patient-years (mean $\pm$ SD 4.1 $\pm$ 2.0 years). The 1692 patients had a total of 2686 aneurysms; 1077 patients had no previous SAH; 615 of the patients had suffered a SAH before enrollment in the study. In this second ISUIA study, for statistical analysis, the aneurysm size was classified differently from the previous study. Aneurysms were grouped into four categories: less than 7 mm, 7–12 mm, 13–24 mm, and 25 mm or greater. Most of the patients were women, and more than half of the patients had multiple aneurysms. Sixty-two per cent of the aneurysms were less than 7 mm in size. A total of 193 patients died during the follow-up period; 51 patients had a confirmed aneurysmal rupture with a 65% mortality rate during the follow-up period. The results confirmed that aneurysm size and location were independent risk factors for rupture. Again, an exceedingly low likelihood of rupture (0.1% per year) was reported for small (< 7 mm) aneurysms in patients with no previous SAH.

The results of the ISUIA studies have generated significant interest and criticism, probably because of the low aneurysm rupture rates of small asymptomatic aneurysms in relation to the published morbidity and mortality rates of the available therapies. Many editorials have cautioned readers not to generalize the results to all patients with unruptured intracranial aneurysms [4,5]. Patient selection bias and a limited follow-up period have been some of the main concerns. It has been suggested that the ISUIA study may have underestimated the overall rate of aneurysm rupture (0.8% per year). In comparison to the ISUIA study, Juvela *et al.* [6], in the longest to date follow-up study of 142 patients with unruptured intracranial aneurysms, found an annual aneurysm rupture incidence of 1.3%. Irrespective of the criticisms that followed those studies, the studies have added significantly to the literature on the natural history of intracranial aneurysms. The studies have also stimulated interest for further studies. However, because of the changing morbidity and mortality rates of endovascular therapies and other ethical considerations, it is unlikely that even well-designed future clinical studies will be able to address ongoing criticisms and eliminate selection bias.

Treatment of unruptured intracranial aneurysms

With the increased use and improvement of imaging technology, unruptured intracranial aneurysms are diagnosed at a greater frequency than ever before. Current treatment options include microsurgical clipping or endovascular coiling of the aneurysm, or conservative therapy (cessation of smoking and blood pressure control) [7,8]. Ideally, treatment decisions are based on several factors, such as the natural history of unruptured intracranial aneurysms (see discussion above), morbidity and mortality rates related to the treatment options, and the patient's age and co-morbidities. A good risk–benefit ratio of the proposed treatment is thus imperative to make the best possible choices. Until such data are available, recommendations relating to treament options for intracranial aneurysms will continue to generate significant controversy.

Endovascular treatment of intracranial aneurysms has become more common after the US Food and Drug Administration's approval of detachable coils in 1995. Because of the relatively short-term availability of this technique, there are limited data on the long-term effectiveness of endovascular coiling of intracranial aneurysms. Also, as with other evolving technologies, the morbidity and mortality rates as well as the efficacy of treatment is changing (improving) over time [9].

Several recent studies have published data on the effectiveness and risks of microsurgical and endovascular treatment for unruptured intracranial aneurysms [2•,10,11]. A prospective part of the most recent ISUIA study compared surgical and endovascular therapies to treat unruptured aneurysms [2•]. In that study, 1917 patients had surgical repair of their unruptured intracranial aneurysm, whereas 451 patients had endovascular repair. Total morbidity and mortality rates at one year in patients with open surgical repair were 12.6% for

patients with no previous SAH and 10.1% for patients with a previous SAH. The respective rates for endovascular repair were 9.8 and 7.1%. Although the overall morbidity and mortality rates were similar for surgical and endovascular treatments, some differences existed. Predictors of poor surgical outcome were advanced age, large aneurysmal size and location in the posterior circulation. The risk of endovascular treatment appeared to be less dependent on age. However, a significant proportion of the aneurysms treated with endovascular coiling were not obliterated completely. More long-term follow up data are needed to evaluate the overall risk, effectiveness and cost of endovascular treatment for unruptured intracranial aneurysms.

The short-term morbidity and mortality data for patients treated for unruptured intracranial aneurysms have been studied using hospital discharge summary databases. In California, during 1990–1998, 2069 patients were treated for unruptured cerebral aneurysms [9]. A total of 1699 patients were treated surgically and 370 patients were treated with endovascular therapy. The short-term adverse outcome rates (inhospital mortality and discharge to other than home) were 25.4 and 9.7% for patient treated with surgery and endovascular coiling, respectively. The respective mortality rates were 3.5 and 0.5%. Patients undergoing endovascular therapy had shorter and less expensive hospital stays. During the 9-year time period the proportion of cases treated with endovascular therapy increased, and the adverse outcomes declined steadily for endovascular therapy. The adverse outcome rates remained stable for surgery during that time period. Although these data have several limitations, they point out the ongoing evolution (increasing frequency and decreasing risk) of endovascular treatment for unruptured intracranial aneurysms. Comparing surgical and endovascular treatments will become more meaningful once the field of endovascular therapy reaches a stable efficacy and adverse outcome rate.

Another short-term, nationwide, retrospective cohort study used the Nationwide Inpatient Sample database to study 421 patients who underwent endovascular treatment and 3498 patients who had surgical clipping of unruptured intracranial aneurysms [12]. Patients in the study accounted for one fifth of all patients in the United States treated for unruptured intracranial aneurysms during 1996–2000. The inhospital mortality rates were 2.1% for surgical patients and 1.7% for endovascular patients ($P = \text{NS}$). More endovascular patients were discharged home (91%) compared with surgical patients (82%). Similar to the study conducted in California, the difference in outcome changed during the study period, presumably as a result of the decreasing adverse event rates of endovascular therapy. When analysing data only from endovascular patients, high-volume institutions and high-volume physicians had lower morbidity but not mortality rates, and shorter hospital length of stays and lower total hospital charges [13]. These data imply that better outcomes would be acheived by concentrating intracranial aneurysm treatment to a few high-volume centers.

Because of the lack of long-term follow-up of endovascular treatment for unruptured intracranial aneurysm, patient selection bias, limitations of hospital discharge databases, and variability in the experience of neurosurgeons and neuroradiologists, recommendations for treatment options should be considered with caution. However, the following recommendations have been made [14]: (1) An incidentally discovered unruptured anterior circulation aneurysm less than 7 mm in diameter should be left untreated in individuals with no family history of SAH; (2) individuals with approximately 20-year life expectancy should be informed that statistically the benefits of treatment do not outweigh the risks; (3) in all other cases, treatment with surgical clipping or coil embolization should be advised; (4) medical hypotensive treatment may be a viable alternative if surgical treatment is not feasible.

Surgical and endovascular treatment of ruptured intracranial aneurysms

The ISAT has created significant controversy, which has resulted in several editorials and symposia [15–17]. This randomized, prospective, multicenter clinical trial was designed to compare the safety and efficacy of endovascular coiling with surgical clipping of ruptured intracranial aneurysms [3]. Only patients who were judged to be suitable for both treatments were enrolled. A total of 2143 patients from 43 centers with SAH from known aneurysms were enrolled between 1997 and 2002. The primary outcome variable was disability-free survival at one year.

The study concluded that the outcome in terms of survival free of disability at one year was significantly better with endovascular coiling. Some 23.7% of the patients allocated to endovascular treatment were dependent or dead at one year, compared with 30.6% allocated to neurosurgery. The relative risk reduction was 22.6%. There was no difference in mortality rates between the treatment groups. At one-year follow-up, 40 and 33 patients who had had endovascular and surgical treatment, respectively, had non-procedural rebleeding from the target aneurysm. Two patients in the endovascular group and none in the surgical group had rebleeding after the one year follow-up. The study plans to continue yearly follow-

ups for 5 years to provide prospective data on the rate of rebleeding.

The study has several recognized limitations. Almost all of the aneurysms (97.3%) were in the anterior circulation. However, most centers considered endovascular treatment the favored option for posterior circulation aneurysms. Another main criticism is that efficacy data are available for only one year, and that this is not sufficient to make clinical decisions. As mentioned above, ISAT and other studies are presently collecting long-term follow-up data. Despite the criticisms, this is one of the few, if not the only, controlled randomized clinical study evaluating the efficacy of different treatments for intracranial aneurysms, and despite its limitations, provides the best available data to date. Because of the potential impact of these results on surgeons and radiologists, it is not surprising that most of the criticism has been in the surgical literature.

Intraoperative hypothermia for neuroprotection

Many animal studies have demonstrated that hypothermia provides significant neuroprotection during many kinds of cerebral insults. Although intraoperative hypothermia is used in approximately 50% of current neurovascular cases, its effectiveness has never been assessed. To study the potential neuroprotective effects of intraoperative hypothermia, 1001 patients were randomly assigned to the IHAST study between 2000 and 2003. The IHAST study is a prospective, randomized clinical trial comparing intraoperative hypothermia (33°C) with intraoperative normothermia (36.5°C). Patients with SAH and a documented intracranial aneurysm scheduled for surgical clipping of the aneurysm were enrolled. The goal was to reach the target temperature before clipping of the aneurysm. Patients were rewarmed immediately after clipping. The primary outcome was the Glasgow Outcome Score 90 days after surgery. Although publication of the final results is pending, a published abstract of the preliminary results suggested that intraoperative hypothermia had no effect on outcome when compared with normothermia. Once published, the IHAST study results will have a significant effect on the intraoperative management of neurovascular patients as well as future studies on intraoperative neuroprotection.

Conclusion

ISUIA, ISAT and IHAST will continue providing valuable data on the management of neurovascular patients. Until now there has been minimal data from prospective randomized, adequately powered clinical studies to provide guidance in the treatment of patients with intracranial aneurysms. The ISUIA and ISAT studies have generated controversy. They have also generated some of the best available data, and interest that will result in additional well-controlled clinical studies. With the further development of endovascular techniques, increasing experience and changing adverse outcome rates, many of these studies will need to be repeated in the future. There is no doubt that vascular neurosurgery is presently undergoing significant changes that have an impact on our patients as well as many surgeons and radiologists. Both surgical and endovascular treatments will play a role in the treatment of intracranial aneurysms for years to come. Both specialties need to remain strong and maintain high quality training of new physicians. To choose the optimal treatment for any individual patient will require mature decisions from a team of physicians. The currently available data also emphasize the importance of physicians' experience on patient outcomes, and support the viewpoint that SAH from aneurysmal rupture should be treated at selected large-volume centers that can provide both surgical and endovascular treatment options. Additional well-controlled clinical studies are needed to help us recommend the best possible treatments for our patients with intracranial aneurysms.

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