Treatment of Poor-Grade Subarachnoid Hemorrhage Trial

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AJNR Am J Neuroradiol 2015, 36 (1) 116-120
doi: https://doi.org/10.3174/ajnr.A4061
http://www.ajnr.org/content/36/1/116
ABSTRACT

BACKGROUND AND PURPOSE: Management of poor-grade subarachnoid hemorrhage is based on limited evidence from small single-center retrospective observational studies. The purpose of this study was to undertake a single-center randomized controlled feasibility trial comparing a strategy of early endovascular aneurysm treatment with treatment after neurologic recovery in this group of patients.

MATERIALS AND METHODS: Patients with poor-grade SAH were randomized within 24 hours of admission to early treatment or treatment after neurologic recovery. If a patient was randomized to early treatment, the aneurysm was treated endovascularly within 24 hours of randomization. Recruitment rate, safety profile, and functional outcome at the time of discharge and at 6 months were assessed.

RESULTS: Fourteen of 51 patients screened were eligible for the trial. Of these 14, 8 patients were randomized (57%). All patients in the early coiling arm received treatment within 24 hours of randomization. There was no treatment-related complication. Overall, good outcome occurred in 25% of patients; the mortality rate was 75%. Patients in the early treatment arm (n = 5) had a good outcome rate of 20%, while those in treatment after neurologic recovery arm (n = 3) had a good outcome rate of 33.3%.

CONCLUSIONS: This was a feasibility study that demonstrated that recruitment and randomization for comparing management strategies in poor-grade SAH are feasible. The recruitment rate among eligible patients was encouraging (57%), though a number of patients had to be excluded due to ineligibility. A multicenter study is necessary to recruit the numbers required to compare the clinical outcomes of these management strategies.

ABBREVIATIONS: ISAT = International Subarachnoid Aneurysm Trial; WFNS = World Federation of Neurosurgical Societies

Intracranial aneurysms are being treated with increasing frequency by endovascular coiling. The International Subarachnoid Aneurysm Trial (ISAT), an international, multicenter, randomized controlled trial comparing coiling with surgical clipping, demonstrated that there was a 6.9% reduction of absolute risk and a 22.6% reduction of relative risk of death or dependency at the end of 1 year in the coiling arm. On the basis this finding, early aneurysm coiling of patients with good-grade subarachnoid hemorrhage has become an established practice. Poor-grade SAHs (World Federation of Neurosurgical Societies [WFNS] grades IV and V) were significantly under-represented in ISAT because these patients are usually not considered for clipping unless they have made substantial clinical improvement. Although they were not under-represented in the Barrow Ruptured Aneurysm trial, this study did not assess treatment timing. ISAT re-raised the question of the balance of risks of aneurysm treatment in the early days after poor-grade SAH but did not provide the data to determine the answer. Early coiling could potentially have the advantage of reducing the rebleeding rate without the increased treatment risks incurred by early surgical clipping in poor-grade SAH patients. The benefit of such a strategy, however, cannot be extrapolated from ISAT and should be supported by robust (randomized controlled trial) data before being adopted as standard practice. We have undertaken a single-center randomized parallel-group feasibility trial between patients with poor-grade SAH who were treated early with endovascular coiling and those who were managed by the traditional method (ie, treated [coiled or clipped] after clinical neurologic improvement) as a first step toward answering this important question. The outcome measures were the following: 1) recruitment rate, 2) trial safety assessed by
Early Treatment Arm. If the patient was randomized to the early treatment arm, the result of randomization was communicated to the interventional neuroradiology team. Appropriate assent for the coiling procedure was then obtained. If amenable to endovascular treatment, the aneurysm was treated within 24 hours of randomization.

Treatment after Clinical Improvement Arm. If the patient was randomized to the treatment after clinical improvement arm, the result was communicated to the intensive therapy unit and neurosurgical team who continued managing the patient as per local established protocol. If and when the patient’s neurologic status improved to WFNS grade III or better, the aneurysm was treated appropriately. There was no specific time-delay criterion for aneurysm treatment in this arm.

Aneurysm Treatment
Standard local procedures for aneurysm treatment were followed. Endovascular treatment of the aneurysms was performed with biplane angiography equipment (Integris Allura; Philips Healthcare, Best, the Netherlands). All patients were treated under general anesthetic and received a standard regimen of anticoagulation with heparin. Balloon assistance was used as required. None of the patients required a stent-assisted technique.

Follow-Up
Angiographic Follow-Up. Angiographic follow-up was performed as per the local established protocol (5 and 24 months following the coiling procedure).

Clinical Follow-Up. Patients were assessed for their functional status at the time of discharge and at 6 months following ictus. Assessment was performed by members of the endovascular team blinded to the results of randomization on the basis of the modified Rankin Scale.

RESULTS
Screening and Recruitment
The study was performed in a single United Kingdom neurosciences center. Fifty-one patients admitted to the intensive therapy unit with poor-grade SAH were screened over 29 months (August 2008 to January 2011). Fourteen patients were found to be eligible for the trial. Eight of 14 eligible were randomized for the study. The other 6 could not be included because assent from the next of kin could not be obtained. The recruitment rate among patients eligible for the trial was therefore 57%, while the recruitment rate of patients screened was 16%.

Thirty-seven patients were excluded from the study because they did not meet the inclusion criteria. A number of factors were responsible for patients being ineligible for the trial, which are summarized in Table 1. Five patients were randomized to the early treatment arm, and 3 patients were randomized to the treatment after recovery arm.

Demographics
Of the 8 patients included in the study, 4 were men and 4 were women. The age of patients ranged between 26 and 64 years, with an average age of 53 years. Of the 5 patients (3 women and 2 men) randomized to early treatment, the age range was 26–64 years with an average age of 53 years. Of the 3 patients (2 men and 1 woman).
of neurologic status before randomization, 8 (23%).

- Expiry of time window for randomization, 5 (13%).
- Emergency clot evacuation, 5 (13%).
- Hemodynamic instability, 5 (13%).
- Beyond age range, 4 (11%).
- Pure intraventricular hemorrhage, 3 (8%).
- Signs of coning, 3 (8%).
- Lack of equipoise, 3 (8%).
- No aneurysm on CT angiogram (AVM found), 1 (3%).

**Treatment-Unrelated adverse events**

| Treatment-Unrelated Adverse Event | No. |
|-----------------------------------|-----|
| Aneurysm rebleeding                | 1   |
| Hydrocephalus (early)             | 5   |
| Hydrocephalus (late)              | 1   |
| Intracerebral hematoma            | 2   |
| Intraventricular hemorrhage       | 2   |
| Diffuse cerebral edema            | 1   |

**Table 2: Treatment-unrelated adverse events**

**Table 3: Summary of outcomes between early treatment and treatment after recovery arms**

| No. of patients | Early Treatment Arm | Treatment after Recovery Arm |
|----------------|---------------------|------------------------------|
| No. of patients | 5                   | 3                            |
| WFNS score on admission | WFNS IV-II | WFNS IV-I |
| Good outcome | 1 (MRS 1) | 1 (MRS 0) |
| Poor outcome | 4 (all MRS 6) | 2 (all MRS 6) |

Discussing the outcomes, we can see that the good outcome rate (mRS 0–2) at 6 months was 25%, and the poor outcome rate (mRS 3–6) at the same time was 75%. The overall mortality rate was also 75%. The good outcome rate in the early treatment arm was 20%, while the good outcome rate in the treatment after recovery arm was 33% (Table 3).

**Discussion**

Endovascular treatment is relatively less invasive than clipping and has been demonstrated to improve outcome in patients with good-grade SAH. As a result, a number of centers are now also treating patients with poor-grade SAH with early endovascular coiling. Several single-center, retrospective, nonrandomized studies on early endovascular treatment of patients with poor-grade SAH have been published, as summarized in Table 4. While these studies provide important data in understanding outcomes in this group of patients, there are a number of difficulties in interpreting their results. First, sizes of the studies are mostly rather modest and vary widely, from 11 to 111 subjects. Second, the inclusion criteria are also extremely variable. For example, while 1 study considers WFNS grade IV and V to be poor-grade, another study has only included WFNS grade V, and some have included patients on the basis of Hunt and Hess grades 4 and 5. Significant heterogeneity also exists in outcome measures and follow-up. A small majority of studies have used the Glasgow Outcome Scale over the modified Rankin Scale. The follow-up also varied between 6 months to up to 2 years. There are also differences in the definition of good and poor outcomes.

With regard to neurosurgical studies, the International Cooperative Study reported a good recovery rate in patients with poor-grade SAH ranging from 10% to 33% in the various subgroups based on the timing of surgery. Some smaller scale single-center studies suggested that early surgical clipping may lead to better results, but mostly in selected groups. A study that included patients with poor-grade SAH who did not receive aneurysm treatment (ie, neither clipping nor coiling) reported a mortality rate of 71%.

Specifically lacking from the endovascular studies are data on the outcomes of patients with poor-grade SAH who received endovascular treatment, which could provide valuable insights into the effectiveness of this approach in this population.
into the process of randomization and treatment, making it difficult to study the benefits of early treatment. In this study, the decision regarding sedation-reversal has been left to the intensive therapy unit team. If a patient’s postreversal neurologic status improved rapidly to the extent that he or she no longer had a poor-grade SAH, then the patient was not randomized. If a patient was randomized, then he or she remained in the allocated trial arm regardless of the speed of recovery. Hydrocephalus was used as a stratification criterion to ensure that an equal proportion of patients with hydrocephalus were included in the 2 arms and that the outcomes were not skewed by this factor.

The overall mortality rate in this study was 75%, which is higher than that in many reported series. This is most probably due to the small size of this study and possible bias toward randomizing more patients with grade V than with grade IV. Most patients in this study had admission WFNS grades V; and 5 of 6 patients who died had an admission WFNS grade of V. Although the numbers are small, our experience suggests that the benefit of early endovascular treatment in a poor-grade SAH population should not be assumed unless there are robust multicenter randomized controlled trial data to support it. In this study, the good outcome rate in the treatment after recovery arm (33%) was better than that in the early coiling arm (20%).

CONCLUSIONS
This study suggests that a randomized controlled trial to evaluate the best management strategy in patients with poor-grade SAH is safe and feasible. While the recruitment rate among eligible patients was encouraging, a significant number of patients could not be randomized due to expiry of the time window for randomization and lack of assent. A fully resourced multicenter study should be able to address these issues and recruit sufficient numbers to achieve robust outcome data.

ACKNOWLEDGMENTS
We acknowledge the contribution of Elaine McColl, Director of Newcastle Clinical Trials Unit, and Nicola Hind, Consultant Neuroradiographer, Royal Victoria Infirmary, Newcastle upon Tyne, for their exceptional help in design and recruitment of this trial.

Disclosures: Anil Gholkar—UNRELATED: Consultancy: Stryker Neurovascular, Codman Neurovascular, MicroVention, Comments: I organize and participate in training

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