Effect of Prophylactic Transluminal Balloon Angioplasty on Cerebral Vasospasm and Outcome in Patients With Fisher Grade III Subarachnoid Hemorrhage

Results of a Phase II Multicenter, Randomized, Clinical Trial

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Background and Purpose—Cerebral vasospasm continues to be a major cause of poor outcome in patients with ruptured aneurysms. Prophylactic Transluminal Balloon Angioplasty (pTBA) appeared to prevent delayed ischemic neurological deficit in a pilot study. A phase II multicenter randomized clinical trial was subsequently designed.

Methods—One hundred and seventy patients with Fisher Grade III subarachnoid hemorrhage were enrolled in the study. Of these, 85 patients were randomized to the treatment group and underwent pTBA within 96 hours after subarachnoid hemorrhage. Main end points of the study included the 3-month dichotomized Glasgow Outcome Score (GOS), development of delayed ischemic neurological deficit (DIND), occurrence of Transcranial Doppler (TCD) vasospasm, and length of stay in the ICU and hospital.

Results—The incidence of DIND was lower in the pTBA group (P=0.30) and fewer patients required therapeutic angioplasty to treat DIND (P=0.03). Overall pTBA resulted in an absolute risk reduction of 5.9% and a relative risk reduction of 10.4% unfavorable outcome (P=0.54). Good grade patients had absolute and relative risk reductions of respectively 9.5 and 29.4% (P=0.73). Length of stay in ICU and hospital was similar in both groups. Four patients had a procedure-related vessel perforation, of which three patients died.

Conclusions—While the trial is unsuccessful as defined by the primary end point (GOS), proof of concept is confirmed by these results. Fewer patients tend to develop vasospasm after treatment with pTBA and there is a statistically significantly decreased need for therapeutic angioplasty. pTBA does not improve the poor outcome of patients with Fisher grade III subarachnoid hemorrhage. (Stroke. 2008;39:1759-1765.)

Key Words: subarachnoid hemorrhage ■ aneurysm ■ vasospasm ■ angioplasty ■ stenting ■ outcome ■ randomized clinical trials

Cerebral vasospasm is the second leading cause of death and disability in patients with ruptured aneurysms. The etiology is poorly understood, and treatment options are limited. Neurointerventional technologies such as transluminal balloon angioplasty (TBA) and intra-arterial infusion of vasodilating agents have been successful in some patients, but a substantial number of patients continue to develop ischemic deficits and poor outcome due to vasospasm.1-10 Exemplifying this, in the largest case series published to date of 109 patients with aneurysmal subarachnoid hemorrhage (SAH) treated with TBA after onset of a delayed ischemic neurological deficit (DIND), clinical improvement was noted in only 44% of patients, and 28% of patients deteriorated further.11 In the clinical setting, it appears that TBA is most effective when applied early in the course of vasospasm.5,10 This is supported by findings in experimental vasospasm, where TBA applied to vessels before onset was found to completely prevent vasospasm.12 We previously published data from a pilot trial of 18 patients with Fisher grade III SAH treated with TBA before onset of vasospasm.13 In this series, no

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*See Appendix for a list of the BPAV study group.

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patients developed a DIND. Moreover, 83% of patients had a favorable outcome, which was much higher than expected when compared with historical controls. A phase II multicenter, randomized, clinical trial was subsequently designed to evaluate the efficacy of prophylactic transluminal balloon angioplasty (pTBA) when tested in a larger population. The results are presented in this article.

Subjects and Methods
Ten centers in the United States, Canada, and the Netherlands participated in this National Institutes of Health–funded study. In all centers, institutional review was completed and approval was granted. Informed consent was obtained from all patients or their families before enrollment.

Enrollment Criteria and Randomization
Patients with Fisher grade III and III+IV SAH were eligible for the study if their aneurysm was satisfactorily secured by clipping or endovascular coiling and if they could be treated with pTBA within 96 hours of SAH. Patients were excluded on the basis of any of the following criteria: (1) vasospasm before randomization; (2) consent unobtainable or denied; (3) patient outside the 96-hour window for ballooning; (4) enrollment in a competing trial; (5) any unsecured aneurysm in the location where the ballooning procedure would occur; (6) known medical conditions that would adversely affect mortality/morbidity; (7) severe cerebrovascular atherosclerosis; and (8) age <16 years.

Patients were randomized by a computer-generated code list in random blocks of 2, 4, and 6 at each center. Sealed envelopes with the treatment assignment code were provided to each participating center. This envelope was opened by the interventionalist after the treatment assignment code were provided to each participating center. Ten centers in the United States, Canada, and the Netherlands participated in this National Institutes of Health–funded study. In all centers, institutional review was completed and approval was granted. Informed consent was obtained from all patients or their families before enrollment.

Standard Management
All patients were managed according to a standardized treatment protocol: Aggressive resuscitation, including intubation, ventilation, and mannitol administration as necessary, was used before hospitalization and continued in the Emergency Department. A member of the neurosurgical service evaluated all patients in the Emergency Department. All patients underwent noncontrast head computed tomography (CT).

Subsequently, a CT angiogram and/or 4-vessel diagnostic cerebral angiogram was obtained. All patients underwent postoperative angiography under anesthesia to evaluate surgical clipping/endovascular coiling, unintentional vessel occlusion, or the presence of early vasospasm. In the absence of vasospasm or other exclusion criteria, the patient was then randomized to pTBA or no pTBA. For blinding purposes, patients randomized to the control group were kept in the Emergency Department. A member of the neurosurgical service evaluated all patients in the Emergency Department. All patients underwent noncontrast head computed tomography (CT).

Prophylactic TBA
All patients were kept under general anesthesia for pTBA. Nondetectable flow-guided or over-the-wire occlusion balloon catheters were used for the procedure, with selection based on patient anatomy and operator preference. Systemic heparinization was used during all balloon manipulations, dosed at 70 U/kg via IV bolus. Target vessels for the anterior circulation were the A1 segment of each anterior cerebral artery, the M1 segment of the middle cerebral artery, and the supraclinoid segment of the internal carotid artery. The posterior circulation target vessels were the P1 segment of each posterior cerebral artery, the basilar artery, and the intradural segment of the dominant vertebral artery. During the study, the protocol was revised to exclude the A1 and P1 segments because of perceived safety issues. Balloons were inflated to the vessel diameter until apposition of the balloon to the vessel wall was identified fluoroscopically. Target arteries that could be entered were treated along their entire length, with a 5-second duration for each inflation and a slight overlap of each segment on sequential inflations. pTBA was considered satisfactory when it could be performed in at least 2 of the 3 parts of the intracranial circulation (right and/or left carotid system and/or vertebralbasilar system) and included the aneurysm-bearing part of the circulation.

Outcome Measures, Data Management, and Statistical Analysis
The main end point of the study was favorable/unfavorable outcome according to the dichotomized Glasgow Outcome Score (GOS) at 3 months. Secondary end points included development of a DIND, occurrence of cerebral vasospasm as determined by TCD measurements, and length of stay in the Intensive Care Unit and in the hospital during the acute phase of the hemorrhage and subsequent treatment.

Power calculations were made according to the guidelines of Armitage and Berry. Our pilot data and data from previously published studies were used to estimate probable outcomes. We estimated that 50% of the patients would have a favorable outcome without treatment and that 70% of the patients would have a favorable outcome with treatment. On the basis of these assumptions, 185 patients were needed to achieve 80% power for a 2-sided test at the 5% significance level. Participating centers entered their data in separate databases, and scheduled visits were performed to evaluate the accuracy of data entry. All data were sent to a central database before analysis. Data were analyzed according to an intent-to-treat paradigm. The χ², continuity-adjusted χ², and Fisher’s exact tests were used for statistical analysis. A stopping rule was implemented when total mortality was significantly higher in either group. We used the sequential probability ratio test to monitor this stopping criterion. The decision boundary was set with α=β=0.05.

Results
Patients (n=1148) were screened for enrollment, and 170 patients were randomized. The Figure outlines the number of patients randomized by each center. Reasons for exclusion.
of patients are listed in Table 1. The trial was halted 3 times by the Data Safety Monitoring Board for review of treatment-related complications. After the third suspension, we elected to analyze the available data because subsequent enrollment became too low to complete the analysis in a timely manner (ie, within the planned period of enrollment 2000 to 2005).

All CT scans were reviewed centrally. Ninety-eight percent of patients were enrolled appropriately. One patient was found to have a Fisher grade II hemorrhage, and 2 patients had mild vasospasm on their angiograms before enrollment. As part of the intent-to-treat paradigm, these patients were analyzed with their respective treatment groups.

Admission/Acute Care Data
Patient characteristics were similar in both groups (Table 2). The mean age for the entire study population was 55 years. The incidence of hydrocephalus was higher in the treatment group, although this difference did not reach statistical significance. Forty-seven percent of patients had hydrocephalus at some point during the first 2 weeks, and 73% of these patients required cerebrospinal fluid diversion, which was done either just before or during surgical clipping or endovascular coiling in most patients. Eighty-seven patients underwent clipping and 81 patients underwent coiling of their aneurysm. In the 2 remaining patients, the aneurysm was secured by wrapping or vessel ligation. The number of patients treated with clipping versus coiling was similar in the pTBA and control groups ($P=0.89$).

Prophylactic TBA
Eighty-five patients were randomized to pTBA and 85 were randomized to the control group. The mean time to balloon-
with pTBA, at least 4 vessel segments (of the possible 6) were successfully treated by angioplasty in 71 patients, at least 3 vessel segments in 74 patients, and at least 2 vessel segments in 78 patients. Three patients underwent treatment of only 1 vessel segment, ie, fewer than dictated by the study protocol.

Complications of treatment are listed in Table 3. Four patients had study-related adverse events, resulting in a procedure-related complication rate of 5%, or an approximate risk of 1% per treated vessel segment. In 2 patients, this involved arterial perforation by a guidewire and in 2 patients, arterial rupture during balloon inflation. Three patients died as result of these complications, and the trial was halted each time for careful evaluation of the treatment-related complications, as well as an interim risk-benefit analysis by the National Institutes of Health Data Safety Monitoring Board (for which the investigators remained blinded to the outcome data of each group).

Medical Management and Therapy Intensity Level
The intensive care management of patients was similar among centers. Nimodipine was used in 98% of patients. Prophylactic volume expansion and hemodilution were instituted as dictated by the study protocol. Induced hypertension was used in 49% of patients, 51% of patients in the pTBA group and 48% of patients in the control group. Fifty-five percent of patients were in vasospasm by TCD criteria (Table 4), and 28% of patients developed a DIND (Table 5, \(P=0.89\)). The incidence of TCD vasospasm was similar in both groups (\(P=0.88\)). Fewer patients in the pTBA group developed a DIND, but the difference was not statistically significant.

There was a trend toward a relation between the presence of a DIND and worse outcome in the control patients. Of the 58 patients in the control group who did not develop a DIND, 29 (50%) had an unfavorable outcome, including 10 (17%) who died. Of the 27 patients in the control group who did develop a DIND, 19 (70%) had an unfavorable outcome (\(P=0.11\)), including 6 (22%) who died (\(P=0.56\)). In the pTBA group, the presence of a DIND did not increase the proportion of patients with a poor outcome. When a DIND was present, 50% of patients had a poor outcome versus 51% when a DIND was absent (\(P=1.0\)). There was no correlation between the number of vessels treated with pTBA and either the presence or absence of a DIND (\(P>0.05\)).

When hypertensive, hypervolemic, hemodilution therapy failed to reverse a DIND, patients underwent angiography followed by therapeutic angioplasty and/or intra-arterial administration of calcium blockers or papaverine. Twenty-six percent of patients in the control group and 12% of patients in the pTBA group required endovascular treatment for medically refractory vasospasm, a statistically significant difference (\(P=0.03\); Table 6). Internal carotid artery dissection occurred during therapeutic angioplasty in 1 patient (3%) but was successfully treated with a stent. This was the only reported complication from therapeutic angioplasty. Of the 32 patients treated with therapeutic angioplasty, sustained reversal of a DIND was achieved in 11 patients (34%). Four patients required multiple angioplasty procedures.

Outcome data were obtained for all patients enrolled in the trial. Outcome analysis as per the dichotomized GOS revealed a trend toward a more favorable outcome in the treatment group, but the differences were not statistically significant (Table 7). pTBA resulted in an absolute risk reduction of 5.9% and a relative risk reduction of a 10.4% unfavorable outcome (\(P=0.54\)). Patients with good Hunt-Hess grades (ie, 1 or 2) were analyzed separately. Sixty-six patients were included in this analysis (Table 7). Again, patients in the pTBA group trended toward a better outcome, but the results were not statistically significant. pTBA resulted in an absolute risk reduction of an unfavorable outcome of 9.5% and a relative risk reduction of a 29.4% unfavorable outcome (\(P=0.73\)). Patients with Hunt-Hess grades 3, 4, or 5 showed no improvement from pTBA. Length of stay was used as a surrogate measure for utilization of medical resources. The average stay in the Intensive Care Unit and total length of hospitalization were similar in both groups (\(P=0.89\) and 0.35, respectively).

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Table 6. Need for Therapeutic Angioplasty With or Without Intra-Arterial Infusions

<table>
<thead>
<tr>
<th></th>
<th>No Therapeutic Angioplasty</th>
<th>Therapeutic Angioplasty</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>pTBA</td>
<td>75 (88.2%)</td>
<td>10 (11.8%)</td>
<td>85</td>
</tr>
<tr>
<td>Control</td>
<td>63 (74.1%)</td>
<td>22 (25.9%)*</td>
<td>85</td>
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<tr>
<td>*P&lt;0.03.</td>
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Discussion

To date, only a single intervention has been shown to have a positive effect on outcomes related to aneurysmal vasospasm, namely, oral administration of nimodipine during the weeks immediately after hemorrhage. The work presented here represents an effort to expand the treatment options for prevention of vasospasm and the associated poor outcomes related to a DIND. The primary outcome measure, dichotomized GOS score at 3 months after hemorrhage, was no different between the patients treated with pTBA and controls. Nor was there a difference in the secondary outcome measures of vasospasm defined by TCD, length of stay in the Intensive Care Unit, or total length of hospitalization. However, the secondary outcome measure, incidence of DIND, trended toward significance, with 24% of pTBA patients developing DIND versus 32% of controls. A significant difference was identified in the need for therapeutic angioplasty, with only 12% of pTBA patients requiring this procedure compared with 26% of controls, reflecting a lower incidence of severe, medically refractory vasospasm in the pTBA group. Further analysis of the clinical outcomes based on initial Hunt-Hess grade suggested a positive therapeutic effect in the better-grade patients, with poor outcomes seen in 22.8% of the pTBA patients versus 32.3% of controls. This 9.5% absolute difference, or 29.4% relative difference, failed to achieve statistical significance due to the smaller number of patients in this subgroup.

Several factors may explain our findings. This phase II study was designed to examine the safety and feasibility of pTBA and to determine whether the effect of treatment would be substantial enough to warrant further testing in a phase III clinical trial. Although an effect was seen, a larger study would be required to determine statistical significance. From the present study, definitive conclusions regarding efficacy cannot be drawn.

Second, other factors that are not offset by treatment with pTBA may influence outcome. The impact of the initial hemorrhage is a major determinant of outcome, which is in part reflected in the Hunt-Hess grade, as described before. Other factors that are known to influence outcome include age, the presence of hydrocephalus, subsequent treatment by surgery or endovascular coiling, habits (eg, smoking), and genetic profile. In our study, patients in the pTBA and control groups were well matched with respect to initial clinical condition and subsequent treatment. The only exception was the occurrence of hydrocephalus, which occurred at a higher but not statistically significantly increased rate in the pTBA group. Most patients received treatment for hydrocephalus early in their hospital course, and we cannot state the exact impact of hydrocephalus on outcome in these patients, nor did we specifically collect long-term data on hydrocephalus, as this was not the focus of the study. Because hydrocephalus is associated with worse outcome after SAH, any bias in this regard would be against the treatment group and favor the control group.

Whether a larger trial should be designed depends on the balance between treatment effect and risk of treatment. Such a trial would likely include only Hunt-Hess grade 1 or 2 patients, as this was the subgroup in which a greater difference in outcome was observed. If the 9.5% absolute reduction in poor outcome between the pTBA patients and the control patients is real and were borne out in further studies, then 10 or 11 patients would need to be treated to prevent 1 poor outcome. Naturally, this needs to be balanced against the procedural risk (number needed to harm) as well as other factors, such as overall incidence of DIND at a particular site and development of new drugs or less invasive treatments that may help to prevent DIND. The number needed to harm in this study would be 19.

Although the statistical design and outcome evaluation tools used in this study are different and no direct comparison can be made, the number needed to treat is within the same range as that of other recent clinical trials, such as the International Subarachnoid Aneurysm Trial (number needed to treat = 14), or the use of intravenous tissue plasminogen...
activator in the setting of acute stroke (number needed to treat=9). Moreover, it is clearly less than that of other interventions that have become accepted as standard treatment, such as carotid endarterectomy for asymptomatic carotid artery stenosis, with a need to treat 85 patients to prevent 1 stroke per year.

The number of vessels that need to be treated in each individual patient to exert an effect on the occurrence of vasospasm remains uncertain. The incidence of DIND was similar in patients who had 2 vessel segments versus 4 vessel segments treated. Whether this reflects an overall lack of treatment effect or that pTBA of 1 or 2 vessels is sufficient to generate a “downstream” effect remains to be determined. Treatment of fewer vessels presumably would be associated with a lower complication rate.

It should be noted that all complications occurred early in the experience of the participating interventionalists. In hindsight, 1 of the patients who died of vessel rupture had previously unsuspected polycystic kidney disease diagnosed at the time of organ donation and had a subtle irregularity of the basilar artery that likely represented a dissecting aneurysm or other inherent weakness of the vessel wall, and the patient should have been excluded from the study. In another patient, a less stiff balloon should have been used for navigation into a vessel with an acute angle of origin, and this could have prevented vessel perforation. With accumulation of experience during our trial, the difficulty and risks associated with navigating into smaller vessels such as the A1 and P1 segments became more apparent. In 2004, the treatment protocol was revised to include only both supraclinoid internal carotid arteries, the M1 portion of the middle cerebral arteries, the basilar artery, and the dominant vertebral artery as target vessels, with a reduction in procedure-related complications after this point.

In summary, although the trial was unsuccessful as defined by the primary end point, the findings are at least somewhat encouraging in that there seems to be proof of concept, with a statistically significantly decreased need for therapeutic angioplasty in the patients who received pTBA. However, it does not appear that pTBA makes a significant impact on clinical course, and as such, as well as because of the difficulties in accruing patients in this trial, we do not recommend further study of pTBA. Although endovascular therapies seem a logical means of averting DIND from aneurysmal SAH, the focus should be on treatments that are less complex and more efficacious.

Appendix

The Balloon Prophylaxis for Aneurysmal Vasospasm (BPAV) Study Group

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Disclosures

None.

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