Endovascular treatment for symptomatic cerebral vasospasm after subarachnoid hemorrhage: transluminal balloon angioplasty compared with intraarterial papaverine

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The authors retrospectively evaluated the short-term neurological improvement of 69 patients undergoing endovascular treatment for symptomatic cerebral vasospasm after aneurysmal subarachnoid hemorrhage (SAH). The patient group observed here is a subset of patients enrolled in the multicenter North American Trial of Tirilazad in SAH. Thirty-one patients were treated with intraarterial administration of papaverine (IAP). Fourteen patients were only treated with transluminal balloon angioplasty (TBA), and 24 patients received a combination of angioplasty and papaverine.

The purpose of this study was to compare the effects of IAP and TBA on short-term clinical improvement of patients. Daily clinical staging with the modified Glasgow Coma Scale and every-other-day transcranial Doppler (TCD) measurements allowed for a close investigation of the clinical course. Furthermore, this study was designed to investigate the effects of treatment timing on short-term outcome.

Although TCD studies demonstrated a decrease in flow velocities in the middle cerebral artery in both treatment groups, indicating a vasodilating effect of both treatment modalities (\(dv = -18.4 \text{ cm/second for papaverine, } dv = -26.04 \text{ cm/second for angioplasty; } p = 0.5509\)), there was no significant difference in clinical improvement at Days 1 and 4 postprocedure (\(p = 0.1996\)). Neither of the two treatment forms showed an effect of therapy timing on neurological outcome.

Neither IAP nor TBA was correlated with a high percentage of short-term neurological improvement. The authors discuss reasons why those procedures may result in limited clinical change.

Key Words * angioplasty * brain * papaverine * subarachnoid hemorrhage * tirilazad

Cerebral vasospasm as a sequel to aneurysmal subarachnoid hemorrhage (SAH) is a well-known entity.
Angiography demonstrates vasospasm in the 2nd week posthemorrhage in as many as 67% of all patients suffering from subarachnoid bleeding. In 30% of SAH patients an ischemic deficit develops as result of vasospasm. The condition is life-threatening and contributes tremendously to the morbidity and mortality rates for patients with SAH. The peak incidence of vasospasm after SAH as shown by angiography occurs on Days 5 to 7. Clinical vasospasm is often delayed and is usually diagnosed on Day 7 after SAH.[12] The mortality or disability rate from ischemic deficits related to cerebral vasospasm ranges as high as 13.5%.[7,11,12]

Standard protocols for the prevention and management of cerebral vasospasm have been established. These management protocols at different centers throughout the U.S. include prophylactic administration of calcium antagonists (nimodipine), hypervolemic therapy, and, after onset of clinical symptoms for spasm, hypertensive and hemodilutional therapy.

Zubkov, et al.,[20] introduced the use of transluminal angioplasty to treat medically refractory vasospasm occurring after SAH. Later, Kassell and coworkers[9] described the use of papaverine as a pharmacological vasodilator as an alternative option to angioplasty in the treatment of vasospasm after SAH. Although recommended only with caution by the authors of this first anecdotal report, intraarterial papaverine (IAP) administration was soon introduced at many centers as an alternative to angioplasty in the treatment of cerebral vasospasm.

In the 14 years after the initial report there have been a large number of studies on the use of endovascular treatment for vasospasm as a sequel to SAH.[1-6,8-11,13,14-17,18,19,21] However, many of the early reports on the benefits of the treatments are anecdotal, and most studies were uncontrolled, involved numbers of patients that were too small to show more than a trend of beneficial effects, or used ambiguous scales to determine clinical improvement in patients after treatment.

Because few studies focus on the comparison between papaverine and percutaneous transluminal balloon angioplasty (TBA) as treatment alternatives, controversy regarding the benefit of one method over the other remains unresolved.

In recent years there have been reports on timing strategies for endovascular treatments.[1,13,17,19] Recommendations range from treatment of vasospasm that presents only angiographically with no clinical symptoms[19] to a lag time as long as 24 hours after the clinical deterioration.[1] In reviewing the literature, we find no consensus on treatment timing.

The present study was designed to compare treatment of TBA with IAP for their effectiveness on short-term neurological improvement and the effects on cerebrovascular flow velocities as measured with transcranial Doppler (TCD) ultrasonography. Retrospectively, we scrutinized the data from 69 patients who were originally enrolled in the North American Trial for Tirilazad and underwent one or two of the endovascular treatment modalities during their clinical course. Furthermore, effects of treatment timing on clinical improvement and on TCD changes were analyzed.

**CLINICAL MATERIAL AND METHODS**

**Patient Population**

Sixty-nine patients who were originally enrolled in the North American Trial of Tirilazad and admitted to the different trial centers between June of 1992 and February of 1994 were treated for clinical vasospasm after aneurysmal SAH by means of endovascular modalities after medical treatment had failed. These
patients constitute only a small subgroup of the original 902 patients who were randomized for the tirilazad trial after informed consent. Of the 69 patients, 31 received IAP and 38 were treated with either TBA only (14 patients) or with a combination of TBA and IAP (24 patients).

In the clinical course prior to development of vasospasm, all patients had undergone surgery for sufficient obliteration of the aneurysm that was causing the SAH.

The mean age of the complete subset of patients studied here was 51.97 years (standard deviation [SD] 10.24 years) and ranged from 30 to 77 years. The treatment groups showed significantly different age distributions (p = 0.0003) (Table 1).

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<td><strong>PATIENT CHARACTERISTICS AND RESULTS</strong></td>
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*Unless otherwise specified, values expressed in parentheses are SD. † Denotes statistical significance.

Most of the aneurysms that caused SAHs arose from the anterior communicating artery (44%), followed by the carotid bifurcation and/or the proximal carotids (23.19%) and the posterior circulation (15.94%). Aneurysm location was not significantly different between the treatment groups (p = 0.318).

On admission to the various trial centers, severity of neurological impairment was determined by the modified Glasgow Coma Scale (mGCS) score, which ranged from 1 to 5, with a score of 1 indicating no or minimal impairment and a score of 5 indicating severe disability. The majority of all patients (37 [53.62%] of 69) presented with a score of 1 or 2. Scores of 3 or 4 were seen in 39.12% of patients. Five patients presented with a score of 5 (7.25%).

Clinically evident vasospasm occurred by a mean of 6.25 days (SD 2.75 days) after SAH. The treatment groups showed no significant difference in the time for development of clinical vasospasm (p= 0.433) (Table 1).

Angiography was performed and used by a blinded reader of the central registry of the tirilazad trial to grade the severity of vasospasm. A 25% decrease in the vessel diameter was defined as mild vasospasm,
moderate vasospasm as a narrowing of the vessel by 50%, and severe vasospasm as a narrowing by 75%.

In the present population angiographically determined vasospasm was found to be mild in 15 patients (21.74%), moderate in 32 (46.38%), and severe in 22 (31.88%). There was no significant difference in severity of vasospasm between both treatment modalities (p = 0.481).

**Neurological Assessment**

To determine the exact effects of either treatment, changes in neurological course were monitored clinically by using the mGCS. In contrast to the GCS, the mGCS uses the worst motor response, recording the extremity with the worst motor performance and, by this, reflecting a focal deficit as well as a decreased level of consciousness. Changes of no less than two points were regarded as significant. Ratings recorded include the mGCS changes from 2 days before treatment, as well as changes from treatment day, to the mornings of posttreatment Days 1 and 4. By this the clinical pre- and posttreatment courses were observed.

**Transcranial Doppler Measurements**

Transcranial Doppler ultrasound measurements were obtained every other day as part of the study protocol for the tirilazad trial. For the present patient subset the last TCD measurement obtained before the actual endovascular treatment (IAP or TBA) was recorded and compared with the TCD measurement after treatment. Thus, the mean flow velocities in the middle cerebral artery (MCA) of the most affected side were determined before and after the endovascular treatment, allowing for an estimation of the change in arterial diameters over the course of treatment. This allowed us to observe immediately the effectiveness of treatment on vasospasm. A change of 20 cm/second in flow velocity was regarded as significant. A significant decrease was taken as evidence for arterial dilation, and an increase of MCA flow velocity was regarded as evidence for narrowing of the vessel diameter.

In the IAP group 29 of 31 patients had regular TCD ultrasound measurements over the complete clinical course. In the TBA group, TCD measurements were recorded for 29 of 38 patients.

**Treatment Timing**

The dates and times of vasospasm onset as well as of endovascular treatments were known for both treatment groups. Furthermore, in a majority of cases, dates and times of neurological worsening were recorded. Given these data the lag time between onset of clinical vasospasm and endovascular treatment could be calculated. Timing groups were established retrospectively for both endovascular treatment modalities. Cases with treatment as soon as 0 to 2 hours after onset of deterioration were combined. The next groups received treatment with a lag of 2 to 6, 6 to 12, 12 to 24, 24 to 48, and more than 48 hours. The treatment groups were subsequently tested for effects on outcomes on Days 1 and 4 as well as on TCD measurements.

**Statistical Analysis**

Statistical analysis was performed using a commercially available software package (STATISTICA; StatSoft, Inc., Tulsa, OK). The two treatment groups were compared for Day 1 and Day 4 outcomes after treatment as well as for pretreatment course, age, gender, admission neurological score, severity of vasospasm, location of aneurysm, TCD velocities, and mGCS on the morning of the treatment day.

To investigate the effect of treatment timing, treatment with IAP and TBA were considered
Independently. Each group was retrospectively subdivided into treatment timing groups, and the timing groups were considered independently and tested for outcome on Days 1 and 4, as well as for TCD velocities and pretreatment course.

Multiple regression analysis was used to examine predictive factors for outcomes on Days 1 and 4 and for TCD velocity changes. This analysis was performed for the two treatment groups as well as for the timing groups retrospectively established within them.

Changes in TCD velocities and in mGCS score through treatment within groups were tested using the paired t-test.

RESULTS

Treatment With Intraarterial Papaverine

Patients who received IAP were treated within a mean of 15.29 hours (range 0-72 hours) after onset of clinical symptoms of cerebral vasospasm.

Over the course of the first 24 hours posttreatment, 21 patients (67.74%) remained neurologically at pretreatment levels, four (12.90%) improved by two or four points on the mGCS, and six (19.35%) deteriorated by two, three, or four points.

Compared with the last pretreatment mGCS, 12 patients (38.71%) in the IAP group improved neurologically in the first 96 hours posttreatment. Five (16%) of these patients gained three or four points on the mGCS and one (3.2%) even improved a dramatic seven points compared with treatment day. All four patients who improved during posttreatment Day 1 showed sustained improvement on posttreatment Day 4. Of the 12 patients who improved over the course of the first 4 days posttreatment, only one (3.22%) had deteriorated by three points during posttreatment Day 1.

There was no correlation between outcome on Days 1 and 4 and lag time between onset of clinical vasospasm and treatment in the IAP group.

Transcranial Doppler Measurements and Papaverine

A significant decrease of MCA flow velocity was detected using the paired t-test. In the IAP group the mean flow velocity dropped from \( v_{pre} = 142 \text{ cm/second} \) to \( v_{post} = 123.61 \text{ cm/second} \), which was statistically significant (\( p = 0.0197 \)).

Timing Groups

Twenty-eight of 31 patients in the IAP-treated group could be entered into treatment timing groups.

Neurologically, no significant different clinical course could be identified between the different timing groups when comparing Day 1 and Day 4 mGCS changes.

However, in examining the timing groups independently, we found that a significant difference for change in TCD flow velocities could be demonstrated in the IAP group for treatment before and 12 hours after onset of symptoms. The group treated within a range of 12 hours after onset of neurological deterioration reacted with a significant decrease in arterial narrowing as determined by TCD flow velocity (v) measurements (\( dv_{lt12h} = -31.9 \text{ cm/second} \)). On the other hand, the group treated with a lag
time of more than 12 hours showed no significant changes in flow velocities ($d_{v_{gt12h}} = 1.54 \text{ cm/second; } p = 0.0353$).

Comparison of demographic data shows significantly different age and gender distributions between treatment timing within 12 hours (younger and more male patients) and treatment after 12 hours of onset ($p_{age} = 0.0385, p_{sex} = 0.0142$).

In an attempt to identify factors that influence the outcomes on Days 1 and 4, as well as the changes in TCD values, the data were entered into a multiple regression analysis. However, no predictive factor for the outcomes on Days 1 or 4 or the changes in vasospasm as determined by TCD ultrasound could be identified.

**Transluminal Balloon Angioplasty**

The 38 patients who were treated with TBA for symptomatic cerebral vasospasm or a combination of TBA and IAP underwent their procedures in a mean of 21.89 hours (range 0-180 hours) after onset of cerebral vasospasm.

**Neurological Improvement**

Of the patients undergoing TBA or a combination of TBA and IAP on Day 1 postprocedure, 25 patients (65.79%) remained neurologically unchanged from treatment-day level, whereas nine patients (23.68%) deteriorated and four (10.53%) improved. All four patients who had improved neurologically on Day 1 maintained improvement through Day 4. Of the originally neurologically unchanged, six patients (15.79%) showed an improvement through Day 4 posttreatment with an increase of two or four points on the mGCS score. Fifteen (39.47%) of those patients who were neurologically unchanged on Day 1 remained unchanged after Day 4 posttreatment. Deterioration was seen in three (7.89%) of the originally unchanged patients. One of these patients showed a dramatic drop of seven points on this scale between Days 1 and 4. For one patient Day 4 data were not available.

Overall, 96 hours posttreatment 11 (28.95%) of the 38 patients treated with TBA showed significant neurological improvement, whereas 17 patients (44.74%) maintained a treatment-day level and nine patients (23.68%) deteriorated clinically.

**Flow Velocity Changes Determined by TCD**

Using the paired $t$-test for dependent subgroups, we were able to demonstrate a significant difference between pre- and posttreatment flow velocities as measured with TCD ultrasound in the mean MCA of the more symptomatic side. For the TBA group, there was a reduction from $v_{pre} = 152.24 \text{ cm/second}$ to $v_{post} = 123.45 \text{ cm/second}$ ($p = 0.0075$).

**Timing Groups**

Thirty-one of 38 patients treated with TBA could be entered into timing groups. The different groups were tested for effects of treatment timing on neurological improvement on Days 1 and 4, as well as for neurological pretreatment course and change in the MCA flow velocity as determined by TCD measurements.

**Timing and Neurological Improvement**
For patients undergoing TBA no overall positive effect on neurological improvement could be identified based on treatment within a limited amount of time.

A significant difference between timing groups could be found at the time mark of 2 hours after onset of symptoms. Comparison of the subset of patients treated within 2 hours after onset of symptoms (four patients) with the subset that gained treatment with a delay of more than 2 hours (27 patients) showed significant differences in Day 1 neurological improvement as determined by the mGCS. The group treated earlier showed a marked deterioration in mGCS scores at that time mark. There was a noted decline of 4.5 points on the mGCS in the group treated within 2 hours compared with a mean decline of 0.222 points in the comparison group (p = 0.0224).

**Timing and TCD Measurements**

Statistical analysis within and among timing groups was performed to search for significant changes in the MCA flow velocities of the side most symptomatic for cerebral vasospasm.

A significant decrease in the MCA flow velocity through treatment could be demonstrated for patients undergoing TBA within 12 and 24 hours after onset of symptoms. Significant decreases in mean MCA flow velocities demonstrated for treatment within 12 hours compared with more than 12 hours after onset of symptoms were determined as $\text{dv}_{12h} = 36.33 \text{ cm/second}$ (SD 54.98 cm/second, $p = 0.0227$). For a lag time of 24 hours until treatment a decrease in MCA flow velocity of $\text{dv}_{24h} = 30.0 \text{ cm/second}$ (SD 54.46 cm/second, $p = 0.0373$) was found.

**Intraarterial Papaverine Compared With Transluminal Balloon Angioplasty**

We were not able to detect any significant differences between the two treatment modalities in terms of neurological improvement on Days 1 and 4 posttreatment.

The difference in the pre- to postprocedural changes of the MCA blood flow velocities between the two treatment modalities were determined by TCD. The IAP group showed an overall decrease of $\text{dv}_{\text{IAP}} = -18.39 \text{ cm/second}$ (SD 39.27 cm/second), whereas the TBA group decreased by a mean of $\text{dv}_{\text{TBA}} = -28.79 \text{ cm/second}$ (SD 55.25 cm/second). This difference, however, was not statistically significant ($p = 0.5509$).

**DISCUSSION**

**Neurological Improvement After TBA**

The present study demonstrates short-term clinical improvement in 28.95% of patients treated with TBA for intractable cerebral vasospasm after SAH.

The literature contains numerous reports on the effectiveness of percutaneous TBA for cerebral vasospasm after SAH. The results range from clinical improvement in 31 to 80% of patients. In their early series of 50 patients treated with TBA, Mayberg and colleagues[13] demonstrated sustained clinical improvement and favorable outcomes in 32 patients (64%). In their 1989 report Newell and coworkers[15] showed sustained clinical improvement in eight of 10 patients treated with balloon angioplasty. In their small series of 13 patients Coyne, et al.,[3] showed neurological improvement after 12 hours in 31% of cases. Eskridge and coworkers[5] treated 50 consecutive patients at the University of Washington. In their retrospective study they analyzed the effectiveness of balloon angioplasty on
cerebral vasospasm. Twenty-eight (61%) of their 46 patients with clinical vasospasm who underwent treatment within 18 hours after onset of symptoms showed sustained clinical improvement (according to the GCS) after 72 hours posttreatment, which was also demonstrated on TCD and angiography studies. In their study of 80 patients treated with TBA for neurological deterioration due to cerebral vasospasm, Rosenwasser and colleagues[17] were able to demonstrate clinical improvement in 70% and angiographic improvement in 90% of patients when they were treated within a lag time of 2 hours after onset of symptoms. Bejjani, et al.,[1] retrospectively studied the outcome of 31 patients after undergoing TBA, and 72% improved within 24 to 36 hours after angioplasty. A group of 21 of their patients treated within 24 hours after onset of deterioration showed dramatic clinical improvement.

Neurological Improvement After IAP

In our group of patients treated for cerebral vasospasm with IAP only, 38.7% showed a clear clinical improvement on Day 4 posttreatment.

The literature provides very few studies on the effectiveness of IAP for cerebral vasospasm after SAH. In an early paper on the use of IAP for cerebral vasospasm, Yoshimura and colleagues[18] showed a beneficial effect in eight of nine cases that demonstrated immediate clinical and angiographic improvement. Clouston, et al.,[2] were able to show significant clinical improvement in seven (50%) of 14 patients treated by administration of IAP. In a recent controlled study, Polin and coworkers[16] used the same group of patients that was treated with IAP as the current study. The 31 patients receiving IAP were matched to a control population of patients with the same clinical characteristics but managed only medically. No statistical difference in 3-month Glasgow Outcome Scale score could be demonstrated (58% favorable in controls, 45% in patients treated with papaverine).

Although there seems to be neurological improvement after balloon angioplasty and superselective infusion of papaverine for intractable cerebral vasospasm after SAH, this effect is not proven in most instances. Because of the paucity of controlled studies on this topic, there are no comparisons of the clinical course under treatment with the natural course of the disease.

Balloon Angioplasty Compared With Papaverine

Elliott and colleagues[4] have compared 52 patients treated for vasospasm who received either infusion of papaverine or underwent balloon angioplasty. However, this study focused not on neurological improvement but on changes of TCD blood flow velocities attributable to the treatment forms. Although showing a mean decrease of 20% in blood flow velocities when treating with papaverine, posttreatment velocities were not significantly lower than pretreatment levels. On the other hand, balloon angioplasty led to a 45% decrease of blood flow velocities to normal-flow levels after treatment. The authors concluded that balloon angioplasty is superior to papaverine administration in the treatment of cerebral vasospasm.

Timing of Endovascular Treatment Modalities

Cerebral vasospasm is known to be self-limited and resolves spontaneously by Day 14 after the initial SAH.[12] During its short occurrence period, it causes devastating damage to the brain tissue supplied by the spastic vascular territory. Furthermore, there is a time lag between onset of angiographically evident vasospasm and what we call clinical or symptomatic vasospasm.[12] Damage to the brain is likely to begin before the onset of symptoms that are attributed clinically to cerebral vasospasm.
In our series, the 38 patients treated with TBA for cerebral vasospasm did not demonstrate significant differences in clinical improvement on Day 1 or 4 between the different timing groups. Thirty-one of our patients suffering from intractable cerebral vasospasm after SAH received IAP alone. As was the case in the TBA group, a positive relationship between an early treatment with IAP and early neurological improvement could not be demonstrated. Early treatment was not predictive of neurological improvement for the first 4 days posttreatment in either subgroup.

However, we were able to determine a significant decrease in mean MCA flow velocities as measured by TCD ultrasonography for the 12 to 24-hour period. This suggests a timing effect in the angioplasty group.

We found a significant decline of Day 1 mGCS points in the timing group treated within 2 hours after onset of symptoms. This decline, however, appears to be an expression of an overall clinical course rather than a true effect of early TBA treatment. The group that was treated early already showed a statistically significant decline of 6.25 points on the mGCS in the pretreatment course compared with a reduction of 1.04 points in the comparison group during that time (p = 0.0149).

Curiously, patients with the shortest duration between diagnosis of vasospasm and treatment had a worse clinical course. The reasons for this unexpected finding are obscure but could represent previous misdiagnosis of neurological decline to causes other than vasospasm.

Several studies focus on the issue of treatment timing in percutaneous TBA for cerebral vasospasm.[1,13,17,19] Zubkov, et al.,[19] advocated endovascular treatment for vasospasm even before the onset of clinical symptoms. In their series 95 consecutive patients were treated for angiographic and clinical vasospasm with balloon angioplasty, and the policy in their protocol was to treat every patient with vasospasm with or without symptoms. The analysis of this study showed best results in patients who presented with a Hunt and Hess Grade III. In this group 85% of patients showed a significant improvement.

In their study, Mayberg and coworkers[13] advocated treatment within 18 hours after the onset of symptomatic cerebral vasospasm. Of their 50 patients undergoing TBA for symptomatic vasospasm after SAH, 64% showed immediate and sustained improvement. Early treatment appeared to produce better outcome, although this was not clearly demonstrated with treatment subgroups.

In their review article and report on 39 patients, Newell and coworkers[14] have advocated early treatment after onset of an ischemic deficit from vasospasm and before cerebral infarctions occur.

Bejjani and colleagues[1] have found significantly better outcomes in patients treated for vasospasm within a range of 24 hours after onset of clinical symptoms. In their retrospective study of 31 patients, 21 received treatment for clinically evident vasospasm within 24 hours after the onset of symptoms.

Rosenwasser and colleagues[17] treated 80 patients with balloon angioplasty for vasospasm after SAH. The 49 patients who underwent treatment within 2 hours after onset of symptoms showed angiographic improvement in 90% of cases and clinical immediate and sustained improvement in 70% of cases. These patients were treated aggressively after medical management with hypertensive, hypervolemic, hemodilutional therapy for 1 hour had failed to show clinical improvement.

There is still no consensus on the issue of treatment timing for percutaneous TBA in cerebral vasospasm. Recommendations range from treatment of only angiographically demonstrated vasospasm with no
clinical symptoms[19] to a lag time as high as 24 hours after clinical deterioration.[1] Based on intuition, for prevention of neurological deficits resulting from ischemic defects secondary to vasospasm, the earliest treatment appears to be the best option.

In an attempt to demonstrate the effectiveness of early treatment we retrospectively introduced our population into timing groups with a very small lag time between deterioration and treatment (treatment within 2 hours after deterioration). However, we were not able to demonstrate a significant effect.

**Limitations of the Present Study**

The results of this study run contrary to the general trend supporting the use of these treatment modalities presented in the literature. The advantage of this kind of database research is that blinded clinical investigators and examiners have the tendency to introduce observer bias into the data, especially considering this was not a goal of the study. However, disadvantages of this design must be acknowledged.

The unencouraging results may indicate that most U.S. centers have not gained the expertise required to obtain favorable results in these procedures. We cannot address this point. Neither can we discuss the technical aspects, aggressiveness, and algorithms used by the individual centers. We have tried to assume the longest possible delay between onset of vasospasm and treatment, although this may be a less accurate recording than in single-center retrospective trials. What is clear is that individual centers performing these procedures must be critical about their own results and indications. Although promising, these therapies have not withstood the critical controlled studies necessary to consider them as "gold standard." Further studies should address the efficacy of TBA or IAP used prophylactically for angiographic vasospasm and more closely examine the role of treatment timing.

**CONCLUSIONS**

We have examined the patterns of neurological improvement after TBA and IAP from a multicenter pharmaceutical trial. Neurological improvement, measured by mGCS, was seen in 10.53 and 28.95% of patients treated with TBA at 1 and 4 days, respectively; treatment with IAP resulted in improvement in 12.9 and 38.7% of patients at the same intervals. Although TBA and IAP tended to result in improved TCD ultrasound values, neither therapy consistently or reliably produced neurological improvement. Although this may represent a lack of treatment efficacy or a low point on the learning curve at the various centers, it does suggest that more prospective data on these treatments should be obtained.

**References**


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