Safety of Intrathecal Sodium Nitroprusside for the Treatment and Prevention of Refractory Cerebral Vasospasm and Ischemia in Humans

Jeffrey E. Thomas, MD; Robert H. Rosenwasser, MD; Rocco A. Armonda, MD; James Harrop, MD; William Mitchell, MD; Irfan Galaria, BA

Background and Purpose—The delayed type of cerebral vasoconstriction known as cerebral vasospasm (DCV) remains an important cause of permanent neurological injury and death following aneurysmal subarachnoid hemorrhage despite best current medical therapy. The mechanism of DCV remains unknown. A new treatment for refractory DCV using intrathecally delivered sodium nitroprusside and results in 21 patients is reported.

Methods—Candidates for treatment were patients with secured cerebral aneurysms presenting with clinical or radiographic SAH of grade 3 or higher. Patients with and without established DCV were treated. In 57% (12/21 patients) the diagnosis of severe DCV refractory to conventional treatment (HHH therapy and nimodipine) was established before treatment. Ten patients received ITSNP prophylactically. All patients with established DCV were in grave neurological condition before treatment. Procedures for vasospasm reversal were performed under simultaneous angiographic control with extensive hemodynamic and neurophysiologic monitoring. ITSNP was delivered by intraventricular or subdural catheter or by direct intraoperative suffusion. End points of intervention for established DCV were (1) durable angiographic reversal of vasoconstriction, (2) failure to effect reversal within 30 minutes, and (3) adverse effect. End points for DCV prevention were (1) post-SAH day 10 without evidence of vasoconstriction and (2) adverse effect. Cerebral angioplasty was used concomitantly in 9 treatments. The total number of treatments recorded was 171.

Results—The overall neurological outcome was good or excellent in 76% of patients (16/21) overall and in 88.9% of patients (16/18) having at least a 1-month follow-up. Of the 5 patients with less-than-good outcome, 4 had presented initially with severe neurological injury (clinical SAH grade 4). Angiography demonstrated reversal or amelioration of vasoconstriction in 83% (5/6 cases) of established DCV treated by ITSNP alone. Among patients treated prophylactically, none developed clinical DCV.

Conclusions—These results suggest that ITSNP is a safe and potentially effective treatment for established DCV and cerebral ischemia refractory to conventional treatment. The preliminary results of prophylactic treatment are also favorable with regard to safety. (Stroke. 1999;30:1409-1416.)

Key Words: cerebral aneurysm ■ human ■ ischemia ■ nitric oxide ■ vasospasm

Cerebral vasospasm is a chronic, delayed type of cerebral vasoconstriction (DCV) that typically occurs after aneurysmal subarachnoid hemorrhage (SAH). The exact cause of cerebral vasospasm is unknown despite awareness of the clinical entity for more than 40 years; vasospasm remains among the most important causes of mortality and neurological morbidity in patients initially surviving the rupture of a cerebral aneurysm, and an important cause of cerebral ischemia and stroke.1–4 Although the treatment protocol of intra-vascular volume expansion, hemodilution, induced hypertension, and cardiac performance enhancement (HHH therapy5–8) and the use of nimodipine9 have had a substantial beneficial effect on the treatment of this condition, it is not tolerated or is ineffective in some patients, who are subsequently susceptible to stroke, congestive heart failure, and death. Additional and alternative treatments for refractory DCV, particularly those specifically targeting the dilation of cerebral vessels, are needed.

Deficiencies in the vasodilatory influence of nitric oxide (NO) in DCV have been suggested by previous investigations.10–13 A new therapy for treatment and prevention of cerebral ischemia due to DCV, targeting the replacement of NO to the vascular wall, was devised and implemented. Recent laboratory and clinical experience indicates that the intrathecal administration of sodium nitroprusside (ITSNP), an NO donor, may specifically effect cerebral vasodilation.
and is durably effective in reversing DCV and salvaging neurological function.\textsuperscript{14–19} The results of 171 treatments of humans with ITSNP are summarized in this report.

**Subjects and Methods**

FDA approval under IND treatment protocol (#52307), Thomas Jefferson University Institutional Review Board approval (IRB control #979035), and informed consent were obtained by the principal investigator (J.E.T.). Patients with secured cerebral aneurysms considered at risk for or exhibiting post-SAH cerebral vasospasm were candidates for treatment. Criteria for determination of vasospasm risk, and hence eligibility for treatment in the prophylactic group, were (1) Hunt and Hess\textsuperscript{20} clinical SAH grade 3 or higher at presentation and (2) CT radiographic SAH scale\textsuperscript{21} of 3 or higher. Patients with established DCV refractory to conventional treatment (HHH therapy and nimodipine) for at least 1 hour were also eligible for treatment. Further absolute eligibility criteria were intracranial pressure (ICP) of <20 cm H$_2$O and facile withdrawal of CSF from the intracranial catheter in postoperative patients.

Exclusion criteria were asymptomatic patients not meeting the criteria for vasospasm risk; patients with unequivocal infarction or substantial intraparenchymal hematoma by CT; patients with unsecured ruptured aneurysms, patients with ICP not reducible below 20 cm H$_2$O, patients with significant hepatic or renal impairment, and patients <18 years of age.

Eligible patients were treated with sodium nitroprusside in solution (1 to 4 mg/mL, admixed with the patient’s cerebrospinal fluid [CSF]) delivered intraventricularly via ventriculostomy or into the subarachnoid space by way of subdural intracranial catheter or directly during microneurosurgery for clip ligation of the aneurysm. CSF (5 to 10 mL) was routinely withdrawn from the catheter before initiation of ITSNP administration, a portion of which was used to administer the medication. In patients treated prophylactically, a protocol was established using a 4.0 mg/mL solution in fresh autologous CSF.

In patients being treated for established refractory DCV, the procedure was monitored by cerebral angiography in addition to continuous arterial blood pressure, invasive cardiac performance measurement, intracranial pressure, and neurophysiological (electroencephalography, somatosensory evoked potential) monitoring. Refractory DCV was defined as progressive elevation in transcranial Doppler (TCD) recordings with or without corresponding delayed and otherwise unexplained neurological deficit. Dosing in these patients was intermittent and was adjusted according to the clinical response of the patient. End points of the intervention were (1) a durable angiographic reversal of vasoconstriction; (2) failure of the treatment to ameliorate vasoconstriction within 30 minutes, in which case cerebral angioplasty was used if appropriate; and (3) any adverse effect observed, such as recurrent systemic hypotension or intracranial hypertension. Early in the course of the investigation, angioplasty was sometimes begun simultaneously with ITSNP; these cases were generally excluded from any evaluations of treatment effectiveness, although the discrete hemodynamic and angiographic effects of angioplasty and ITSNP often appeared to be discernible.

Cerebral angiography in the DCV group was performed by transfemoral selective technique using the Philips Integris 3000 biplane digital subtraction angiography unit. Control cerebral angiograms were obtained at approximately 15-minute intervals during treatments intended to reverse DCV.

In patients being treated prophylactically the route of administration was via ventriculostomy exclusively. ITSNP/CSF (4.0 mg/mL, 1 to 2 mL in 2 divided doses) was delivered at consecutive 6-hour intervals to achieve 3 treatments per 24 hours. One of 10 patients receiving prophylactic treatment also received concomitant HHH therapy using phenylephrine hydrochloride (Neo-Synephrine, Bayer Corp) for induced hypertension. This patient had previously failed HHH therapy and underwent treatment for reversal of established DCV before prophylactic treatment was instituted. The remaining patients in the prophylactic group received no HHH therapy for cardiac performance enhancement other than intravascular volume expansion with crystalloid solutions.

TCD recordings were made twice per day per patient by a single operator specifically trained in the technique. To accommodate variations in readings secondary to hemodynamic changes, the carotid index was used as the criterion for measurement. The carotid index was defined as the mean middle cerebral artery velocity divided by the mean velocity in the cervical internal carotid artery.

Additional monitoring procedures associated with this treatment were arterial blood gases and serum and CSF assays for the presence of cyanate ion. Arterial blood gas determinations were made at the time of treatment for DCV patients and on a regular basis at least once a day in the intensive care unit for all patients.

**Results**

Results of treatments are summarized in Tables 1 and 2. See Figures 1 through 4 for angiograms of patients profiled in the tables.

**Adverse Effects**

Adverse treatment events were rare. Three episodes of brief hypotension occurred, all associated with relatively high doses of ITSNP early in the course of the investigation, all in patients receiving emergency treatment for refractory DCV, and all of <1 minute’s duration. No episode of profound hypotension occurred; no episode of intracranial hypertension occurred. A majority (6/10) of patients in the prophylactic group experienced nausea in the setting of treatments. This effect was blunted by pretreatment with the antiemetic Zofran (ondansetron HCl, 4.0 mg IV). No overt manifestation of cyanate toxicity occurred, and cyanate determinations in the serum were undetectable. In 3 patients who had their treatments briefly interrupted because of severe nausea, TCD elevations subsequent to treatment interruption were reversed by reinstitution of ITSNP. Because of the emergency nature of ITSNP treatments for established refractory DCV, TCD data immediately before and after treatment were inconsistently obtained. When these data were obtained, reductions in flow velocities were observed in most cases (data not shown).

**Outcome**

No adverse outcome related to treatment with ITSNP occurred. All patients treated were discharged from the hospital uneventfully. Condition at discharge was good or excellent in all patients initially presenting with clinical grade 3 SAH or better at this institution. One grade 4 patient was discharged to rehabilitation in poor condition and subsequently made an excellent recovery. Two patients were treated at outside institutions after having had severe DCV, manifest by profound neurological deficits (including obtundation and hemiplegia or paraplegia), for >12 hours. These patients (2 and 11) subsequently made fair and good neurological recoveries, respectively, with good ambulatory capability and moderate expressive speech dysfunction.

**Angiographic Effects**

Complete and rapid reversal of cerebral vasoconstriction in the DCV group with eventual good clinical outcome was achieved without the use of angioplasty in all\textsuperscript{3} patients receiving at least 30 mg of ITSNP. Four other patients receiving this amount of ITSNP simultaneously had angio-
plasty performed in constricted proximal vessels, and no attempt was made to evaluate the effectiveness of the treatment in these patients, although clinical outcome was also good to excellent in this group. One patient did not demonstrate an immediate angiographic response to ITSNP (no significant vasodilation observed after 30 minutes, prompting cerebral angioplasty of the basilar artery), but TCD improved in anterior circulation vessels not treated by angioplasty and the patient did not require retreatment, eventually achieving excellent clinical outcome. The effect was demonstrated by angiography to be long lasting (12 to 72 hours) and permanent in several cases, in which clinical and TCD improvement obviated further treatment. In a total of 7 cases a definite angiographic effect of ITSNP was observed in which angioplasty was either not used or the effect of ITSNP was discernible from that of angioplasty (eg, dilation of distal or contralateral cerebral vessels). The angiographic effect was of the following 2 main types: (1) obvious reversal of vasoconstriction in relatively large conductance vessels and (2) decrease in cerebral circulation time, controlled for mean arterial blood pressure, with or without an obvious change in caliber of conductance vessels.

### TABLE 1. Results of Treatment in Group 1: Patients With Established DCV

<table>
<thead>
<tr>
<th>Treatment No.</th>
<th>Patient No.</th>
<th>Age, y/SEX</th>
<th>Initial SAH Clinical Grade</th>
<th>Manifestation of DCV</th>
<th>ITSNP Dose Total, mg/Route of Administration</th>
<th>Angiographic Response Type</th>
<th>Angioplasty</th>
<th>Adverse Event/Outcome/ Follow-Up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>38/F</td>
<td>3</td>
<td>Obtundation</td>
<td>7/IV</td>
<td>NA</td>
<td>Y</td>
<td>None/excellent/14</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>45/F</td>
<td>3</td>
<td>Hemiplegia, coma</td>
<td>30/IV</td>
<td>Reversal, SSCCT</td>
<td>N</td>
<td>None/fair/12</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>38/F</td>
<td>2</td>
<td>TCD elevation</td>
<td>10/IV</td>
<td>Y</td>
<td>None/10</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>58/F</td>
<td>3</td>
<td>MCA spasm</td>
<td>4/IO</td>
<td>Reversal</td>
<td>N</td>
<td>None/excellent/6†</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>50/M</td>
<td>3</td>
<td>Hemiplegia, aphasia</td>
<td>30/IV</td>
<td>Reversal</td>
<td>N</td>
<td>Hypotension/excellent/10</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>50/M</td>
<td>3</td>
<td>TCD reelevation</td>
<td>7/IV</td>
<td>N/A</td>
<td>Y</td>
<td>None/excellent/10</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>35/M</td>
<td>4</td>
<td>TCD elevation</td>
<td>48/IV</td>
<td>None</td>
<td>Y</td>
<td>None/good/8</td>
</tr>
<tr>
<td>8</td>
<td>8</td>
<td>36/F</td>
<td>3</td>
<td>Hemiparesis</td>
<td>48/IV</td>
<td>N/A</td>
<td>Y</td>
<td>None/excellent/7</td>
</tr>
<tr>
<td>9</td>
<td>9</td>
<td>40/M</td>
<td>4</td>
<td>Hemiparesis, dysphasia</td>
<td>12/IV</td>
<td>N/A</td>
<td>Y</td>
<td>None/good/7§</td>
</tr>
<tr>
<td>10</td>
<td>11</td>
<td>65/F</td>
<td>4</td>
<td>TCD elevation</td>
<td>32/IV</td>
<td>N/A</td>
<td>Y</td>
<td>None/poor/5</td>
</tr>
<tr>
<td>11</td>
<td>12</td>
<td>41/F</td>
<td>3</td>
<td>Severe angiographic spasm</td>
<td>88/IV</td>
<td>Reversal</td>
<td>N</td>
<td>None/excellent/5</td>
</tr>
<tr>
<td>12</td>
<td>13</td>
<td>54/M</td>
<td>4</td>
<td>Paraplegia, obtundation, unsecured aneurysms, S/P previous craniotomy</td>
<td>8/0</td>
<td>Reversal</td>
<td>N</td>
<td>Hypotension/good/3</td>
</tr>
<tr>
<td>13</td>
<td>14</td>
<td>54/M</td>
<td>4</td>
<td>TCD elevation</td>
<td>16/IV</td>
<td>Reversal</td>
<td>Y</td>
<td>None/good/3</td>
</tr>
<tr>
<td>14</td>
<td>15</td>
<td>51/F</td>
<td>3</td>
<td>Obtundation, hemiparesis</td>
<td>8/0</td>
<td>Improved; mild effect</td>
<td>N</td>
<td>None/excellent/3</td>
</tr>
</tbody>
</table>

Excellent outcome was defined as absent neurological deficit or premorbid level of neurological function. All patients designated as having good outcome were independently ambulatory at last evaluation. IV indicates intraventricular; IO, intraoperative; SD, subdural; S/P, status post; and SSCCT, siphon-to-sinus cerebral circulation time (length of interval in seconds).

*Ambulatory; †death occurred from lung cancer 6 mo after treatment; ‡duration of <60 s; §postoperative course complicated by symptomatic hydrocephalus and ventriculoperitoneal shunt infection, with moderate persistent expressive dysphasia.

### TABLE 2. Results of Treatment in Group 2: Patients at Risk for DCV Treated Prophylactically

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y/SEX</th>
<th>Initial Hunt and Hess Grade</th>
<th>CT Grade</th>
<th>Post-SAH Days Treated</th>
<th>Dosage</th>
<th>Adverse Effects</th>
<th>DCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>11*</td>
<td>62/M</td>
<td>4 (paraplegia)</td>
<td>4</td>
<td>12–17</td>
<td>8 mg TID</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>13</td>
<td>75/F</td>
<td>3 (hemiplegia)</td>
<td>3</td>
<td>2–3, 10–12</td>
<td>8 mg TID</td>
<td>Nausea</td>
<td>No</td>
</tr>
<tr>
<td>14</td>
<td>67/F</td>
<td>3 (stupor)</td>
<td>4</td>
<td>2–9</td>
<td>8 mg TID</td>
<td>Nausea</td>
<td>No</td>
</tr>
<tr>
<td>15</td>
<td>80/F</td>
<td>3 (stupor)</td>
<td>4</td>
<td>2–7</td>
<td>8 mg TID</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>16</td>
<td>52/F</td>
<td>4 (coma)</td>
<td>3</td>
<td>1–3, 5</td>
<td>4 mg TID</td>
<td>Nausea</td>
<td>No</td>
</tr>
<tr>
<td>17</td>
<td>51/F</td>
<td>3</td>
<td>3</td>
<td>9–11</td>
<td>4 mg TID</td>
<td>Mild nausea</td>
<td>No</td>
</tr>
<tr>
<td>18</td>
<td>64/M</td>
<td>4 (hemiplegia)</td>
<td>3</td>
<td>4–6</td>
<td>4 mg TID</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>19</td>
<td>75/M</td>
<td>4 (hemiplegia)</td>
<td>4</td>
<td>1–4, 9</td>
<td>4 mg TID</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>20</td>
<td>56/M</td>
<td>3</td>
<td>3</td>
<td>4–7</td>
<td>4 mg TID</td>
<td>Mild nausea</td>
<td>No</td>
</tr>
<tr>
<td>21</td>
<td>39/F</td>
<td>2</td>
<td>2</td>
<td>2, 4–10</td>
<td>4 mg TID</td>
<td>Nausea</td>
<td>No</td>
</tr>
</tbody>
</table>

All patients received medication via an intraventricular route of administration. All patients presenting with hemiplegia or paraplegia had concomitant obtundation or coma.

*Prophylactic treatment began 24 h after vasospasm reversal treatment; HHH therapy was used concomitantly in this patient after initial treatment (see text).
ITSNP intraoperatively, a much smaller amount of medication was required to effectively dilate a specific arterial segment.

**Discussion**

Delayed cerebral vasospasm, now the leading cause of permanent neurological disability and death in patients surviving the rupture of a cerebral aneurysm, has remained a mystery to investigators for many years. Bagley, in 1928, systematically studied the effects of repeated hemorrhages in the subarachnoid space. The review and experimental examination by Jackson of the condition he refers to as “aseptic hemogenic meningitis” alludes to the extraordinary toxicity of the subarachnoid deposition of the supernatant fraction of hemolysed blood, which he noted to contain, among other things, oxyhemoglobin. Only relatively recently has light begun to be shed on possible molecular mechanisms of DCV, and among the more plausible molecules in this regard are NO and ET-1 (reviewed in Reference 24). Because little is known as yet of the fundamental pathophysiology of DCV, treatments for the condition to date have been relatively nonspecific. Examples include calcium channel blockade, HHH therapy, and selective mechanical (balloon) cerebral angioplasty.7,9,25

DCV resulting in delayed cerebral ischemia often presents as an evolving ischemic stroke subsequent to a hemorrhagic stroke (SAH). Although the exact molecular mechanisms of DCV remain unknown, it is intriguing that oxyhemoglobin appears to be simultaneously capable of activating the gene for the most potent known mammalian vasoconstrictor, increasing levels of ET-1 mRNA in the CSF,27–29 and also removing the influence of the potent vasodilator NO, the physiological antagonist of ET-1, from the blood vessel wall by direct binding.30–33

If ET-1 and NO are important factors in maintaining a dynamic equilibrium in vasomotor tone, the liberation of
oxyhemoglobin from erythrocytes spilled into the subarachnoid space by SAH might be expected to result in a profound disequilibrium between the vasomotor effects of these molecules, resulting in unmitigated vasoconstriction. That DCV is a substrate-driven phenomenon characterized by delayed availability and exhaustibility of the substrate and susceptible to being overwhelmed by repletion of NO is suggested by its limited time course and its possible response to exogenously administered NO. The delayed liberation of oxyhemoglobin by lysis of erythrocytes after SAH may provide a partial explanation for the delay almost uniformly observed in DCV.

Although NO had not been “discovered” until 1980, when it was proposed as the equivalent of EDRF by Furchgott and Zawadzki, the drugs known as nitrovasodilators, whose actions were mediated by this molecule, had already been in use for many years in provoking vasodilation. Intravascular nitrovasodilators were also used to combat DCV before their fundamental nature as NO donors was known, and intrarterial administration of sodium nitroprusside in particular has been used to combat cerebral vasospasm.

The tendency of intravascular sodium nitroprusside to induce arterial hypertension has been a deterrent to its clinical use for cerebral vasospasm. The physical properties, however, of NO, a free radical gas and the smallest known biologically active molecule, make its effectiveness by an adventitial route of administration somewhat predictable, in that it would be expected to readily penetrate the vascular wall. The short biological half-life of the molecule would also favor local vasodilator action; thus, the intrathecal strategy appears to have particular advantages for DCV treatment.

The preliminary nature of these investigations is emphasized by the numerous adjustments to dosage described in this report. It does appear, however, that if ITSNP can reverse DCV, relatively large doses of it are required to do so in a time interval short enough to be helpful to the patient. The range of doses in the present study was 30 to 88 mg.

Toxicities related to ITSNP in this range that might be anticipated include arterial hypotension, intracranial hypertension, and cyanate toxicity, none of which were observed. Possible explanations for this include variations in CSF circulation, the amount of blood in the subarachnoid space, and the tendency of intravascular sodium nitroprusside to induce arterial hypertension.

**Figure 2.** A, 58-year-old female patient presenting with large bilobed ruptured aneurysm of the left middle cerebral artery (MCA) (patient 4, Table 1), which also manifested severe vasospasm. The patient had sustained a second subarachnoid hemorrhage while in the hospital, and microsurgical clip ligation was recommended. The vasospasm was simultaneously treated intraoperatively by direct sulfusion onto the constricted MCA. B, Intraoperative angiography demonstrated elimination of the aneurysm and restoration of caliber of the MCA. Vasospasm did not recur. The patient required no further intervention and made a full neurological recovery.

**Figure 3.** A 54-year-old male presented with unsecured anterior cerebral artery aneurysms and right middle cerebral artery aneurysm after unsuccessful craniotomy at an outside institution (patient 11, Table 1). The patient presented 10 days after hemorrhage with stupor and paraplegia from severe cerebral vasospasm (A). The risks of endovascular technique (both coil embolization and cerebral angioplasty) were believed to be excessive; microsurgical repair with subsequent aggressive treatment for severe symptomatic vasospasm was elected by the patient’s family after detailed discussion. Intraoperative angiogram after clip ligation of 3 aneurysms and intraoperative sulfusion of ITSNP demonstrated elimination of aneurysms and restoration of caliber in spastic vessels (B). Postoperatively the patient was awake, alert, and able to move both legs on command. No further treatment was undertaken.
Same patient as shown in Figure 3. A, Severe vasospasm refractory to HHH therapy returned 24 hours postoperatively, involving both right- and left-sided anterior circulation. The right supraclinoid internal carotid artery and proximal right middle cerebral artery were dilated by cerebral angioplasty while ITSNP was administered simultaneously; the left-sided vessels were treated by ITSNP alone, without angioplasty. A substantial improvement in the perfusion of both hemispheres was observed 30 minutes after initiation of treatment (B). Prophylactic treatment with ITSNP was then begun and continued for 5 days (Table 2), at which time cerebral angiography was repeated (C). Dramatically improved cerebral perfusion was present at the same mean arterial blood pressure and intracranial pressure. The patient made a slow but steady neurological recovery, with full ambulatory and motor capability and moderately expressive speech dysfunction. 4.1, Right internal carotid artery (ICA) injection, anteroposterior projection; 4.2, left ICA injection, anteroposterior projection; 4.3, right ICA injection, lateral projection; and 4.4, left ICA injection, lateral projection. Angiographic frames corresponding in computer-determined time sequence are shown. No changes in arterial blood pressure or in intracranial pressure were observed.
and the inadvertent removal of drug from the intrathecal compartment by the mandatory withdrawal of CSF before a new injection. The effect of blood in the subarachnoid space on the vasodilatory influence of ITSNP is complex and includes effects on the circulation of CSF, and therefore ITSNP, and the role of hemoglobin in capturing the NO and cyanate molecules: the heme moiety binds NO directly, and methemoglobin traps the cyanate ion as cyamethemoglobin in a nonenzymatic oxidation reaction.\textsuperscript{44} \textsuperscript{45}

Although safety and not efficacy is the focus of this brief report, these preliminary data suggest that this treatment may become a useful tool for the reversal and prevention of cerebral ischemia due to DCV. The majority of patients treated thus far by this method have had satisfactory clinical outcomes, and several dramatic improvements in vasospasm have been observed. How much of this is attributable to ITSNP alone, however, remains a matter of conjecture. Because of angiographic observations consistent with improved collateral circulation throughout the brain (decreased cerebral circulation time) in the setting of ITSNP treatment, further investigations using a more formal measurement of cerebral blood flow, such as xenon-enhanced CT, are warranted. Such observations are not inconsistent with earlier reports regarding the influence of intravenous sodium nitroprusside on cerebral autoregulation.\textsuperscript{45} \textsuperscript{46}

These data also suggest that DCV may be preventable by the early and constant repletion of NO to the blood vessel wall by way of the subarachnoid space after aneurysmal SAH during the known period of DCV risk (4 to 14 days).\textsuperscript{34} This is also conjectural and can be determined only by a randomized prospective trial, which is now underway at this institution.

We conclude that ITSNP represents a potentially useful treatment for the chronic delayed type of human cerebral vasospasm following aneurysmal SAH, with implications both for larger conductance vessels and smaller resistance vessels below the level of angiographic resolution. If these results are validated by further studies, better clinical outcomes may be achievable in a group of patients historically at high risk for neurological disability and death.

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References
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