Management of hypertensive emergencies in acute brain disease: evaluation of the treatment effects of intravenous nicardipine on cerebral oxygenation

Clinical article

PRADEEP K. NAROTAM, M.D., VARUN PURI, M.D., JOHN M. ROBERTS JR., M.S., CHARLES TAYLON, M.D., YASHAIL VORA, M.D., AND NARENDRA NATHOO, M.D., PH.D.
Division of Neurosurgery, Creighton University Medical Center, Omaha, Nebraska

Object. Inappropriate sudden blood pressure (BP) reductions may adversely affect cerebral perfusion. This study explores the effect of nicardipine on regional brain tissue O₂ (PbtO₂) during treatment of acute hypertensive emergencies.

Methods. A prospective case–control study was performed in 30 patients with neurological conditions and clinically elevated BP. All patients had a parenchymal PbtO₂ and intracranial pressure bolt inserted following resuscitation. Using a critical care guide, PbtO₂ was optimized. Intravenous nicardipine (5–15 mg/hour) was titrated to systolic BP < 160 mm Hg, diastolic BP < 90 mm Hg, mean arterial BP (MABP) 90–110 mm Hg, and PbtO₂ > 20 mm Hg. Physiological parameters—intracranial pressure, PbtO₂, central venous pressure, systolic BP, diastolic BP, MABP, fraction of inspired O₂, and cerebral perfusion pressure (CPP)—were compared before infusion, at 4 hours, and at 8 hours using a t-test.

Results. Sixty episodes of hypertension were reported in 30 patients (traumatic brain injury in 13 patients; aneurysmal subarachnoid hemorrhage in 11; intracerebral and intraventricular hemorrhage in 3 and 1, respectively; arteriovenous malformation in 1; and hypoxic brain injury in 1). Nicardipine was effective in 87% of the patients (with intravenous β blockers in 4 patients), with a 19.7% reduction in mean 4-hour MABP (115.3 ± 13.1 mm Hg preinfusion vs 92.9 ± 11.40 mm Hg after 4 hours of therapy, p < 0.001). No deleterious effect on mean PbtO₂ was recorded (26.74 ± 15.42 mm Hg preinfusion vs 27.68 ± 12.51 mm Hg after 4 hours of therapy, p = 0.883) despite significant reduction in CPP. Less dependence on normobaric hyperoxia was achieved at 8 hours (0.72 ± 0.289 mm Hg preinfusion vs 0.626 ± 0.286 mm Hg after 8 hours of therapy, p < 0.01). Subgroup analysis revealed that 12 patients had low pretreatment PbtO₂ (10.30 ± 6.49 mm Hg), with higher CPP (p < 0.001) requiring hyperoxia (p = 0.02). In this group, intravenous nicardipine resulted in an 83% improvement in 4- and 8-hour PbtO₂ levels (18.1 ± 11.33 and 19.59 ± 23.68 mm Hg, respectively; p < 0.01) despite significant reductions in both mean MABP (120.6 ± 16.65 vs 95.8 ± 8.3 mm Hg, p < 0.001) and CPP (105.00 ± 20.7 vs 81.2 ± 15.4 mm Hg, p < 0.001).

Conclusions. Intravenous nicardipine is effective for the treatment of hypertensive neurological emergencies and has no adverse effect on PbtO₂. (DOI: 10.3171/JNS.2008.109.12.1065)

Key Words • acute brain disease • brain tissue oxygen • nicardipine

Hypertensive emergencies are characterized by severe BP elevations; according to international guidelines on cardiopulmonary resuscitation and emergency cardiovascular care, immediate BP reduction is required to prevent or limit acute target-organ damage. In many neurocritical care patients, acute hypertension is not the primary precipitating cause of neuronal injury but rather a modulating factor. Initial high BP (> 160/90 mm Hg) has been shown to be associated with adverse outcomes in patients with stroke and ICH. Inappropriate and sudden BP reductions in patients with neurological disorders can adversely affect cerebral perfusion, particularly in patients with ischemic stroke, raised ICP due to ICH, traumatic mass lesions, and brain swelling, thereby aggravating cerebral ischemia and often leading to cerebral infarction. However, uncontrolled BP may result in cerebral edema, hypertensive encephalopathy, ICH, and elevated ICP. In addition, BP control

Abbreviations used in this paper: ACVS = acute cerebrovascular syndrome; BP = blood pressure; CBF = cerebral blood flow; CPP = cerebral perfusion pressure; FiO₂ = fraction of inspired O₂; ICH = intracerebral hemorrhage; ICP = intracranial pressure; MABP = mean arterial BP; PbtO₂ = regional brain tissue O₂; SAH = subarachnoid hemorrhage; TBI = traumatic brain injury.
following neurological procedures is essential to minimize postoperative complications. Despite these implications, limited clinical evidence exists regarding optimal BP management in neurocritical care patients.2,65

Low cerebral oxygenation, identified by partial pressure of PbtO₂ and jugular venous O₂ saturation monitoring, has been associated with a poor neurological outcome in patients with TBI and aneurysmal SAH.7,32,30,35,62 Among the many acute physiological parameters used to predict cerebral oxygenation in the past, CPP and percentage of O₂ saturation had emerged as key determinants. Experience accrued in the past decade has shown that CPP, alveolar–arterial difference in PaO₂, FiO₂, and ICP individually affect cerebral oxygenation and that manipulation of each of these factors produces some benefit in improving cerebral O₂ delivery.17,30,33,38,51 Recent evidence suggests that PbtO₂-directed clinical protocols improve O₂ delivery by manipulating the patient’s physiology, are superior to ICP/CPP-directed protocols, and have been associated with an improved clinical outcome.23,26,32,55,60 Although the direct effects of antihypertensive agents on PbtO₂ have not been previously studied, nimodipine has shown to have a deleterious effect on PbtO₂ in patients with severe SAH and may contribute to poor outcome following stroke.1,3,46,56

Nimodipine, a dihydropyridine Ca channel blocker, acts as an arterial dilator thereby increasing blood flow to the brain and ameliorating cerebral vasospasm following aneurysmal SAH. It also has also been shown to have a positive effect on neuronal function in patients with ischemia.18,21,24,25 In this prospective, case–control study we investigated the role of intravenous nimodipine in the management of acute hypertensive emergencies associated with acute neurological disorders, and herein we report its effect on regional cerebral O₂ delivery.

Methods

Patients who required intravenous antihypertensive therapy between January 2004 and July 2005 and who met the following criteria were included in the study: age ≥ 16 years; a diagnosis of an acute neurological disorder such as TBI, aneurysmal SAH, or spontaneous or hypertensive ICH; and having been classified with 1 of the following hypertensive clinical syndromes12—ACVS, posttraumatic hypertension,48 or acute postoperative hypertension.25 The evaluation of all patients was performed prospectively. An institutional review board approved the study, and informed consent was obtained from patients’ next of kin for the placement of a triple-lumen bolt for neuromonitoring, critical care management to optimize PbtO₂, and for data collection. Patients with prior cardiovascular disease who were chronically treated with β blockers, preexisting hypertension requiring ≥ 2 antihypertensive agents, a known allergy or intolerance to Ca channel antagonists, renal or liver failure, or who had experienced previous undesirable side effects from intravenous nimodipine were excluded from the study.

Upon admission to the intensive care unit, resuscitation was aimed at the following physiological goals: PaO₂ > 100 mm Hg; PaCO₂ 30–35 mm Hg; systolic BP > 120 mm Hg; central venous pressure 5–10 mm Hg; and urine output 0.5–1 ml/kg/hr. The bolt was inserted in a CT scan–evidenced “normal” area to measure ICP (Camino, Integra LifeSciences Corp), PbtO₂, and brain temperature (Licox, Integra LifeSciences Corp). Confused or infarcted brain was avoided to prevent erroneous readings.51 Invasive multimodal continuous monitoring included placement of an arterial line for blood sampling, continuous MABP monitoring, and a central venous catheter for measurement of central venous pressure.

The surgical and or medical treatment of elevated ICP was performed using current neurosurgical guidelines (in brief, the removal of surgical mass lesion; use of cerebrospinal fluid drainage via ventriculostomy, mannitol and hyperventilation [range 30–35 mm Hg] for intracranial hypertension, sudden neurological deterioration, or signs of herniation and ICP > 20 mm Hg; maintenance of CPP > 60 mm Hg; and the use of barbiturate coma and decompressive craniectomy for refractory intracranial hypertension). A craniotomy was performed urgently to evacuate intracranial mass lesions when clinically indicated. Optimization of regional cerebral oxygenation was performed using a PbtO₂-directed critical care–guided protocol as recently described.38 Therefore, episodes of cerebral ischemia, defined as PbtO₂ < 20 mm Hg, were minimized via the use of normobaric hyperoxia and the manipulation of ventilator parameters, triple-H therapy, and hemoglobin manipulation. Patients with aneurysmal SAH underwent angiography and craniotomy for aneurysm clipping. Mannitol, sedatives, paralytics, thiopental sodium, and cerebrospinal fluid drainage via ventriculoscopy were used to treat persistently elevated ICP, as clinically indicated.

Intravenous nimodipine was administered at an initial dose of 5 mg/hour and was gradually titrated (maximum dose 15 mg/hour) to achieve the following parameters: systolic BP < 160 mm Hg, diastolic BP < 90 mm Hg, MABP 90–110 mm Hg, and PbtO₂ > 20 mm Hg. Treatment was continued for as long as deemed clinically necessary by the attending physician. Drug infusion was suspended when the patient’s BP was within the preset parameters but was restarted if the BP rose. These were counted as treatment episodes. Other antihypertensive agents were added as clinically indicated. Patients with persistent hypertension were treated with oral antihypertensive agents upon discharge from the hospital.

The primary end point of the study was an effective clinical reduction in BP. For the secondary end points we examined the effect of nimodipine on PbtO₂. The changes in PbtO₂ and its relationship to the acute physiological parameters—such as systolic BP, diastolic BP, MABP, ICP, central venous pressure, FiO₂, and CPP—were examined on admission, following PbtO₂ optimization, preinfusion, at 4 and 8 hours during infusion, and at each of the treatment episodes (using paired t-tests).15,39,48,64 The effect of the acute physiological parameters on PbtO₂ was explored using Spearman correlation coefficients, and multiple logistic regression analyses were performed to evaluate the factors predictive of low PbtO₂. Nonlinear estimation examined variance in PbtO₂. The t-tests were used to examine differences in the acute physiological
Brain tissue oxygen and intravenous nicardipine parameters for ischemia (dichotomized at \( \text{PbtO}_2 < 20 \) mm Hg), the role of preexisting hypertension, and renal disease. Intergroup comparisons of the various clinical pathological entities, clinical syndromes, and treatment episodes were performed using t-tests and multivariate analysis of variance. The effect of nicardipine therapy on patients dichotomized as ischemic was performed using unpaired t-tests.

Results

Clinical and Demographic Data

All 30 patients with acute brain disease requiring intravenous nicardipine for treatment of hypertensive emergencies were prospectively evaluated, the majority of whom presented with TBI or aneurysmal SAH (80%). The ICP/PbtO2 bolts were inserted in the right frontal lobe in 26 patients, whereas in 4 patients left-sided bolts were placed to avoid contused or “abnormal” CT-documented areas. The mean patient age was 55.1 ± 19.4 years, with a male/female ratio of 1:1.2. Preexisting hypertension was present in 40% of patients and renal abnormalities were detected in 10%. A history of seizures was reported in 40% of patients and 20% had persistent neurological disability (Table 1).

Intravenous nicardipine was effective as a single first-line agent for the treatment of hypertension in 26 patients (87%) and in 54 (90%) of the hypertensive episodes. The mean duration of treatment was 2.85 ± 2.78 days (range 0.5–12 days). In 4 patients (6 episodes), intravenous esmolol was used to suppress tachyarrhythmia (2 cases) and to control the patient’s BP when maximal doses of nicardipine were ineffective (2 cases). Sixty episodes of acute hypertension were reported, with 63% of patients experiencing ≥ 1 hypertensive episode. Intravenous nicardipine was restarted and stopped according to clinical needs. A single patient with aneurysmal SAH receiving intravenous propofol experienced transient hypotension; nicardipine was withheld briefly and restarted later at a lower dose. Oral antihypertensive agents were used in 12 patients at hospital discharge. A single agent was required in 9 patients and multiple agents in 3 (Table 1). No relationship to preadmission hypertension was detected.

Optimization of PbtO2 Prior to Nicardipine Infusion

Low \( \text{PbtO}_2 \) was detected in 50% of patients following initial resuscitation (TBI in 9 and aneurysmal SAH in 6). Although ICP had a negative correlation to \( \text{PbtO}_2 \) (\( r = -0.427, p = 0.04 \)), multiple logistic regression analysis failed to show any effect of the acute physiological parameters on \( \text{PbtO}_2 \) following bolt placement. We found that ICP, CPP, and FiO2 accounted for 7–11% of the variation in \( \text{PbtO}_2 \) (nonlinear estimation). A significant improvement in \( \text{PbtO}_2 \) was achieved over 11.06 ± 11.09 hours, using the \( \text{PbtO}_2 \)-directed critical care guide (\( p = 0.049, \chi^2 \)-square analysis). No significant differences were noted in the acute physiological parameters before and after cerebral resuscitation (Table 2).

Effects of Nicardipine on \( \text{PbtO}_2 \), Physiological Parameters, and Ischemia

Prior to initiation of nicardipine, low \( \text{PbtO}_2 \) was documented in 36% of patients despite the \( \text{PbtO}_2 \)/critical care–guided protocol treatment. Treatment with intravenous nicardipine (first episode) resulted in a significant reduction in systolic BP, diastolic BP, and MABP with 4 hours of continuous infusion, an effect that was sustained at 8 hours (\( p < 0.0001 \), t-test) (Fig. 1 upper). None of the patients received blood transfusion during this period. No effect on ICP was observed. The \( \text{PbtO}_2 \) values remained unchanged despite a significant reduction in CPP (\( p < 0.001 \)) (Fig. 1 lower; Table 3). The FiO2 requirement was lower at 8 hours compared with preinfusion. Multiple logistic regression analysis revealed the strong relationship of FiO2 variation on \( \text{PbtO}_2 \) before drug infusion (\( R^2 = 0.656, p = 0.029 \)) at 4 hours (\( R^2 = 0.59, p = 0.05 \)) and 8 hours (\( R^2 = 0.75, p = 0.0065 \)) of treatment.

Further analysis was undertaken in patients with low \( \text{PbtO}_2 \) prior to nicardipine treatment. Twelve patients (40%) had a significantly higher FiO2 requirement than

### Table 1

Summary of clinical data in 30 patients with neurological conditions

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean admission GCS score (± SD)</td>
<td>7.68 ± 4.40</td>
</tr>
<tr>
<td>≤8</td>
<td>19 (63)</td>
</tr>
<tr>
<td>9–12</td>
<td>6 (20)</td>
</tr>
<tr>
<td>13–15</td>
<td>5 (17)</td>
</tr>
<tr>
<td>op procedures</td>
<td>15 (50)</td>
</tr>
<tr>
<td>craniotomy</td>
<td>14 (46.6)</td>
</tr>
<tr>
<td>ventriculostomy</td>
<td>30</td>
</tr>
<tr>
<td>acute brain disease</td>
<td>11 (37)</td>
</tr>
<tr>
<td>aneurysmal SAH</td>
<td>13 (43)</td>
</tr>
<tr>
<td>TBI</td>
<td>3 (10)</td>
</tr>
<tr>
<td>IVH</td>
<td>1 (3)</td>
</tr>
<tr>
<td>AVM</td>
<td>1 (3)</td>
</tr>
<tr>
<td>hypoxic brain injury</td>
<td>1 (3)</td>
</tr>
<tr>
<td>clinical syndromes</td>
<td>60</td>
</tr>
<tr>
<td>ACVS</td>
<td>19 (32)</td>
</tr>
<tr>
<td>acute postop hypertension</td>
<td>18 (30)</td>
</tr>
<tr>
<td>posttraumatic hypertension</td>
<td>23 (38)</td>
</tr>
<tr>
<td>efficacy of nicardipine</td>
<td>26 (87)</td>
</tr>
<tr>
<td>IV β blockers</td>
<td>4 (13)</td>
</tr>
<tr>
<td>oral antihypertensive agents</td>
<td>12 (40)</td>
</tr>
<tr>
<td>β blockers</td>
<td>6</td>
</tr>
<tr>
<td>Cu channel blockers</td>
<td>6</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>3</td>
</tr>
<tr>
<td>mean discharge GOS score (± SD)</td>
<td>3.8 ± 1.45</td>
</tr>
<tr>
<td>1</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>2</td>
<td>2 (6.67)</td>
</tr>
<tr>
<td>3</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>4</td>
<td>6 (20)</td>
</tr>
<tr>
<td>5</td>
<td>14 (46.6)</td>
</tr>
</tbody>
</table>

* ACE = angiotensin-converting enzyme; AVM = arteriovenous malformation; GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale; IV = intravenous; IVH = intraventricular hemorrhage; SD = standard deviation.
those in the nonischemic group (p = 0.01) (Table 4). Although at 4 hours 6 patients were still below the ischemic threshold, near doubling of mean PbtO2 was observed (10.55 ± 6.69 vs 19.25 ± 13.14 mm Hg, p = 0.0021), despite the significant reduction in MABP and CPP (Fig. 2 upper). Normobaric hyperoxia was still necessary at 8 hours (FiO2 0.77 ± 0.279) to sustain adequate PbtO2 in this group (R2 = 0.316, p = 0.04) (Fig. 2 lower).

**Clinical Syndromes, Disease, and Other Variables**

When the clinical syndromes were reviewed, pretreatment PbtO2 was the highest in the acute posttraumatic hypertension group (34.76 ± 18.32 mm Hg) followed by posttraumatic hypertension (26.78 ± 9.10 mm Hg) and ACVS (20.59 ± 17.26 mm Hg) (p = 0.02). The presence of preexisting hypertension or renal disease had no effect on any of the acute physiological parameters including PbtO2. No significant difference among the SAH, TBI, or stroke and those with elevated ICP; controlled treatment of acute hypertensive emergencies and their selection must be based on clinical indication.10,12,59 An ideal antihypertensive agent should provide the following: immediate and controlled BP reduction of 15–20% to clinical effect within 30–60 minutes; reduction in MABP of 10–15% (rapid-acting and titratable intravenous therapy); and a safeguard against uncontrolled hypotension. Furthermore, in patients with acute brain disease there should be no reduction in cardiac output and CBF; maintenance of adequate CPP in patients with ischemic stroke and those with elevated ICP; controlled treatment of postoperative hypertension in previously normotensive patients; and no adverse effects on cerebral oxygenation.48,59

Although ICP/CPP protocols and even triple-H therapy have improved clinical outcomes, death due to SAH, TBI, and stroke remains unacceptably high. Over the past 10 years, since the introduction of brain tissue O2 monitoring, attempts had been made to use normobaric hyperoxia, CPP elevation, induced hypertension, and optimization of hemoglobin to influence PbtO2.7,16,30,37,61,63 In May 2001, brain tissue O2 monitoring was introduced at our institution, and patients have been treated with a PbtO2-guided protocol. This treatment paradigm incorporates ICP/CPP management, triple-H therapy, normobaric hyperoxia, and hemoglobin manipulation when necessary in a multipronged escalating therapy intensity. In a recent review, Haitsma and Maas25 called for a targeted therapy for improving cerebral oxygenation guided by PbtO2.
Most recently, Stiefel et al.\textsuperscript{57,58} have reported that a PbtO\textsubscript{2}-directed clinical protocol is superior to using just ICP/CPP following severe brain injury.

Clinical deterioration in neurologically impaired patients may be attributable to raised ICP and low CPP, cerebral edema, impaired cerebral autoregulation, cerebral vasospasm, ischemia and/or infarction, or from a combination of these factors. Furthermore, systemic factors such as BP, cardiac output, arterial O\textsubscript{2} content, and hemoglobin may reduce O\textsubscript{2} delivery to the brain resulting in anaerobic metabolism, lactic acidosis, excitatory neurotransmitter release, and neurotoxicity, thereby aggravating cerebral ischemia and resulting in cell death.\textsuperscript{23} Although all patients were resuscitated using conventional means, 60\% were found to have low PbtO\textsubscript{2}. This is not surprising because standard resuscitation protocols have been shown to be inadequate to prevent cerebral ischemia.\textsuperscript{38,58}

In this study, prior to nicardipine infusion, the PbtO\textsubscript{2}/critical care–guided protocol optimized cerebral oxygenation within 26 hours with a relative risk reduction for ischemia of 78\%. Normobaric hyperoxia was most influential in affecting PbtO\textsubscript{2}. Collectively, however, the various acute physiological parameters could only account for no more than 20\% of the variation in PbtO\textsubscript{2}. The development of low cerebral oxygenation in 40\% of our patients prior to drug treatment may be attributed to microvascular spasm and/or cerebral dysautoregulation related directly to the ictus.\textsuperscript{27}

The management of acute hypertension in acute cerebrovascular conditions is challenging, and consensus on optimal BP reductions or selection of pharmaceutical agent remains controversial.\textsuperscript{9,10,22,43,48,59} On the one hand, treatment of BP may decrease the risk for further hemorrhage in patients with ICH, minimize the risk for rupture of cerebral aneurysms, and, in the acute postoperative period, prevent reperfusion bleeds after resection of an arteriovenous malformation. On the other hand, in patients with low PbtO\textsubscript{2}, BP lowering may reduce CPP and thereby
into cardiac and smooth muscle without changing serum bile, requiring frequent dose adjustments to prevent hyponatremia, and not producing any ICP elevations.6 In an open-labeled randomized trial comparing the combinations of nicardipine/enalaprilat and enalaprilat/labetalol for the treatment of postcraniotomy hypertension, both groups were shown to effectively control systolic BP.31

Although α–β blockers are also popular, their effects on cardiac output are marginal. Qureshi et al.43 have shown effective BP control within 24 hours when using labetalol (α–β blocker) as a first-line agent, augmented by nitroprusside or hydralazine, in patients with intracerebral hematomas. The effect of nitroprusside on BP is quite labile, requiring frequent dose adjustments to prevent hypotension, and the risk of toxicity is ever present during prolonged infusion. The use of this agent should therefore be avoided in patients with neurological conditions.39,42,48 Clonidine has sedative effects whereas nicardipine has positive effects on electroencephalography.12 Moreover, these agents have not been evaluated in relation to their effect on brain oxygenation.

The reduction in BP was achieved while maintaining CPP at > 70 mm Hg (mean 79 mm Hg in this study). Reinert et al.44 have shown that CPP elevations beyond 78 mm Hg have no significant effect on PbtO₂, whereas Robertson et al.47 have cautioned that complications may increase simply because ICP/CPP protocols have been used. The 20% reduction in CPP had no deleterious effect on PbtO₂ levels, and this is probably due to the arterial dilatation which reduces systemic vascular resistance, but has no effect on ventricular preload, cardiac output, or left ventricular systolic performance and is particularly advantageous over other Ca channel blockers (diltiazem and verapamil), which are associated with cardiac suppression.11

In addition, nicardipine has no venodilatory effects. This is particularly useful in preventing hypotensive episodes, providing stricter BP control, facilitating ease of titration, and not producing any ICP elevations.4 In an open-labeled randomized trial comparing the combinations of nicardipine/enalaprilat and enalaprilat/labetalol for the treatment of postcraniotomy hypertension, both groups were shown to effectively control systolic BP.31

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**TABLE 3**

*Effects of nicardipine on acute physiological parameters in 60 treatment episodes*  

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preinfusion</th>
<th>Level at 4 Hrs (mm Hg)</th>
<th>Level at 8 Hrs (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>Mean ± SD</td>
<td>p Value (t-test)</td>
</tr>
<tr>
<td>FIO₂</td>
<td>0.21–1.0</td>
<td>0.72 ± 0.289</td>
<td>NS</td>
</tr>
<tr>
<td>systolic BP</td>
<td>113–211</td>
<td>175.9 ± 17.85</td>
<td>NS</td>
</tr>
<tr>
<td>diastolic BP</td>
<td>57–138</td>
<td>85.65 ± 14.51</td>
<td>NS</td>
</tr>
<tr>
<td>MABP</td>
<td>94–165</td>
<td>115.33 ± 13.44</td>
<td>NS</td>
</tr>
<tr>
<td>CVP</td>
<td>2–18</td>
<td>8.33 ± 3.96</td>
<td>NS</td>
</tr>
<tr>
<td>ICP</td>
<td>1–47</td>
<td>14.37 ± 9.94</td>
<td>NS</td>
</tr>
<tr>
<td>CPP</td>
<td>70–159</td>
<td>100.68 ± 16.39</td>
<td>NS</td>
</tr>
<tr>
<td>PbtO₂</td>
<td>0.80–84.10</td>
<td>26.74 ± 15.42</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Control of BP was achieved without impact on PbtO₂ or ICP, despite the marked reduction in CPP. Less dependence on normobaric hyperoxia was also recorded.
Brain tissue oxygen and intravenous nicardipine

Effects on both small and large vessels of the brain, whereas intraarterial nicardipine has an immediate and sustained effect on cerebral vasospasm. In addition, locally applied nicardipine in prolonged-release implants has reduced the incidence of delayed ischemic deficits.

The neuroprotective effects of nicardipine may extend beyond its well-described role as an antihypertensive and antivasospastic agent. It reverses endothelin-1–related vasospasm in experimental SAH and counteracts the microanatomical changes in spontaneously hypertensive rats. In 1985, Gaab et al. demonstrated that nicardipine dilates cerebral blood vessels and increases cerebral O₂ tension, whereas Rosenbaum et al. reported that patients treated with intravenous nicardipine therapy within 6 hours had more favorable outcomes than those beginning therapy after 6 hours and that hyperbaric O₂ and nicardipine accelerated neurological recovery after 15 minutes of complete global ischemia. Furthermore, nicardipine has been reported to decrease aneurysmal vasospasm. Additionally, in patients with small- to medium-sized acute intracerebral bleeds, autoregulation of CBF (determined by PET scanning) was preserved with MABP reductions using nicardipine.

Although our study findings may be weakened by the size of the cohort, the absence of a comparison with other standard antihypertensive agents on PbtO₂ response, the presence of heterogeneous disease, and regional PbtO₂ readings, the present study is, to our knowledge, the first to evaluate the effects of nicardipine on cerebral oxygenation in the setting of acute brain pathological entities.

In patients with low PbtO₂, treatment with nicardipine resulted in an 87% mean improvement in PbtO₂, with a relative risk reduction for ischemia of 31%, despite 18% reduction in MABP and 19% reduction in CPP. Because the acute physiological parameters accounted for no more than 20% of the variation in PbtO₂ and no blood transfusion was necessary, nicardipine therapy itself probably resulted in significant improvement in regional O₂ delivery even though there was a continued need for normobaric hyperoxia, suggesting that not all the microvascular spasm could be reversible with nicardipine.

The Hagen–Poiseuille law, which represents flow of
Comparison of the effects of intravenous nicardipine on systemic and neurological parameters for all 60 treatment episodes.

<table>
<thead>
<tr>
<th>Neurophysiological Parameters</th>
<th>Systolic BP</th>
<th>Diastolic BP</th>
<th>MABP</th>
<th>FiO2</th>
<th>ICP</th>
<th>CPP</th>
<th>PbtO2</th>
<th>Infusion Interval</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
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<th>Yes</th>
<th>No</th>
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</thead>
<tbody>
<tr>
<td>Narrowed PbtO2</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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</tr>
<tr>
<td>Narrowed Infusion</td>
<td>0.667</td>
<td>0.647</td>
<td>0.647</td>
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<td>0.647</td>
<td>0.647</td>
<td>0.647</td>
<td>0.05</td>
<td>&lt;0.0001</td>
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Patients with low PbtO2 presented with higher systolic BP, MABP, and FiO2 prior to nicardipine treatment. An improvement in PbtO2 was recorded following nicardipine infusion at 4 and 8 hours despite reduction in CPP in this group. This resulted in lower FiO2 titration to maintain adequate cerebral oxygenation. The preinfusion, 4-hour and 8-hour values are presented as the mean ± SD.

Conclusions

Intravenous nicardipine is safe and effective as a first-line agent for the treatment of hypertensive emergencies associated with acute brain disease such as aneurysmal SAH, ICH, TBI, as well as in postoperative neurosurgically treated patients. Repeated episodic treatment of BP to physiological levels resulted in reduction of CPP without deleterious effect on PbtO2. In patients with low cerebral oxygenation, nicardipine improved PbtO2 most probably via dilation of the cerebral arteries and arterioles. Therefore, together with a PbtO2-directed protocol, nicardipine resulted in improvement of CBF and O2 delivery with the potential to reduce cerebral ischemia.

Disclosure

Dr. Narotam serves as a consultant for Integra Life Sciences. He has no direct financial gain from the sale of Licox or nicardipine (Cardene).

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P. K. Narotam et al.

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Current address for Dr. Nathoo: Alegent Health Neuroscience Specialists, Council Bluffs, Iowa.
Address correspondence to: Pradeep K. Narotam, M.D., Union Hospital Neuroscience, 1530 N. 7th Street, #501, Terre Haute, Indiana 47807. email:narotam@mac.com.