Hourly Blood Pressure Monitoring After Intravenous Tissue Plasminogen Activator for Ischemic Stroke Does Everyone Need It?

Venkatesh Aiyagari, MBBS, DM; Arunodaya Gujjar, MBBS, DM; Allyson R. Zazulia, MD; Michael N. Diringer, MD

Background and Purpose—Blood pressure (BP) control is considered essential in patients treated with tissue plasminogen activator (tPA) for ischemic stroke, and it is recommended that BP be monitored every 15 minutes to 1 hour for 24 hours in these patients. We postulated that patients whose BP is not initially elevated are unlikely to have elevated BP later and, therefore, may not need prolonged BP monitoring.

Methods—We performed a retrospective chart review of patients treated with intravenous tPA for ischemic stroke over a 3-year period. Patients with incomplete records were excluded.

Results—Seventy-nine patients (35 male, age 68.8 ± 14.3 years) were studied. Before tPA treatment, 16 patients (20%) had hypertension (systolic BP ≥ 185 or diastolic BP ≥ 110 mm Hg). All 16 patients had subsequent hypertension over the next 24 hours. Of the remaining 63, 27 patients (43%) had hypertension (systolic BP ≥ 180 or diastolic BP ≥ 105 mm Hg) within the first 6 hours. An additional 4 had minor transient systolic elevations (≥ 182 mm Hg) after 6 hours that normalized without treatment. Neurological worsening, seen in 13 patients (17%), was not associated with the presence of hypertension (initial or subsequent).

Conclusions—in patients receiving tPA for stroke, absence of hypertension at presentation does not preclude subsequent increase in blood pressure. However, if blood pressure is not elevated during the first 6 hours, subsequent hypertension over the next 18 hours is unlikely. This study is small and retrospective, and needs to be repeated in a larger prospective cohort. However, our results provide preliminary evidence to suggest that where resources are scarce, these patients may be discharged from the intensive care unit earlier than the recommended 24 hours, provided that they are not at high risk for neurological deterioration. (Stroke. 2004;35:2326-2330.)

Key Words: blood pressure ■ stroke ■ stroke units ■ tissue plasminogen activator

The American Academy of Neurology and the Stroke Council of the American Heart Association recommend that patients treated with intravenous recombinant tissue plasminogen activator (rt-PA) for stroke be admitted to an intensive care unit (ICU) or acute stroke care unit (ASCU). They recommend neurological assessments and blood pressure (BP) monitoring every 15 minutes for 2 hours, every 30 minutes for 6 hours, and every 60 minutes until 24 hours after starting treatment.1,2 It is also recommended that a systolic BP ≥ 180 mm Hg or a diastolic BP ≥ 105 mm Hg during and after treatment with tPA be treated with antihypertensive agents.

The rationale for recommending ICU/ASCU admission is not explicitly stated in those recommendations but is considered to be BP management and monitoring for neurological deterioration. The incidence of symptomatic intracerebral hemorrhage (ICH) is higher in patients treated with tissue plasminogen activator (tPA); however, the overall incidence of neurological deterioration from all causes in the first 24 hours in patients with an acute ischemic stroke (16%) is not significantly higher among those treated with tPA.2 Therefore, BP monitoring and treatment appear to be the primary reasons for admission to an ICU/ASCU.

Based on studies demonstrating the association between baseline hypertension and the development of ICH in patients treated with tPA, it is recommended that elevated BP be effectively treated before administering tPA. The rationale for antihypertensive treatment after treatment with tPA is less clear. In the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA stroke trial, hypertensive tPA patients who were treated with antihypertensives after randomization were less likely to have a favorable 3-month outcome than hypertensive patients who were not.
Investigators recommend treatment of hypertension according to the NINDS trial protocol.4

What has not been addressed in detail is whether patients who are initially normotensive also need frequent BP monitoring for 24 hours. Elevated BP immediately after stroke is known to spontaneously decline over the next few hours.5 Our hypothesis was that patients who do not have early elevation of BP are less likely to have hypertension later. If this were true, patients who are normotensive and not at high risk for neurological deterioration could be discharged from the ICU/ASCU much earlier than 24 hours, allowing better resource use. In this article, we describe the 24-hour BP profile in a cohort of patients treated with tPA and subsequently managed according to current recommendations in an ICU.

Materials and Methods
We performed a retrospective chart review of all patients admitted to a major university-affiliated tertiary care hospital over a 3-year period (June 1999 to May 2002) after treatment with intravenous tPA for acute ischemic stroke. All patients were admitted to the Neurology/Neurosurgery Intensive Care Unit (NNICU) and 24-hour monitoring and treatment of hypertension was performed according to the protocol outlined by the American Heart Association.1 Noninvasive automated BP recording was used in all patients and hypertension was defined according to criteria used in the NINDS tPA trial, namely systolic or diastolic BP >185 or >110 mm Hg, respectively, before receiving tPA and systolic or diastolic BP ≥180 or ≥105 mm Hg, respectively, after receiving tPA.6 The study was approved by the institutional review committee who also waived the requirement for informed consent.

We included patients who received tPA at our institution as well as those who received tPA at other institutions and were immediately transferred to our NNICU for further care. Patients were excluded if they received tPA after 3 hours from the onset of symptoms, had no complete documentation of serial BP or neurological examination findings during the 24 hours after tPA administration. The following baseline variables were studied: demographic data, past history of hypertension and whether it was treated, site and side of stroke, admission National Institute of Health Stroke Scale (NIHSS) score, and presence of early ischemic changes on the first CT scan (as noted on the radiology report). We also studied serial BP recordings and treatment of hypertension on presentation, as well as during the 24-hour period after the administration of tPA. Presence of neurological decline (defined by a decrease in Glasgow Coma Scale score by ≥2 points) and ICH and their relation to BP were also noted. Categorical variables were compared using the χ² test and continuous variables were compared using the 1-way ANOVA or Kruskal–Wallis test, and P<0.05 was considered significant.

Results
Over a 3-year period, 92 patients were admitted to the NNICU after being treated with intravenous tPA for ischemic stroke. Baseline BP recordings were unavailable in 7 patients and records were unavailable for 6 patients. Of the remaining 79 patients who formed the study population, 17 patients received tPA at another hospital and were subsequently transferred to our NNICU.

Mean age was 68.8±14.3 years and 35 (44%) were male. Sixty-seven percent had a past history of hypertension and 57% were being treated with antihypertensives. On presentation, the median NIHSS score was 12 (range 4 to 25) and 11% had an admission NIHSS score >20.

Initial BP recordings were available in all patients; however, between 1 and 2 hours after receiving tPA, only half of the patients had BP recordings according to the prescribed schedule (Figure 1). This was because of partial nonadherence to the monitoring protocol during the process of transfer from other hospitals or the emergency room to the NNICU. Once patients were admitted to the NNICU, BP recordings were according to protocol >90% of the time. As expected, the mean systolic and diastolic BP in the study population gradually declined over 24 hours (Figure 2). Six patients had their previous antihypertensive medication continued. Intravenous boluses of labetalol and hydralazine were used in the emergency room and the NNICU to treat BP that exceeded established limits. In addition, 1 patient received nitroglycerin infusion and 1 received intravenous diltiazem in the emergency room.

Of the 79 patients, 16 (20%) were hypertensive at presentation and 69% of all instances of hypertension before tPA treatment were treated. All 16 patients had elevated BP recorded during the subsequent 24 hours, as well. Of the remaining patients, 27 (43%) had hypertension in the 24 hours after receiving tPA, whereas 36 (57%) remained normotensive. Increase in systolic BP alone was most commonly seen (54%), whereas an isolated increase in diastolic BP was uncommon (5%). Fifty-four percent of all instances of hypertension in the NNICU were treated. On comparing groups of patients who were hypertensive on presentation, hypertensive after tPA, and normotensive, hypertensive patients were likely to be older (Table). The incidence of neurological deterioration, including ICH-related neurological deterioration, was not different among the 3 groups.
When we looked at the times when elevated BP was first recorded, most of the hypertensive patients had high BP recorded within the first 2 hours (Figure 3). High BP was first recorded/tPA administered elsewhere (%) 6 (37) 1 (4) 10 (28) 0.016
Early ischemic changes (%) 5 (31) 7 (28) 9 (25) NS
Intracranial hemorrhage (%) 1 (6) 1 (4) 2 (6) NS
Neurological deterioration (%) 5 (31) 3 (11) 5 (14) NS

NNICU indicates neurology/neurosurgery intensive care unit; NS, P=0.05; ICA, internal carotid artery; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator.

Variables Compared With BP

<table>
<thead>
<tr>
<th>Hypertensive at Presentation (n=16; 20%)</th>
<th>Hypertensive in NNICU (n=27; 34%)</th>
<th>Normotensive (n=36; 46%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean±SD)</td>
<td>75.3±12.4</td>
<td>70.9±12.9</td>
<td>64.4±14.9</td>
</tr>
<tr>
<td>Male (%)</td>
<td>7 (44)</td>
<td>12 (44)</td>
<td>16 (44)</td>
</tr>
<tr>
<td>Left cerebral infarction (%)</td>
<td>7 (44)</td>
<td>13 (48)</td>
<td>22 (61)</td>
</tr>
<tr>
<td>ICA territory affected (%)</td>
<td>16 (100)</td>
<td>25 (93)</td>
<td>33 (92)</td>
</tr>
<tr>
<td>History of hypertension (%)</td>
<td>13 (81)</td>
<td>19 (70)</td>
<td>21 (58)</td>
</tr>
<tr>
<td>Median NIHSS score (range)</td>
<td>11 (5–22)</td>
<td>10 (4–25)</td>
<td>15 (4–24)</td>
</tr>
<tr>
<td>tPA administered elsewhere (%)</td>
<td>6 (37)</td>
<td>1 (4)</td>
<td>10 (28)</td>
</tr>
<tr>
<td>Early ischemic changes (%)</td>
<td>5 (31)</td>
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Discussion

The incidence of hypertension at presentation in our study (20%) was similar to that in the NINDS rt-PA trial (18%). However, hypertension at presentation was treated twice as often in our patients when compared with the patients in the NINDS rt-PA trial (69% versus 34%). In the post-tPA period, the incidence of hypertension (43%) and the frequency of treatment of hypertension (54%) were similar to the NINDS trial (56% incidence, 37% treated). In contrast to the NINDS trial, the frequency of neurological deterioration was not higher in treated hypertensive patients in our study, although we treated hypertension more often.4 However, the fact that our definition of neurological decline (>2 points of the GCS) was different from NINDS definition (>4 points of the NIHSS) needs to be taken into account. It should also be mentioned that throughout this article, the term “hypertension” is not used in the traditional sense, but rather it is defined according to criteria for treatment of elevated blood pressure that was used in the NINDS rt-PA trial.6

Currently, only 1% to 5% of all patients with ischemic stroke receive tPA, although it is estimated that up to 15% of patients with acute ischemic stroke are eligible.7 Presently, even in the United States, adequate resources are not available to appropriately administer tPA to every eligible patient and provide adequate post-tPA care. The shortage of ICU/ASCU beds and critical care nurses is one of the many limiting factors. In a study performed in North Carolina during 2003, only 48% of the population lived in a county that had an acute stroke unit.8 In a recent survey of US hospitals, 57% reported that critical care nursing positions had the highest vacancy rate and were the most difficult to fill.9 This shortage of resources is likely to be more critical in most other countries. Recognizing that it might not be possible to make ideal resources universally available, one must try to provide the best possible care within the available framework.

To obtain results similar to those of the NINDS rt-PA trial, tPA should be used in accordance with the protocol used in the trial. Deviations from the protocol have been associated with a higher complication rate.10–12 However, not all deviations from the protocol are necessarily associated with a high complication rate. In the Connecticut cohort, the most frequent minor protocol violation was “blood pressure not monitored per recommendation.” Although concern for ICH is stated as the most important reason for BP monitoring and treatment, in this cohort, deviation from the BP monitoring
protocol was not associated with a higher incidence of ICH.\textsuperscript{13} It is also interesting to note that in our study, a significantly large proportion of patients was not monitored per protocol during the interval between administration of tPA and admission to the NNICU. A number of these patients were administered tPA at other institutions and were transferred to our institution because of the lack of resources to manage potential tPA-associated intracranial hemorrhage at these institutions. Given the fact that the highest incidence of hypertension occurs in the first few hours, it is important to stress the need for continuing BP monitoring and treatment during the process of transfer to the ICU/ACSU from the emergency room or another facility.

In our cohort, absence of hypertension at presentation did not preclude subsequent hypertension, but patients without BP elevation in the first 6 hours remained normotensive throughout the 24-hour period. Therefore, monitoring BP for a 6-hour period could identify a subset of patients who are unlikely to have subsequent BP elevation needing treatment and therefore might not need hourly BP monitoring thereafter.

Our study has limitations. It is a retrospective single-center study with a relatively small number of patients. These findings should be evaluated prospectively in a larger sample before the results can be generalized. Nonetheless, our findings raise the question, can one make the argument that patients who receive tPA do not need mandatory ICU/ACSU monitoring beyond a 6-hour period if no BP elevation has been noted? Receiving tPA does not put a patient at higher risk for neurological deterioration despite a higher incidence of ICH; therefore, frequent ICU/ACSU neurological assessment is not warranted merely based on the fact that tPA was administered. However, patients with certain risk factors such as high baseline NIHSS score (\textgreater{}20) and certain characteristics of the initial computed tomography scan, such as presence of cerebral edema, mass effect, dense middle cerebral artery sign, and, in some studies, presence of early ischemic change, are at increased risk for ICH when treated with tPA and they should be monitored closely.\textsuperscript{12,14–19} In the NINDS rt-PA trial, of the 18 hemorrhages occurring in the first 24 hours, 8 were in the first 6 hours. Of the remainder, 6 had a baseline NIHSS score \textgreater{}20. Details of the BP profile of the remaining 4 patients are not available; however, if one assumes that half of these 4 patients had hypertension, then the incidence of ICH in nonhypertensive patients with NIHSS score \textless{}20 after 6 hours appears to be similar to that of the placebo group. Thus, nonhypertensive patients with an NIHSS score \textless{}20 do not seem to have a particularly high incidence of symptomatic ICH after 6 hours.\textsuperscript{20} Although hourly neurological assessment might permit earlier detection of ICH, it is not clear that earlier detection will improve patient outcome. The efficacy of any form of treatment for tPA-associated ICH is ineffective and unknown. Twelve of 13 patients who received blood products for ICH in the NINDS rt-PA trial died, as did the only patient in whom the clot was surgically evacuated.\textsuperscript{20} We do not suggest that patients with stroke do not benefit from monitoring. Organized inpatient care (stroke units) has been proven to reduce death and disability, albeit at an increased cost.\textsuperscript{21} The value of intensive continuous monitoring for all patients in an ICU/ACSU is, however, debatable.\textsuperscript{22–24} Two recent studies have suggested that intensive monitoring might lead to improved outcomes.\textsuperscript{25,26} Both studies, however, monitored patients for longer durations (at least 48 to 72 hours), and Sulter et al specifically excluded patients who were treated with tPA.\textsuperscript{26} Other than BP monitoring and monitoring for neurological deterioration, there could clearly be other reasons for admission to admit patients to an ICU/ACSU. Treatment modalities such as hypothermia and continuous glucose-insulin infusion are being currently evaluated in multicenter trials. If shown to improve outcome, then these treatments would require admission to an ICU/ACSU. However, at the present time, treatment with tPA is perhaps the only universally accepted indication for admission of otherwise stable patients to an ICU/ACSU for at least 24 hours. The results of our study raise the question of whether all such patients require intensive 24-hour monitoring. The ICU/ACSU cost of monitoring patients who receive tPA for 1 day is 4-times that of a nonintensive care unit bed.\textsuperscript{27} When resources are scarce and cost is an issue, the results of our study suggest that it might be possible to identify a subset in whom a lesser duration of intensive monitoring, perhaps even in the emergency room, may suffice.

**Conclusions**

In summary, stroke patients treated with tPA who remain normotensive for the first 6 hours are unlikely to have subsequent hypertension. Provided they do not have risk factors for ICH, they could be monitored similar to stroke patients who did not receive tPA. These findings need confirmation in a larger prospective cohort.

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