

EBEM Commentator
Latha G. Stead, MD

*From the Department of Emergency Medicine, Mayo Clinic
 Rochester, MN.*

Blood Pressure Control in Acute Stroke

[*Ann Emerg Med.* 2004;43:129-132.]

SYSTEMATIC REVIEW SOURCE

This is a systematic review abstract, a regular feature of the *Annals'* Evidence-Based Emergency Medicine (EBEM) series. Each features an abstract of a systematic review from the Cochrane Database of Systematic Reviews and a commentary by an emergency physician knowledgeable in the subject area.

The source for this systematic review abstract is: Blood Pressure in Acute Stroke Collaboration (BASC). Vasoactive Drugs for Acute Stroke (Cochrane Review). In: *The Cochrane Library*. Issue 2. Oxford, United Kingdom: Update Software; 2003.

The *Annals'* EBEM editors helped prepare the abstract of this Cochrane systematic review as well as the Evidence-Based Medicine Teaching Points.

OBJECTIVE

To assess the effect of lowering or elevating blood pressure in people with acute stroke, and the effect of different drugs on blood pressure in acute (ischemic or hemorrhagic) stroke.

DATA SOURCES

The Cochrane Stroke Group Trials Register was searched up to March 1999. Additional searches were conducted in EMBASE (1980 onwards), MEDLINE (1966 onwards), and

the Bath Information and Data Services Institute for Scientific Information (BIDS ISI; 1981 onwards). The Cochrane database of systematic reviews and other reviews of drugs included in this review were studied. Additionally, pharmaceutical companies and researchers in the field were contacted in an effort to identify unpublished and ongoing trials. This review was updated in September 2002 from the previous one published in April 2000.

STUDY SELECTION

Studies were included if they were randomized unconfounded, blinded, controlled clinical trials. Patients had to receive a blood pressure controlling agent or placebo within 2 weeks of their acute stroke, whether ischemic or hemorrhagic, irrespective of their hypertension status. The agents included in this review are oral angiotensin-converting enzyme inhibitors (eg, perindopril, captopril), oral β -blockers (eg, atenolol, propranolol), intravenous calcium channel blockers (eg, flunarizine, isradipine, nimodipine), oral calcium channel blockers (eg, nimodipine, nifedipine), intravenous diaspirin cross-linked hemoglobin (a hemoglobin analog), intravenous magnesium sulfate, intravenous naftidrofuryl, transdermal glyceryl trinitrate, intravenous piracetam, intravenous prostacyclin, and intravenous streptokinase. All of the above agents are expected to lower blood pressure, except for diaspirin cross-linked hemoglobin, which is supposed to elevate blood pressure.

DATA EXTRACTION

Two authors independently selected trials, extracted data, and assessed the quality of the trials. The drugs' effects on blood pressure, heart rate, death, and disability were analyzed.

MAIN RESULTS

A total of 65 trials involving 11,500 patients were identified; all trials treated blood pressure within a week and the majority in less than 72 hours. Included in this review are the 34 trials (5,368 patients) for which data were available. The effects of the drugs on blood pressure and heart rate are summarized in [Table 1](#).

0196-0644/\$30.00

Copyright © 2004 by the American College of Emergency Physicians.

doi:10.1016/j.annemergmed.2003.10.032

The effect on outcome of the drugs shown to reduce blood pressure in acute stroke is summarized in [Table 2](#).

CONCLUSION

There is insufficient evidence to evaluate the effect of altering blood pressure on outcome after acute stroke. Some agents lowered (eg, calcium channel blockers, ϵ -blockers, and probably angiotensin-converting enzyme inhibitors, prostacyclin and nitric oxide), whereas others had limited effect (eg, magnesium, naftidrofuryl, piracetam) on blood pressure in the acute stroke period. It does appear, however, that treatment of acute stroke with ϵ -blockers or streptokinase is associated with higher case fatality.

Table 1.
Summary of vasoactive agents' effects on blood pressure and heart rate.

Significant Results	Decrease	No Effect	Increase
Blood pressure	Oral and IV calcium channel blocker ϵ -Blocker Glyceryl trinitrate ACE inhibitors Prostacyclin Streptokinase	Magnesium Piracetam Naftidrofuryl	DCLHb
Heart rate	ϵ -Blocker Oral calcium channel blocker	IV calcium channel blocker DCLHb Magnesium Naftidrofuryl Glyceryl trinitrate	Prostacyclin

IV, Intravenous; ACE, angiotensin-converting enzyme; DCLHb, diaspirin cross-linked hemoglobin.

Cochrane Systematic Review Author Contact

Philip Bath, MD
 Division of Stroke Medicine
 University of Nottingham
 City Hospital Campus
 Nottingham, United Kingdom
 E-mail Philip.Bath@nottingham.ac.uk

COMMENTARY: CLINICAL IMPLICATION

As the third leading cause of death and the number one cause of disability,¹ stroke is a common clinical problem facing the emergency physician. Indeed, potential strokes comprise 2% of all 911 calls and 4% of hospital admissions in the United States.² A good number of patients with acute ischemic stroke will present with elevated blood pressure, which may in part be due to pain, anxiety, a full bladder, or other physical ailments. Elevated blood pressure can also be a reflection of the body's desire to maintain cerebral perfusion pressure (cerebral perfusion pressure=mean arterial pressure–intracranial pressure), which becomes dependent on systemic blood pressure once the ischemic brain has lost its ability to autoregulate. Elevated blood pressure in stroke, however, is not considered an emergency unless acute myocardial infarction or aortic dissection accompanies it. The other scenario to treat elevated blood pressure would be in candidates for thrombolytic therapy.

The latest American Heart Association (AHA) Guidelines recommend treatment for systolic pressure greater than 220 mm Hg or diastolic pressure greater than 140 mm Hg in stroke.³ Once the decision to treat elevated blood pressure has been made, the question of which agent to use arises. This Cochrane Review examined the evidence from randomized controlled trials treating blood pressure

Table 2.
Summary of antihypertensive drugs on outcome after acute stroke.

Antihypertensive Drug	Early Case Fatality (<1 mo), RR (95% CI)	Case Fatality at the End of the Trial Period, RR (95% CI)	Early Case Fatality and Deterioration (<1 mo), RR (95% CI)	Case Fatality and Deterioration at the End of Trial Period, RR (95% CI)
IV calcium channel blocker	1.02 (0.63–1.65)	0.92 (0.59–1.41)	1.24 (0.75–2.06)	0.84 (0.57–1.23)
Oral calcium channel blocker	0.96 (0.70–1.31)	0.97 (0.72–1.29)	1.03 (0.78–1.38)	1.28 (0.98–1.67)
ϵ -Blocker	1.77 (1.05–3.00)*	1.50 (0.94–2.40)	1.32 (0.84–2.06)	1.18 (0.76–1.84)
Prostacyclin	0.52 (0.13–2.03)	1.06 (0.32–3.51)	1.92 (0.39–9.30)	2.45 (0.42–14.35)
Streptokinase	2.27 (1.40–3.67)*	2.06 (1.31–3.25)*	Not estimable	1.12 (0.74–1.70)

RR, Relative risk.
*Significant results.

in patients with proven stroke. Only 1 trial involving 16 patients limited enrollment to those with elevated blood pressure, defined as systolic blood pressure 170 to 220 mm Hg or diastolic blood pressure 95 to 120 mm Hg. Two other small trials had mean systolic blood pressure between 170 and 180 mm Hg. All other trials enrolled patients regardless of baseline blood pressure. The mean blood pressure for most of the trials in both treatment and control groups was approximately 150/95 mm Hg. Overall, the authors found evidence of some physiologic effects (lowered blood pressure and pulse); however, they failed to find evidence of a clinically meaningful benefit from any specific treatment for blood pressure in acute stroke. Other research, however, confirms that long-term treatment of hypertension after stroke can significantly reduce stroke recurrence.⁴ Furthermore, they document evidence that use of β -blockers is associated with higher early case mortality.

With regard to the relationship between blood pressure and outcome, the authors conclude that “the number of trials and subjects with data on blood pressure and outcome were not identical, [therefore] it was not possible to relate group differences in blood pressure with group differences in outcome.” It should also be noted that an earlier Cochrane review examining treatment for blood pressure in acute stroke exists.⁵ That review primarily focused on the 5 trials (218 patients) investigating nimodipine, nicardipine, capropril, clonidine, glyceryl trinitrate, and perindopril. Conclusions were similar for both reviews.

The AHA Guidelines for the management of acute ischemic stroke recommend labetalol as the first-line agent for control of elevated blood pressure. The second-line agent recommended by the AHA is nicardipine. Nitroprusside is recommended for diastolic blood pressure greater than 140 mm Hg. The results of this Cochrane Review clearly show an early harmful effect of β -blocker therapy. Furthermore, not one of the identified trials investigated nitroprusside, so the recommendations appear to be based entirely on consensus, rather than on strong evidence.

TAKE HOME MESSAGE

On average, every 45 seconds in the United States¹ and every 10 minutes in Canada,⁶ someone suffers the potentially devastating consequences of a stroke. To date, few interventions have unequivocally proven to be beneficial, despite a multitude of stroke trials. Even for those treatments that might intuitively seem reasonable, such as

controlling hypertension in acute stroke, the evidence is weak. There remains considerable controversy regarding the class of agent and route of administration required to reduce blood pressure and hypertension, and the benefits of such action are dubious. Furthermore, large-scale trials are necessary before this issue will be resolved. In the meantime, emergency physicians should approach this treatment option with caution.

EBEM Commentator Contact

Latha G. Stead, MD
 Department of Emergency Medicine
 Mayo Clinic
 Rochester, MN
 E-mail stead.latha@mayo.edu

EBEM TEACHING POINT

Baseline Mismatching. Baseline mismatching of study outcomes (such as blood pressure in this review) can confound apparent effects of treatment. This type of baseline mismatching can both underestimate and overestimate a treatment effect, unless accounted for in the analysis. For example, assume a trial of antihypertensive agent A compared with placebo reports baseline differences of 10 mm Hg in blood pressure between the 2 groups (Agent A 10 mm Hg lower than placebo). If the drug is ineffective at altering blood pressure, the end-of-trial results could be interpreted as a 10 mm Hg difference between the treatment groups. This contribution to the systematic review would result in an overestimation of the effect of antihypertensives in blood pressure control. Conversely, if the 10 mm Hg imbalance favors the control group, and Agent A is effective at reducing blood pressure by 10 mm Hg, the end-of-trial results could be interpreted as showing no difference between the treatment groups. One way to reduce bias is to report mean differences (baseline systolic blood pressure–end-of-trial systolic blood pressure=systolic blood pressure difference) for all trials. Because not all trials perform this analysis and not all individual databases are available for review, the end-of-trial results are commonly used to construct the pooled analyses. Readers should be wary of results from trials with imbalances at baseline.

For dichotomous outcomes (eg, alive/dead, admitted/discharged), baseline differences in prognostic factors more often influence the results of the systematic review. The conclusion of this review is that there is no evidence that altering blood pressure in stroke significantly affects

EBEM/SYSTEMATIC REVIEW ABSTRACT

outcome. Had the baseline blood pressures been matched and enrollment limited to persons with elevated blood pressure (as defined by the AHA or Emergency Cardiovascular Care Group), it is possible that lowering the blood pressure in acute stroke would indeed have shown a treatment effect.

REFERENCES

1. American Heart Association Web site. Heart Disease and Stroke Statistics: 2003 update. Available at: <http://www.americanheart.org/presenter.jhtml?identifier=3000090>. Accessed October 31, 2003.
2. Kothari RU, Brott T, Broderick JP, et al. Emergency physicians' accuracy in the diagnosis of stroke. *Stroke*. 1995;26:2238-2241.
3. Adams HP, Adams RJ, Brott T, et al. Guidelines for the early management of patients with ischemic stroke: a scientific statement from the Stroke Council of the American Stroke Association. *Stroke*. 2003;34:1056-1083.
4. Friday G, Alter M, Lai SM. Control of hypertension and risk of stroke recurrence. *Stroke*. 2002;33:2652-2657.
5. Blood Pressure in Acute Stroke Collaboration (BASC). Interventions for deliberately altering blood pressure in acute stroke (Cochrane Review). In: *The Cochrane Library*. Issue 2. Oxford, United Kingdom: Update Software; 2003.
6. Canadian Stroke Network Web site. Available at: <http://www.canadianstrokenet-work.ca>. Accessed July 12, 2003.