Effect of Nitric Oxide Donors on Blood Pressure and Pulse Pressure in Acute and Subacute Stroke

Laura J. Gray, MSc,* Nikola Sprigg, MRCP,* Parveen A. Rashid, MD,† Mark R. Willmot, MRCP,* and Philip M. W. Bath, FRCP*

High blood pressure (BP), pulse pressure (PP), and rate pressure product (RPP) are each associated independently with a poor outcome in acute ischemic stroke. Whereas nitric oxide (NO) donors, such as glyceryl trinitrate (GTN), lower blood pressure in acute ischemic stroke, their effect on other hemodynamic measures is not known. We performed a systematic review of the effects of NO donors on systemic hemodynamic measures in patients with acute/subacute stroke. Randomized controlled trials were identified from searches of the Cochrane Library, Pubmed, and Embase. Information on hemodynamic measures, including systolic BP (SBP), diastolic BP (DBP), and heart rate, were assessed, and hemodynamic derivatives of these were calculated: PP (PP = SBP − DBP), mean arterial pressure (MAP = DBP + PP/3), mid blood pressure (MBP = (SBP + DBP)/2), pulse pressure index (PPI = PP/MAP), and RPP (RPP = SBP × HR). The effect of treatment on hemodynamic measures was calculated as the weighted mean difference (WMD) between treated and control groups with adjustment for baseline. Three trials involving 145 patients were identified; 93 patients received the NO donor, GTN, and 52 patients composed the control group. Compared with placebo, GTN significantly reduced SBP (WMD, −9.80 mm Hg; $P < .001$), DBP (WMD, −4.43 mm Hg; $P < .001$), MAP (WMD, − 6.41 mm Hg; $P < .001$), MBP (WMD, −7.33 mm Hg; $P < .001$), PP (WMD, −6.11 mm Hg; $P < .001$), and PPI (WMD, −0.03; $P = .04$). GTN increased HR (WMD, +3.87 bpm; $P < .001$) and lowered RPP insignificantly (WMD, −323 mm Hg · bpm; $P = .14$). Our findings indicate that the NO donor GTN reduces BP, PP, and other derivatives in acute and subacute stroke while increasing HR. **Key Words:** Acute stroke—blood pressure—glyceryl trinitrate—heart rate—pulse pressure.

High blood pressure (BP), a key risk factor for the development of cerebrovascular disease, is common in acute ischemic and hemorrhagic stroke and is associated independently with increased death or dependency.[1] A number of hemodynamic measures can be derived directly from blood pressure and heart rate and may provide additional prognostic information in stroke. These include pulse pressure (PP), the difference between systolic BP (SBP) and diastolic BP (DBP); mean arterial pressure (MAP); mid blood pressure (MBP), which may be a better predictor of cardiovascular events than either SBP or DBP alone[2]; and rate pressure product (RPP), an index of myocardial workload. Each of these measures is associated independently with poor outcome (as measured by death or dependency) in ischemic stroke.[3] Increased heart rate (HR) may also be associated with poor outcome.[4,5]

Because high BP is associated with a poor functional outcome, several large randomized controlled trials are

From the *Institute of Neuroscience, University of Nottingham, Nottingham, United Kingdom and †Department of Gerontology, Raddcliffe Infirmary, Oxford, United Kingdom.

Received April 19, 2006; revised June 12, 2006; accepted June 14, 2006.

Address reprint requests to Professor Philip Bath, FRCP, Division of Stroke Medicine, University of Nottingham, D Floor, South Block, Queen's Medical Centre, Nottingham NG7 2UH, UK. E-mail: philip.bath@nottingham.ac.uk.

1052-3057/$—see front matter

doi:10.1016/j.jstrokecerebrovasdis.2006.06.002

currently studying whether lowering BP might improve functional outcome.[6-8] However, the effect of the various antihypertensive agents on other hemodynamic measures has not been reported.

Nitric oxide (NO), a neurotransmitter with vasoactive properties, is a regulator of blood pressure, cerebral blood flow (CBF), and tissue perfusion.[9] In experimental stroke, NO donors are neuroprotective, reduce infarct volume, and modulate CBF[10]; as such, NO donors are a candidate treatment for acute stroke. Several small trials of NO donors in patients with recent stroke have been published and found that NO, given as glyceryl trinitrate (GTN), lowered SBP.[11-14] However, the effect of NO donors on these derived hemodynamic measures has not been reported. Consequently, we performed a systematic review of the effect of NO donors on systemic hemodynamic measures in patients with acute/subacute stroke.

Methods

Trials and Data

Completed nonconfounded randomized controlled trials of NO donors in acute/subacute stroke (randomization within 1 week of stroke) were identified from searches of the Cochrane Library, PubMed, and Embase. The search included articles up to May 2006 and used 3 primary search terms (glyceryl trinitrate, stroke, and trial). Additional trials were identified through searches of nonsystematic reviews and reference lists. The searches were limited to human studies reported in English. Individual patient data were sought for each included trial. Study quality was assessed across 5 domains: method of randomization, blinding to treatment, reporting of withdrawals, generation of random numbers, and allocation concealment. Trials scored 1 point for each area addressed, thus receiving a score between 0 and 5, with 5 reflecting the highest level of quality.[15]

Hemodynamic Measures

Data on the method of BP measurement, SBP and DBP, and HR were identified for measurements made at baseline and after treatment with the NO donor or control therapy. Derivative hemodynamic measures were calculated as follows: PP = SBP − DBP, MAP = DBP + PP/3, MBP = (SBP + DBP)/2, PPI = PP ÷ MAP, and RPP = SBP × HR.

Statistical Methods

Data were analyzed using RevMan, version 4.2 (Cochrane, Oxford, UK) and Stata, version 7 (Stata Corp, College Station, TX). Individual patient data were analyzed on treatment, with adjustment for baseline measures by analysis of covariance. The difference in measurements between patients randomized to NO donor and controls is expressed as weighted mean difference (WMD, with 95% confidence intervals), calculated using a random-effects model. Statistical heterogeneity was assessed using the χ^2 test.

Results

Trial Characteristics

Three completed randomized controlled trials of NO donors in acute/subacute stroke were identified.[11-13] A nonrandomized comparison of intravenous sodium nitroprusside in patients with acute ischemic stroke and normal older volunteers was excluded.[16] The trials included a total of 145 patients (93 NO donors and 52 controls) and assessed transdermal GTN, an organic nitrate. Each trial was randomised, and treatment allocation was concealed; 1 trial was double-blinded, placebo-controlled[11] and the other 2 trials were single-blinded (Table 1).[12,13] All 3 trials included patients with either ischemic stroke or primary intracerebral hemorrhage. Patients were enrolled within 75 hours of stroke onset (see Table 1).

Table 1. *Characteristics of included trials*

Trial	Dose	Active (n)	Control (n)	Mean time, stroke-enrolment (hours)	BP timing	BP method	Primary outcome	Quality score (/5)
Bath et al[11]	GTN 5 mg	16	21	99.6	Baseline day 1	ABPM Spacelabs	BP	5
Rashid et al[12]	GTN 5 mg/GTN 5/10 mg/GTN 10 mg	20/20/20	30	54.4	Baseline day 1	ABPM Spacelabs	24-hour MAP	4
Willmot et al[13]	GTN 5 mg	12	6	72.2	Baseline 1 hour	Omron 705CP	CBF	4

ABPM, ambulatory BP measurement.