TITLE PAGE

Full title:

Effect of nitric oxide donors on blood pressure and pulse pressure in acute and subacute stroke

Short title:

NO donors lower blood pressure in stroke

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ABSTRACT

Introduction: High blood pressure (BP), pulse pressure (PP), and rate pressure product (RPP) are each associated independently with a poor outcome in acute ischaemic stroke. While nitric oxide (NO) donors such as glyceryl trinitrate (GTN) lower blood pressure in acute ischaemic stroke, their effect on other haemodynamic measures is not known.

Methods: We performed a systematic review of the effects of NO donors on systemic haemodynamic measures in patients with acute/subacute stroke. Randomised controlled trials were identified from searches of the Cochrane Library, Pubmed and Embase. Information on haemodynamic measures were assessed, including systolic and diastolic BP and heart rate; haemodynamic derivatives of these were calculated: pulse pressure (PP=SBP-DBP), mean arterial pressure (MAP=DBP+PP/3), mid blood pressure (MBP=(SBP+DBP)/2), pulse pressure index (PPI=PP/MAP), and rate pressure product (RPP=SBPxHR). The effect of treatment on haemodynamic measures was calculated as the weighted mean difference (WMD) between treated and control groups with adjustment for baseline.

Results: Three trials involving 145 patients were identified; 93 patients received the NO donor, GTN, and 52 control. As compared with placebo, GTN significantly reduced SBP (WMD -9.80 mmHg, $p< 0.001$), DBP (WMD –4.43 mmHg, $p< 0.001$), MAP (WMD –6.41 mmHg, $p< 0.001$), MBP (WMD –7.33 mmHg, $p<0.001$), PP (WMD –6.11 mmHg, $p<0.001$) and PPI (WMD –0.03, $p=0.04$).

GTN increased HR (WMD +3.87 bpm, $p<0.001$) and non-significantly lowered RPP (WMD –323 mmHg.bpm, $p=0.14$).

Conclusion: The NO donor GTN reduces BP, PP and other derivatives in acute and subacute stroke whilst increasing heart rate.

INTRODUCTION

High blood pressure (BP), a key risk factor for the development of cerebrovascular disease, is common in acute ischaemic and haemorrhagic stroke, and is associated independently with increased death or dependency.[1] A number of haemodynamic 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 blood pressure (SBP) and diastolic blood pressure (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 work load. Each of these measures is associated independently with a poor outcome (as measured by death or dependency) in ischaemic stroke.[3] An increased heart rate (HR) may also be associated with a poor outcome.[4, 5]

Since high BP is associated with a poor functional outcome, several large randomised controlled trials [6-8] are now studying whether lowering BP might improve functional outcome. However, the effect of the various antihypertensive agents on other haemodynamic 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, nitric oxide 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 GTN, lowered systolic BP. [11-

14] However, the effect of NO donors on these derived haemodynamic measures has not been reported. We performed a systematic review of the effect of NO donors on systemic haemodynamic measures in patients with acute/subacute stroke.

METHODS

Trials and data

Completed non-confounded randomised controlled trials of NO donors in acute/sub acute stroke (randomisation within one week of stroke) were identified from searches of The Cochrane Library, PubMed and Embase. The search included articles up to May 2006 and employed three primary search terms (glyceryl trinitrate, stroke and trial). Additional trials were identified through searches of non-systematic 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 five domains: method of randomisation, blinding to treatment, reporting of withdrawals, generation of random numbers and allocation concealment. Trials scored one point for each area addressed, therefore receiving a score between 0-5, with 5 reflecting the highest level of quality.[15]

Haemodynamic measures

Data on the method of BP measurement, systolic (SBP) and diastolic (DBP) BP, and heart rate (HR) were identified for measurements made at baseline and following treatment with the NO donor or control therapy. Derivative haemodynamic measures were calculated as follows: pulse pressure (PP=SBP-DBP), mean arterial pressure (MAP=DBP+PP/3), mid blood pressure (MBP=(SBP+DBP)/2), pulse pressure index (PPI=PP/MAP), and rate pressure product (RPP=SBP*HR).

Statistical methods

Data were analysed using the Cochrane RevMan software [16] and Stata (version

7).[17] Individual patient data were analysed on treatment with adjustment for baseline measures by analysis of covariance. The difference in measurements between patients randomised to NO donor and control is expressed as the weighted mean difference (WMD, with 95% confidence intervals), calculated using a random effects model. Statistical heterogeneity was assessed using a χ^2 test.

RESULTS

Trial characteristics

Three completed randomised controlled trials of NO donors in acute/subacute stroke were identified.[11-13] A non randomised comparison of intravenous sodium nitroprusside in patients with acute ischaemic stroke and normal older volunteers was excluded.[18] The trials included a total of 145 patients (NO donor 93, control 52) and each assessed transdermal glyceryl trinitrate (GTN), an organic nitrate. Each trial was randomised and treatment allocation was concealed; one trial was double-blind placebo controlled [11] and the other two single-blind (table 1).[12, 13] All three trials included patients with either ischaemic stroke or primary intracerebral haemorrhage. Patients were enrolled within 75 hours of stroke onset (table 1).

Two trials studied GTN given at a dose of 5 mg,[11, 13] the other had three active arms with GTN used at (i) 5mg for 10 days; (ii) 5mg for 4 days followed by 10mg for 6 days; and (iii) 10mg for 10 days (table 1). To allow for this difference in doses, the data from this trial were separated into two, patients receiving 5mg or 5mg followed by 10mg (the increased dose was started at day 4 and therefore will not have affected BP measurements at baseline or after first dosing) and those receiving 10mg for the duration of the trial. Two trials used 24 hour ambulatory blood pressure monitoring,[11, 12] whereas one reported BP using a validated digital readout oscillometric device (Omron 705CP) at 1-2 hours post treatment.[13] Use of automated BP monitors means readings were effectively made blinded to treatment allocation.

Patient characteristics

Patients across the three trials have similar ages and types of presenting stroke. The trial of Willmot et al had a lower proportion of males and patients with cortical stroke, and the trial of Bath et al had a higher proportion of patients with a history of hypertension (table 2).

NO donors on haemodynamic measures

GTN significantly reduced SBP (WMD -9.8 mmHg), DBP (WMD –4.4 mmHg), MAP (-6.4 mmHg), MBP (-7.3 mmHg), PP (-6.1) and PPI (-0.03) (table 3, figures 1A-C); additionally, GTN non-significantly reduced RPP (table 3). In contrast, GTN increased HR (WMD +3.9 bpm) (table 3). No heterogeneity in measures was observed between trials.

DISCUSSION

This systematic review has found that the NO donor, GTN, reduces a variety of systemic haemodynamic measures including systolic BP, diastolic BP, mean arterial BP, mid blood pressure, pulse pressure and pulse pressure index in patients with acute/subacute stroke. GTN increased heart rate but tended to reduce rate pressure product, presumably representing a balance between decreasing BP, and modestly increasing heart rate. The non significant reduction in RPP suggests that GTN may tend to reduce myocardial work.

As these haemodynamic measures are associated independently with a poor outcome, [1, 3] so that there reduction (apart from HR) might improve functional outcome after stroke. Several trials are assessing lowering BP in patients with acute stroke with a variety of drugs including candesartan (angiotensin receptor antagonist, SCAST [6]), GTN (ENOS [7]), labetalol (ß-receptor antagonist, CHHIPS [8]), and lisinopril (angiotensin converting enzyme inhibitor, CHHIPS [8]); another study is using a variety of agents as chosen by the local investigator (INTERACT[19]). However, only one small trial has reported the effect of any of these antihypertensive agents on BP derived haemodynamic measures.[12] Previous studies have suggested that some BP lowering approaches may be detrimental such as atenolol/propranolol (ß-receptor antagonists) and nimodipine (dihydropyridine calcium antagonist).[20-22] Hence, the class of antihypertensive agent may be important when considering how to lower BP in acute stroke.[23]

BP measurements were automated in the three studies and therefore were effectively made blinded to treatment assignment. However, they were not standardised [24] in respect of the measurement technique; one trial used office measurements made 1-2 hours post first treatment therefore reflecting peak BP lowering effects;[13] in contrast, the other two studies relied on 24 hour ambulatory BP monitoring.[11, 12] Although ambulatory BP monitoring is a good predictor of outcome in acute stroke,[25] it measures average rather than peak haemodynamic effects; as such the upper limit of 'normal' for each vary (office ≤ 135/85, ABPM ≤ 130/80).[26] Hence, the weighted mean difference in haemodynamic measures reported here are a mix of peak and average effects, so the findings are robust to measurement variations and the effects of GTN may be underestimated.

The identified trials of GTN were all small (18-90 subjects) and could not assess the effect of GTN on functional outcome; this is being investigated in the ongoing 'Efficacy of Nitric Oxide in Stroke' (ENOS) trial.[7]

CONCLUSION

In summary, GTN reduces haemodynamic measures known to be related to poor prognosis in patients with acute/subacute stroke and as such is a suitable candidate agent for testing whether BP should be lowered in patients with acute stroke.

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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 [11]	GTN 5mg	16	21	99.6	Baseline Day 1	ABPM Spacelabs	Blood pressure	5
Rashid [12]	GTN 5mg/ GTN 5/10mg/GTN 10mg	20/20/20	30	54.4	Baseline Day 1	ABPM Spacelabs	24 hour MAP	4
Willmot [13]	GTN 5mg	12	6	72.2	Baseline 1 hour	Omron 705CP	Cerebral blood flow	4

TABLE 2

Characteristics of included patients in each trial. Mean (standard deviation) or %

Characteristic	Bath [11]	Rashid [12]	Willmot [13]
Number of patients	37	90	18
Age (years)	73.7 (9.1)	71.8 (11.8)	69.4 (7.4)
Gender, male (%)	48.6	45.6	27.8
History of hypertension (%)	62.2	40.0	38.9
Ischeamic stroke (%)	89.2	93.3	88.9
Cortical syndrome (%)	54.1	53.3	33.3
Scandinavian stroke scale (/58)	-	32.6 (11.7)	42.1 (10.5)

TABLE 3

Effect of first dose of NO donor on haemodynamic measures in 145 patients (All measures adjusted for baseline value)

Outcome	Comparisons	Control group mean	WMD	95% CI	p value	Heterogeneity p value
Systolic blood pressure	4	161.1	-9.8	-12.9, -6.7	<0.0001	0.50
Diastolic blood pressure	4	88.4	-4.4	-6.4, -2.5	<0.0001	1.00
Heart rate	4	72.9	3.9	1.7, 6.1	0.001	0.91
Mean arterial pressure	4	112.8	-6.4	-8.5, -4.3	<0.0001	0.86
Mid blood pressure	4	124.9	-7.3	-9.6, -5.0	<0.0001	0.69
Pulse pressure	4	73.7	-6.1	-9.4, -2.8	0.0003	0.11
Pulse pressure index	4	0.66	-0.03	-0.06, 0.00	0.04	0.07
Rate pressure product	4	11768	-323	-746, 101	0.14	0.87

TITLES AND LEGENDS TO FIGURES

FIGURE 1

A) Forest plot of effect of NO donors on systolic blood pressure; weighted mean difference

FIGURE 1

B) Forest plot of effect of NO donors on diastolic blood pressure; weighted mean difference

FIGURE 1

C) Forest plot of effect of NO donors on pulse pressure; weighted mean difference

FIGURE 1

A) Forest plot of effect of NO donors on systolic blood pressure; weighted mean difference

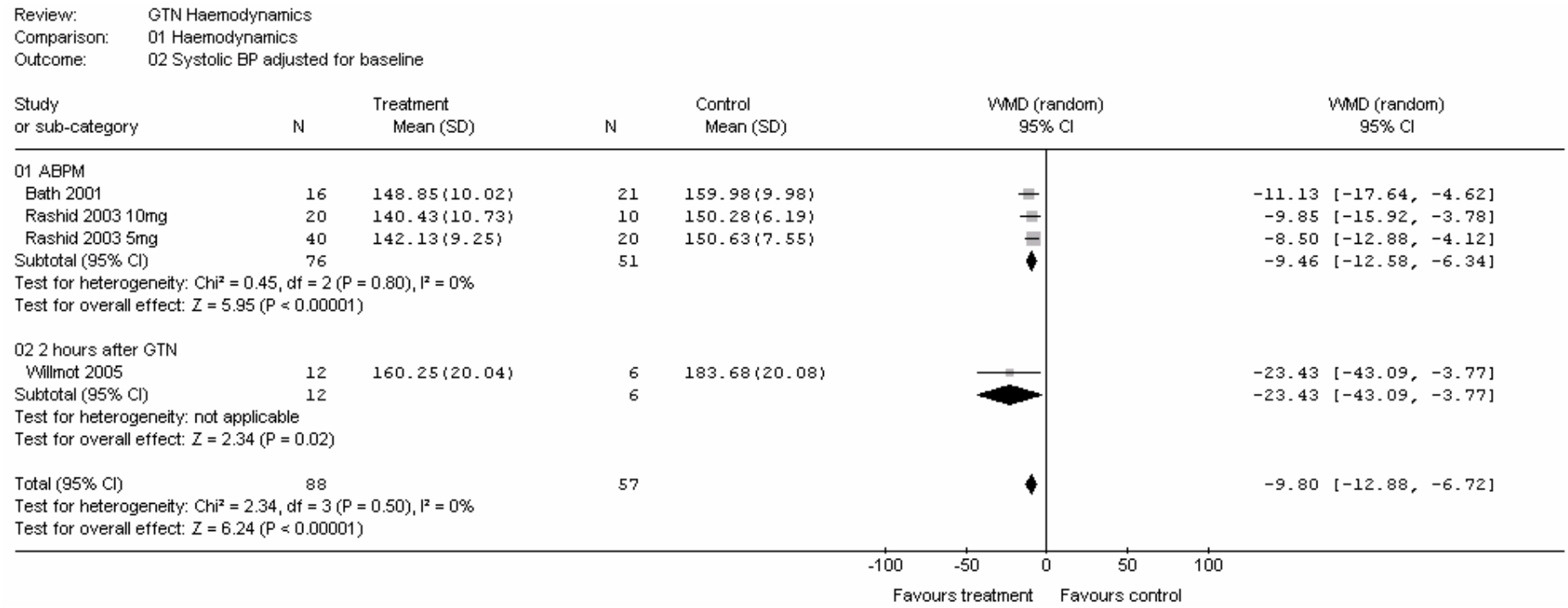

FIGURE 1

B) Forest plot of effect of NO donors on diastolic blood pressure; weighted mean difference

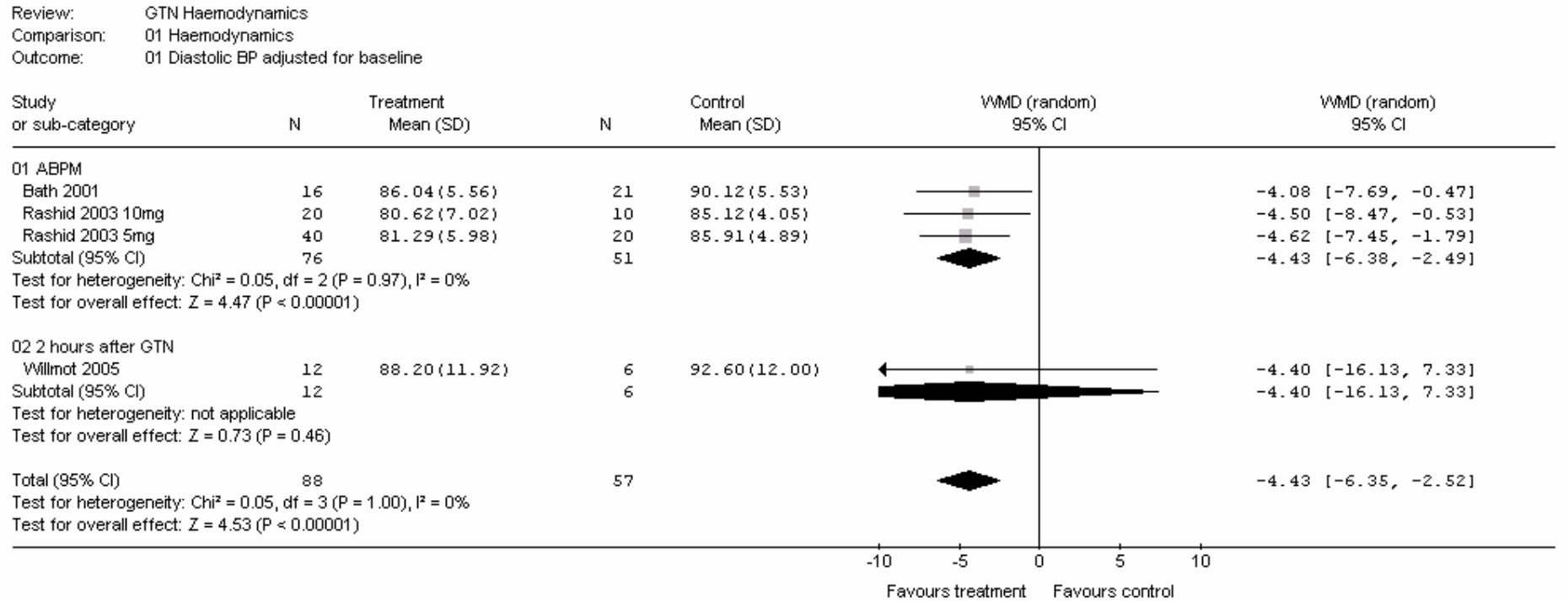

FIGURE 1

C) Forest plot of effect of NO donors on pulse pressure; weighted mean difference