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RELATIONSHIP BETWEEN THERAPEUTIC CHANGES IN BLOOD PRESSURE AND OUTCOMES IN ACUTE STROKE: A META-REGRESSION

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SHORT TITLE

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ABSTRACT

Both low and high blood pressure (BP) during the acute phase of stroke are associated independently with a poor outcome. Several small clinical trials have involved the alteration of BP and this study assessed the relationship between change in BP and functional outcome. Randomised controlled trials of interventions that would be expected, on pharmacological grounds, to alter BP in patients within one week of the onset of acute ischaemic or haemorrhagic stroke were sought using electronic searches. Data were collected on BP and clinical outcome. The relationship between the difference in on-treatment BP and odds ratios (OR) for outcomes was assessed using meta-regression.

Thirty-seven trials involving 9,008 patients were included. A 'U' or 'J' shaped relationship were found between on-treatment BP difference and early death, death at the end of 90 day follow up, and combined death or dependency at the end of follow up. Although outcomes were not significantly reduced at any level of change in BP, the lowest odds occurred at: early death (OR 0.87, 95% confidence interval, CI 0.54 to 1.23) - 8.1 mmHg; death at end of follow up (OR 0.96, 95% CI 0.31 to 1.65) - 14.4 mmHg; and combined death or dependency at end of follow up (OR 0.95, 95% CI 0.11 to 1.72) - 14.6 mmHg. Although large falls or increases in BP are associated with a worse outcome, modest reductions may reduce death, and combined death or dependency, although the confidence intervals are wide and compatible with overall benefit or hazard.

Keywords

Acute stroke, blood pressure, meta-regression, randomized controlled trial

INTRODUCTION

Both acute ischaemic stroke and primary intracerebral haemorrhage (PICH) are associated with high blood pressure in 75% or more of patients.[1, 2] Blood pressure (BP) falls spontaneously in most patients over the first week although a third of patients remain with an elevated BP.[3-5] The mechanisms underlying hypertension in stroke are complex but pre-existing hypertension (present in 50-60% of patients), hospitalization stress, activation of the neuro-endocrine pathways, and the Cushing reflex, each contribute.[6]

Several studies have identified a 'U-shaped' relationship such that both low and high blood pressure are associated independently with increased early death and later death or dependency.[7-9] A high blood pressure is also associated with increased early recurrence.[7, 10] In ischaemic stroke, high BP also appears to affect adversely outcome through increasing the risk of cerebral oedema, but not haemorrhagic transformation.[7] Haematoma expansion is related to high blood pressure in patients with PICH although this relationship may be confounded by stroke severity and time to presentation.[11]

Although debated more than 22 years ago, it still remains unclear whether high BP should or should not be treated acutely following stroke.[12, 13] Recent guidelines recommend that acute lowering of blood pressure should be delayed for several days or even weeks unless blood pressure other life-threatening conditions are present (e.g. hypertensive encephalopathy, aortic dissection, cardiac ischaemia, pulmonary oedema, acute renal failure).[14-17] Unfortunately, these guidelines are inconsistent and are based on theoretical arguments and individual case reports, and not on the results of systematic overviews or large intervention trials of blood pressure manipulation in acute stroke.

Low blood pressure is not common in acute stroke but it, like high blood pressure, is associated with a poor outcome.[7] Possible reasons for low blood pressure include hypovolaemia, sepsis, impaired cardiac output secondary to cardiac failure, arrhythmias or cardiac ischaemia, and aortic dissection.[18] Guidelines recommend that causes of hypotension in the setting of acute stroke should be sought with the view to correcting reversible causes such as hypovolaemia and cardiac arrhythmias.[16]

This systematic review assessed the relationship between drug-induced BP changes following stroke and subsequent clinical outcomes and used data from existing randomised controlled trials and the technique of meta-regression. Implicit in the review is the hypothesis that BP changes, whether positive or negative, may drive outcome after stroke.

METHODS

Types of studies

Included studies comprised published and unpublished randomised controlled trials in acute ischaemic stroke or acute PICH of drugs that had the potential for altering BP. Therapy had to be initiated within one week of stroke onset. Uncontrolled studies, confounded trials (where interventions were compared with each other rather than control/placebo), studies of patients with subarachnoid haemorrhage, and studies where BP or clinical outcome data were unobtainable were excluded.

Type of participants

Adults (age>18) of either sex with acute ischaemic or haemorrhagic stroke who were eligible for randomization to either active treatment or placebo/open control were included.

Study search

The Cochrane library (issue 2, 2008), MEDLINE (1966 to January 2009), EMBASE (1980 to January 2009), and Science Citation Index (ISI Web of Science, 1981 to January 2009) were searched. No language restrictions were applied. The search strategy for MEDLINE, EMBASE and Science Citation Index are detailed in the online supplement (please see http://hyper.ahajournals.org). Trials were also identified from reference lists of relevant trial publications and existing review articles, including earlier reviews from the 'Blood pressure in Acute Stroke Collaboration' (BASC).[19, 20]

Data collection

Early (within one month) and end of trial mortality, end of trial death or dependency, baseline and on-treatment systolic BP in active and control groups were collected. Disability or dependency were defined as a Barthel Index 0-55 or Rankin score 3-5. Information on the methods of randomization, concealment of allocation, blinding, analysis (intention to treat or efficacy analysis), stroke type (ischaemic or haemorrhage), drug dose, route of administration (oral, transdermal or intravenous)

and timing, and measurement of BP and primary outcome were all collected. The methodological quality of trials was also assessed. In instances where BP or outcome data were unavailable in the trial publications, authors and principle investigators were also contacted to obtain relevant data. Otherwise, BP data were obtained by enlarging published graphs and measuring data using a "screen grab" program (Mac Grab).

Data analysis

Odds ratios and 95% confidence intervals (CI) were calculated using random effect models for clinical outcomes using RevMan version 5 for Macintosh. Random-effects models were used since biological heterogeneity was expected among the trials taking account that different trial protocols, including different vasoactive drugs and classes, time to and length of treatment, functional outcome measures, and type of stroke (ischaemic, haemorrhagic). Heterogeneity was calculated using Tau-squared test and the I^2 statistic. This approach is recommended by the Cochrane collaboration and is the one we use routinely in meta-analysis.[21] Odds ratio <1 indicate a beneficial effect while those >1 indicate a detrimental effect of the intervention. On-treatment systolic BP differences were calculated as the difference between the treatment groups; negative values indicate BP was higher in the active group. A scatter plot between each clinical outcome and on-treatment BP differences was drawn using *Stata 10* for Mac (StataCorp College Station, Texas); meta-regression lines were then plotted with 95% confidence intervals (CI) to assess the relationship between BP and clinical outcome. Sensitivity analyses were performed in subgroups of studies by time to recruitment: $\leq$ 24 hours, $\leq$ 48 hours; baseline SBP: $\leq$ 160 mmHg, $\leq$ 180 mmHg, and length of treatment: $\leq$ 14 days, $\leq$ 28days. Egger's test and Beggs funnel-plot were performed to assess any publication bias in included trials.[22, 23]

RESULTS

Thirty-seven trials involving 9,008 patients were included (4,705 active and 4,303 control, figure 1). The patients receiving placebo or control treatment in 8 trials acted as controls for more than one group of actively treated patients explaining the difference in patient numbers in the groups; control subjects in these studies were divided equally between each active treatment group to avoid artificially inflating patient numbers and narrowing confidence intervals artificially (table S1 please see http://hyper.ahajournals.org). 86 studies were excluded (table S2 please see http://hyper.ahajournals.org). Patients were recruited into trials within 6 to 120 hours from stroke onset; most were enrolled within 24-168 hours (table S1 please see http://hyper.ahajournals.org). The treatment duration varied from 24 hours to 9 months (table S1 please see http://hyper.ahajournals.org).

Thirteen drug classes were studied: angiotensin converting enzyme inhibitors (ACE-I, lisinopril); angiotensin receptor antagonists (ARA, candesartan); ß-receptor antagonists (ß-RA, atenolol, labetalol, propranolol); calcium channel blockers (CCB, flunarizine, isradipine, nicardipine, nimodipine); basic fibroblast growth factor (fiblast) haemoglobin analogues (DCLHb); magnesium sulphate; naftidrofuryl; nitric oxide donors (glyceryl trinitrate); piracetam; prostacyclin, phenylephrine and mixed/'usual' antihypertensive therapy (table S1 please see http://hyper.ahajournals.org). Of these, ß-receptor antagonists, calcium channel blockers (po), nitric oxide donors, and prostacyclin significantly reduced SBP, and DCLHb and phenylephrine increased it (figure S3 please see http://hyper.ahajournals.org). Some drugs were given in two phases, initially intravenously then orally (CCB, naftidrofuryl, piracetam).

When assessing different drug classes, ß-RA and DCLHb showed a tendency for adverse outcomes while candesartan showed a favourable trend towards mortality at the end of follow up (figure 2,

figure S1 S2, please see http://hyper.ahajournals.org). Other drug classes showed no significant effect on clinical outcomes, whether assessed as death, or combined death or dependency.

'U' or 'J' shaped relationships were observed between on-treatment BP difference and early death (<1 month), mortality at the end of 90 day follow up, and combined death or dependency at the end of follow up (figure 3,4,5). The lowest odds of early death (i.e. best treatment effect, OR 0.87, 95% CI 0.54 to 1.23) occurred at on-treatment BP difference of 8.1 mmHg (figure 3). Similarly, the lowest odds for death at the end of follow-up (OR 0.96, 95% CI 0.31 to 1.65) was present at a BP difference of 14.4 mmHg (figure 4). The lowest odds for combined death or dependency at the end of follow-up (OR 0.95, 95% CI 0.11 to 1.72) occurred at a BP difference of 14.6 mmHg (figure 5). Increases or large falls in BP in the active group were associated with poor outcomes, whether assessed as death or combined death or dependency (figure 3, 4, 5); in the case of vasopressor effects, the increase in death, and combined death or dependency were significant. When early mortality was analysed by time to recruitment (table 1), <24 hours (12 data sets) and <48 hours (24 data sets) OR were 0.69 (95% CI 0.14 to 1.24), 0.94 (95% CI 0.50 to 1.39). There were insufficient data sets to analyse shorter times of <6 hours (4 data sets), and <12 hours (9 data sets).
When data were analysed by baseline SBP (<160mmHg, <180mmHg), there was no statistical association between early death and baseline SBP (table 1). Analysis of data by treatment duration showed treatment <14 days associated significantly with early mortality (table 1). No evidence of publication bias using Egger's test (p for bias 0.13) and there was no asymmetry on visual inspection of the Begg's funnel plot (plot not shown).

DISCUSSION

Individual trials involving the alteration of BP have varied in their findings on the effect of treatment on outcome. Treatment with antihypertensive agents such as ARA and ACE-I in small studies have been associated with reduced recurrent vascular events (ARA) or death (ACE-I) although these findings need confirmation in larger trials.[24, 25]

Conversely, a trial of DCLHb was associated with an increase in BP and a worse outcome;[26] similarly, some trials where BP was lowered have also found a worse outcome, as seen with CCBs and ß-RAs.[27, 28] However, most trials were neutral reflecting, in part, that many were too small to detect reliably effects on outcome. As a result, integration of the existing data using meta-analysis and meta-regression techniques is necessary to provide a sufficient sample size for further analysis.

The present study covered 13 drug classes and included 37 trials involving 9,008 patients with acute stroke. For each of early death, end of trial death, and end of trial death or dependency, a 'U' or 'J' shaped curve was present for the relationship between outcome and systolic BP. Both large reductions, and any increase, in BP were associated with a worse outcome. The nadir of these curves, where active BP lowering might improve outcome, had reductions in systolic BP ranging between 8.1 mmHg (early death), and 14.4 mmHg (end of trial death) with combined death and dependency at 14.6 mmHg. However, in no case was outcome significantly improved (the 95% CI for odds ratios all included 1) and these modest reductions in BP might either be beneficial (40% or more reduction in poor outcome) or hazardous (30 or more increase in poor outcome). In respect of vasopressor effects, significant elevations in SBP were associated with significant increases in death, and combined death or dependency. These data support the rationale for several ongoing large randomised controlled trials of lowering BP in stroke, including ENOS, INTERACT 2, and SCAST.[29-31]

These findings are subject to several caveats. First, the BP data relate to a comparison of on-treatment measurements and are not adjusted for baseline values. Several trials had mismatching of baseline BP such that a comparison of on-treatment BP in these appears to suggest that vasodepressing drugs actually increased BP, as evident in the graphs for some trials of ß-RA, CCB and nitrates.[28, 32-35] Unfortunately, baseline BP was not available for some trials so it was not possible to correct on-treatment values for those at baseline. Second, the on-treatment BP differences are not adjusted for other baseline prognostic factors such as age, stroke severity and type of stroke. Baseline imbalances in these would have profound effects on outcome and therefore change the BP-outcome relationship.[28, 32, 35-37] Third, individual patient data were not available; the presence of this would have addressed the first two issues. Fourth, although we performed a comprehensive search for trials where BP changes may have occurred, it is conceivable that some studies will have been missed, especially trials where there was no intention to change BP. Last, 86 identified trials had to be excluded because they did not publish data for on-treatment BP and/or outcome (table S2 please see http://hyper.ahajournals.org).

Although SBP was not adjusted for baseline blood pressure, sensitivity analysis showed no significant association between baseline SBP and outcome (table 1). Similarly variations in treatment duration was assessed and the results suggest that short term treatment (<2 weeks) might reduce early mortality; this supports the rationale of shorter treatment durations in several ongoing large randomised controlled trials of lowering BP in acute stroke. Further BP lowering treatment might be more efficiently started very soon after the stroke, e.g. within 6-12 hours of onset. Unfortunately there were insufficient data to analyze treatment effects in the hyperacute phase (<6 hours).

PERSPECTIVES

Although large falls or increases in BP were associated with a worse outcome, modest reductions might be associated with improved outcome although the confidence intervals were wide and

compatible with benefit or hazard. Ongoing large trials such as ENOS, SCAST, and INTERACT 2 will be able to answer this issue.[29-31]

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None

DISCLOSURES

The authors were involved with 3 completed trials that were included in this analysis. [32], [38], [39] PB is the Stroke Association Professor of Stroke Medicine. The funding sources have no involvement in this project.

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FIGURE LEGENDS

Figure 1. Search process for relevant studies

Figure 2. Death or dependency by class of vasoactive drug

Figure 3. Relationship between death within 1 month and on-treatment systolic blood pressure difference (active minus control)

Figure 4. Relationship between death at the end of follow up and on-treatment systolic blood pressure difference (active minus control)

Figure 5. Relationship between death or dependency at end of follow up and on-treatment systolic blood pressure difference (active minus control)

TABLES

TABLE 1 Sensitivity analyses by time to treatment, baseline SBP, and duration of treatment

Variable	**Early mortality**		**End of trial mortality**		**End of trial death or dependency**	
	N	**OR (95%CI)**	**N**	**OR (95%CI)**	**N**	**OR (95% CI)**
All trials	29	0.87 (0.54 to 1.23)	43	0.96 (0.31 to 1.65)	34	0.95 (0.11 to 1.72)
Time to recruitment						
≤ 24 hours	12	0.69 (0.14 to 1.24)	25	0.96 (0.58 to 1.35)	16	0.46 (0.00 to 2.91) *
≤48 hours	24	0.94 (0.50 to 1.39)	36	0.95 (0.68 to 1.24)	25	0.81 (0.00 to 2.31) *
Baseline SBP						
≤ 160 mmHg	22	0.96 (0.54 to 1.38)	32	1.10 (0.29 to 1.83) *	16	0.23 (0.00 to 1.77) *
≤180 mmHg	26	0.94 (0.55 to 1.30)	37	1.06 (0.13 to 1.96) *	31	0.94 (0.00 to 1.94)
Treatment duration						
≤ 14 days	14	**0.41 (0.00 to 0.85)**	26	0.87 (0.00 to 2.17) *	21	0.90 (0.00 to 2.14)
≤ 28 days	23	0.90 (0.45 to 1.33)	35	0.96 (0.00 to 1.92) *	29	0.94(0.00 to 1.87)

N: number of data sets. Significant results are in bold. * No 'U'/'J' shape curve