

Controlling Hypertension and Hypotension Immediately Post Stroke (CHHIPS) – a randomised controlled trial

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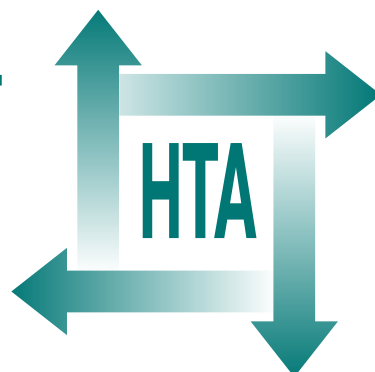
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Executive summary

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Executive summary

Background

Elevated blood pressure (BP) levels are common following acute stroke and may have an adverse prognostic effect. Observational data, however, suggest that both high and low BP levels in the acute stroke period are associated with a poor short- and long-term prognosis.

The limited data available from randomised controlled trials of BP reduction following acute stroke suggest that beta-blockers and calcium channel blockers commenced within 24–48 hours of stroke onset are unlikely to have benefit in terms of reducing short- or long-term disability or death. Other trials suggest that labetalol and the angiotensin receptor blockers may be effective post stroke, with one trial showing that candesartan nearly halved the number of subsequent fatal and non-fatal vascular events in severely hypertensive, non-dysphagic, acute ischaemic stroke patients. Conversely, an induced BP increase is a standard treatment for cerebral ischaemia in patients with vasospasm after subarachnoid haemorrhage, but few data exist to support this therapy in acute ischaemic stroke.

In view of the equivocal evidence and marked variations in clinical practice, the placebo-controlled Controlling Hypertension and Hypotension Immediately Post Stroke (CHHIPS) pilot trial was established to assess the safety and efficacy of therapeutically reducing BP with labetalol or lisinopril (depressor arm) in patients with hypertension (systolic BP > 160 mmHg) and acute cerebral infarction or haemorrhage and of therapeutically raising BP with phenylephrine (pressor arm) in ischaemic stroke patients with 'low' BP.

Objectives

The primary outcome measure was death and dependency at 2 weeks following pressor or depressor therapy compared with placebo. The secondary objectives were: (1) to determine the safety of acute pressor or depressor therapy post stroke assessed by early neurological deterioration; (2) to assess if stroke type (ischaemic versus

haemorrhagic) affected the BP changes due to depressor therapy; (3) to evaluate the BP effects of sublingual lisinopril and intravenous labetalol; (4) to study whether the effects of therapy on BP manipulation were influenced by the time to treatment; (5) to assess the short-term (2 week) cost-effectiveness of active treatment in relation to death and dependency and the medium-term (3-month) cost-effectiveness in relation to mortality.

Methods

Inclusion criteria included age over 18 years with a clinical diagnosis of suspected stroke and either (1) symptom onset < 36 hours and hypertension, defined as systolic BP (SBP) > 160 mmHg (depressor arm), or (2) symptom onset < 12 hours and hypotension, defined as SBP ≤ 140 mmHg (pressor arm).

Exclusion criteria included being on antihypertensive therapy on admission and having an indication for urgent BP lowering, a contraindication to trial therapy, significant comorbidity or a life expectancy of less than or equal to 6 months. Patients who were dysphagic and on antihypertensive treatment were included after a trial protocol amendment.

SBP levels, time of stroke onset, swallowing status and functional assessments including the modified Rankin Scale (mRS) and National Institutes of Health Stroke Scale (NIHSS) were determined before central randomisation in a ratio of 2:1 between active treatment and placebo for the depressor arm and 1:1 between active treatment and placebo for the pressor arm. The depressor non-dysphagic patients were assigned to stepped doses of oral lisinopril 5 mg, labetalol 50 mg or matching placebo with a target SBP of 145–155 mmHg or a SBP fall of ≥ 15 mmHg, with patients receiving additional doses at 4 and 8 hours post randomisation if target BP levels were not met. The established treatment regime was continued for 14 days post randomisation. Dysphagic patients underwent a similar titrated dose regime, receiving either sublingual lisinopril 5 mg, intravenous labetalol 50 mg or matching placebo for 72 hours

and then therapy orally if able to swallow or via a nasogastric tube if not until day 14.

Hypotensive (SBP < 140 mmHg) patients recruited within 12 hours of ischaemic stroke and who were euvoalaemic could be randomised to normal saline infusion and either intravenous phenylephrine or matching placebo, to be continued up to 24 hours after stroke onset, after which normal BP management was allowed.

At 72 hours the NIHSS was repeated to assess early stroke deterioration and at day 14 functional assessments including mRS and NIHSS were measured again. At 3 months the cause and date of death, length of hospital stay and discharge destination were recorded by the co-ordinating centre.

The primary analysis was on an intention to treat basis, comparing the numbers of subjects who were dead or dependent (mRS > 3) at 2 weeks post randomisation. Analyses were first undertaken of active treatment compared with placebo, followed by comparisons across the three treatment groups where indicated. Logistic regression analysis was used to assess the effect of depressor or pressor treatment separately on death and dependency at 2 weeks. Repeated measures analysis of BP at baseline and at 4, 8 and 24 hours was performed using a generalised estimating equations (GEE) model. Differences in 3-month mortality and cost-effectiveness data were also assessed. Significance levels were set at 5%.

Results

A total of 180 patients were recruited over the 36-month trial period, 179 in the depressor arm and one in the pressor arm (who received placebo). Study recruitment was less than anticipated (being 11% in the depressor arm), primarily related to the number of centres enrolled and the presence of study exclusion criteria in the majority of patients screened for study eligibility. Thus, there was limited statistical power for many of the study end points. The labetalol, lisinopril and placebo depressor groups were well matched for age, baseline BP, stroke type, time to treatment, NIHSS score and prevalence of dysphagia. In the depressor group the primary outcome measure of death and dependency at 2 weeks was assessed in 172 patients (seven patients being excluded because of non-stroke diagnosis, protocol violation or withdrawal of consent) and occurred in 61%

of the active depressor treatment group and 59% of the placebo group ($p = 0.82$). There was no evidence of early neurological deterioration with labetalol or lisinopril compared with placebo and study numbers were too small to detect any differences by stroke subtype. The active depressor treatment group (lisinopril and labetalol combined) had a significantly greater fall in SBP within the first 24 hours than the placebo group [21 mmHg, 95% confidence interval (CI) 17–25, vs 11 mmHg, 95% CI 5–17; $p = 0.004$ at 24 hours], although time effects of BP lowering differed between the labetalol, lisinopril and placebo groups. Sublingual lisinopril and intravenous labetalol also significantly reduced BP within the first 24 hours compared with placebo. Patients on active treatment also had a significantly greater fall in SBP at 2 weeks than patients in the placebo group (31 mmHg, 95% CI 27–36, vs 24 mmHg, 95% CI 17–30; $p = 0.045$) although there was no significant difference in fall in diastolic BP (DBP; 13 mmHg, 95% CI 8–15, vs 9 mmHg, 95% CI 5–13; $p = 0.10$). No major safety problems were observed with labetalol or lisinopril treatment, no significant differences were seen in serious adverse events between active treatment and placebo, and no differences were found in discontinuation rates between those randomised to active treatment and those randomised to placebo. The study was too small to detect any differences in the response to hypotensive therapy between patients with cerebral infarction and those with cerebral haemorrhage. Survival analysis showed that the active treatment group had a lower mortality at 3 months ($p = 0.05$) with a hazard ratio of 2.2 (95% CI 1.0–5.0) for increased risk of death in the placebo group. Economic evaluation suggested that, on average, active treatment is both more effective and less expensive than placebo at 3 months.

Conclusion

Both labetalol and lisinopril lowered BP to a greater degree than placebo in acute stroke patients within 24 hours of symptom onset without causing serious adverse effects or an early increase in stroke severity. However, depressor therapy did not reduce death and dependency at 2 weeks, but because of the reduced numbers recruited to the trial (only 11% of the target numbers were randomised) the study was underpowered to answer this primary outcome measure. Both sublingual lisinopril and intravenous labetalol were effective hypotensive agents in the immediate post-stroke period in dysphagic patients. Of interest was

the reduction in stroke mortality at 3 months with active therapy, a finding in keeping with one other acute BP-lowering stroke trial with a 12-month follow-up period, although care must be taken in interpretation of the CHHIPS results in view of the sample size. Further work is now needed to confirm these results and to assess if there are differences in the effectiveness of labetalol compared with lisinopril in terms of reducing death or dependency after acute stroke, and whether the introduction of earlier BP lowering post stroke than was achieved in CHHIPS would be of greater benefit. That we are still uncertain as to the best management of BP in the acute stroke situation is a matter of serious concern. However, the CHHIPS pilot trial indicates that BP can be safely reduced with labetalol or lisinopril after acute stroke and

that this may translate into a decrease in mortality at 3 months. These findings need to be acted on by formulating the definitive trial of BP lowering in acute stroke. The role of increasing BP in acute stroke remains unresolved, although the numbers in whom this therapy could be applied are very small based on the CHHIPS trial entry criteria.

Publication

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