Controlling Hypertension and Hypotension Immediately Post Stroke study

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Introduction

The Controlling Hypertension and Hypotension Immediately Post Stroke CHHIPS[1] study was conducted in order to assess the effects of acute pressor (phenylephrine) and depressor (lisinopril and labetalol) blood pressure manipulation on 2-week death and dependency following acute stroke and to investigate the safety and efficacy of such treatments. The primary outcome measure was death and dependency at 2 weeks. The study also aimed to determine the safety of acute pressor and depressor blood pressure manipulation in stroke patients; whether effects of blood pressure reduction are influenced by stroke type (ischaemic versus haemorrhagic); whether alternative routes for administration (sublingual or intravenous) of the anti-hypertensive therapies are effective in dysphagic patients; whether effects of blood pressure manipulation are influenced by the time-to-treatment; and the short- and medium-term cost-effectiveness of these therapies in the acute post-stroke period on subsequent disability or death. The results from the study suggested that there was no significant difference in death or dependency at 2 weeks between those receiving active depressor therapy and those receiving placebo. However, only 179 patients were studied in the depressor arm and one patient in the pressor arm so the results from the study cannot be used to justify these blood pressure manipulation therapies on acute post-stroke patients. In addition, the pressor arm study was discontinued due to problems with recruitment so no conclusions were drawn.

Element	Criteria	Comments
Study Design Assessment	Is the design appropriate to the research question? Is the research question useful? • For **efficacy**, use of **experimental study design** (meaning study subjects and others were not allowed choice in determining interventions) • **Clinically significant area** for study (morbidity, mortality, symptom relief, functioning and health-related quality of life) and reasonable **definitions for clinical outcome such as response, treatment success or failure** • If **composite endpoints** used, reasonable combination used – and used for safety if used for efficacy	CHHIPS was a multicentered, prospective, double blinded, randomized controlled trial to assess the effectiveness of immediate post-stroke treatment with blood pressure manipulation on 2-week outcomes of death and dependency.
Internal Validity Assessment	Can bias, confounding or chance explain the study results? • Ensure prespecified and **appropriate** 1) research questions, 2) populations to analyze, 3) outcomes, 4) group assignment methods, 5) study conduct methods, 6) analysis methods, and 7) level for statistical significance	Threat: Study is fatally flawed as described in the following sections.
Selection Bias	• Groups are appropriate for study, of **appropriate** size, **concurrent** and **similar** in **prognostic variables** • Methods for generating the group assignment sequence are truly random, sequencing avoids potential for anyone **affecting assignment** to a study arm and **randomization remains intact** • **Concealment of allocation** strategies are employed to prevent anyone affecting assignment to a study arm	The participants were patients at 5 sites in England. Threat: Randomization was hampered by inclusion criteria which resulted in groups of inappropriate size. For the pressor arm, n=1. Threat: Authors did not indicate their strategy for concealment of allocation.
Performance Bias	• **Double-blinding** methods employed (i.e., subject and all working with the subject or subject's data) and achieved • Reasonable **intervention** and reasonable comparator used (e.g., placebo) • **No bias or difference, except for what is under study, between groups during course of study** (e.g., intervention design and execution, co-interventions, concomitant medication use, adherence, inappropriate exposure or migration, cross-over threats, protocol deviations, measurement methods, study duration, etc.)	Researchers and patients were double blinded without mention of the details. Threat: Protocols were amended midway through the study in order to introduce an additional study arm, dysphagics, and to increase the study duration due to lack of participants.
Attrition Bias	• Zero or minimal **missing data points** or loss from randomization (e.g., approximately 5% with differential loss, or approximately 10% without differential loss) unless good ITT analysis (see ITT below)	Threat: Approximately 20-30% of participants in each study arm dropped out.

Element	Criteria	Comments
Assessment Bias	• Assessors are **blinded** • Low likelihood of findings due to **chance, false positive and false negative outcomes** (judgment call on statistical significance, including **confidence intervals**) • Non-significant findings are reported, but the confidence intervals include clinically meaningful differences • **Intention-to-Treat Analysis (ITT)** performed (all people are analyzed as randomized + reasonable method for imputing missing values which puts the intervention through a challenging trial or reasonable sensitivity analysis) • Use of **modeling** only with use of reasonable assumptions	Threat: The authors state that researchers were blinded but make no mention of assessors specifically. Due to the multiple objectives of this study, the chance of a positive study outcome increases. Survival analysis reported that active treatment had lower mortality at 3 months (p=0.05) with a HR of 2.2, but the confidence interval was inclusive of unity. The authors also indicated that all results underwent an intention-to-treat analysis however a simple look at their tables (ie. Tablet 24) yielded an N not equal to randomization.
Usefulness Assessment	• **Clinically significant area + sufficient benefit size** = meaningful clinical benefit (consider efficacy vs effectiveness)	Maximizing positive outcomes in immediate post-stroke patients is a clinically significant area of study, however the authors stated that the outcomes presented were either not statistically significant or may have occurred due to chance resulting from very small sample sizes.
External Validity	**How likely are research results to be realized in the real world considering population and circumstances for care?** • Review n, inclusions, exclusions, baseline characteristics and intervention methods - this is a **judgment call**.	Threat: The population was highly selected and limited, threatening the external validity of the study.
Patient Perspective	• Consider benefits, harms, risks, costs, uncertainties, alternatives, applicability to which patients, adherence issues, potential for abuse, dependency issues and patient satisfaction	Given the unreliable nature of this study, no conclusions can be drawn.
Provider Perspective	• Satisfaction, acceptability, likely appropriate application and actionability (e.g., FDA approval, affordability, external relevance, circumstances of care, able to apply, tools available)	Given the unreliable nature of this study, no conclusions can be drawn.

*Chart taken from the Delfini Group,LLC. Short Critical Appraisal Checklist: Updated 02/19/08

Author's Conclusions

Both labetalol and lisinopril are capable of manipulating blood pressure immediately post-stroke compared to placebo. However, treatment with these depressors did not reduce death and dependency at 2 weeks. The study was also underpowered to determine smaller potentially significant changes. Additional studies should be performed to realize the definitive effect of blood pressure lowering in acute stroke.

Reviewer's Conclusions

Although the CHHIPS study focused on a clinically significant area of study that can potentially influence the management of stroke patients, the threats to validity limit its application in clinical practice. The low number of participants recruited into the study was a major downfall of this study. Due to problems with recruitment, the investigators had to amend their original protocol in an effort to improve recruitment, which increased potential for bias regarding performance and assessment. The practicality of applying the results of this study, should it have provided beneficial evidence, is also hampered by the study's lack of external validity. A highly restrictive enrollment process that excluded patients with known risk factors for stroke including antihypertensive treatment was employed. However, we do agree that further studies must be done in order to find the best treatment plan for acute post-stroke patients.

Overall Grade: U = Uncertain in validity and usefulness

About the Authors

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Craig Stern, PharmD, MBA is president of ProPharma Pharmaceutical Consultants, Inc. and Chair of the CPhA Editorial Review Committee. Dr. Stern has no bias to disclose.

Guest Editors Dr. Michael E. Stuart and Sheri A. Strite of Delfini Group are experts at systematic literature reviews.

The chart template is adapted from "Delphini Group, LLC. Short Critical Appraisal Checklist: U"

Delfini Evidence Grading Scale

Grade A: Useful

The evidence is strong and appears sufficient to use in making health care decisions – it is both valid and useful (e.g., meets standards for clinical significance, sufficient magnitude of effect size, physician and patient acceptability, etc.).

Grade B: Possibly Useful

The evidence appears potentially strong and is probably sufficient to use in making health care decisions - some threats to validity were identified.

Grade B-U: Possible to uncertain usefulness

The evidence might be sufficient to use in making health care decisions; however, there remains sufficient uncertainty that the evidence cannot fully reach a Grade B and the uncertainty is not great enough to fully warrant a Grade U.

Study quality is such that it appears likely that the evidence is sufficient to use in making health care decisions; however, there are some study issues that raise continued uncertainty. Health care decision-makers should be fully informed of the evidence quality.

Grade U: Uncertain Validity and/or Usefulness

There is sufficient uncertainty that caution is urged regarding its use in making health care decisions.