Do Calcium Antagonists Decrease Mortality or Dependency in Acute Ischemic Stroke?

TAKE-HOME MESSAGE

The use of calcium antagonists in acute ischemic stroke does not reduce mortality or dependency in activities of daily living.

METHODS

DATA SOURCES

An information specialist searched the Cochrane Stroke Group Trials Register, the Cochrane Central Register of Controlled Trials, PubMed, Ovid EMBASE, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform, EU Clinical Trials Register, Stroke Trials Registry, ISRCTN Registry, and Chinese Clinical Trial Registry. The authors also searched the Chinese Biological Medicine Database, China National Knowledge Infrastructure, Chinese Scientific Periodical Database of VIP information, and Wanfang Data. The Cochrane review authors then evaluated reference lists of identified publications.

STUDY SELECTION

Two authors independently assessed studies for relevance and resolved disagreements through discussion or involvement of a third author. To aid with trial selection, authors developed an inclusion/exclusion document, which evaluated general information, trial characteristics, interventions, participants, and outcomes. Investigators included randomized controlled trials of adult patients

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Results

Calcium antagonists versus placebo for acute ischemic stroke.

Outcome	No. of Studies (No. of Patients)	Relative Risk (95% CI)	Evidence Quality (GRADE)
Death or dependency at the end of follow-up*	22 (6,684)	1.05 (0.98–1.13)	Moderate
Recurrence of stroke at the end of follow-up	9 (2,460)	0.93 (0.56–1.54)	Moderate
Adverse events during treatment period	13 (5,095)	1.18 (0.81–1.74)	Moderate
Unpublished trials: death or dependency at the end of follow-up*	4 (788)	1.14 (1.00–1.30)	—†

CI, Confidence interval; *GRADE*, Grading of Recommendations Assessment, Development and Evaluation.
*Primary outcome.
†Evidence quality not assessed because data were unpublished. Heterogeneity assessment revealed I^2=28%.

with presumed or definitive acute ischemic stroke who received a calcium antagonist within 14 days of stroke onset by any route versus placebo or medical treatment alone. Authors also included randomized controlled trials evaluating different doses and routes of administration.

DATA EXTRACTION AND SYNTHESIS

Two investigators independently extracted data from included studies. The primary outcomes included all-cause mortality and dependency in activities of daily living as defined by modified Rankin Scale or Oxford Handicap Scale score greater than 3, Glasgow Outcome Coma Scale score less than 4, Barthel Index score less than 60, Toronto Stroke Scale score greater than 3, or Mathew Impairment Scale score equal to 7. Secondary outcomes included death from any cause during scheduled treatment; death from any cause during long-term follow-up with a minimum of 3 months; recurrent stroke during long-term follow up; adverse effects of the drug during the treatment period (eg, reduced renal function, impaired liver function, local infection irritation, nausea); hypotension defined as substantial decrease in blood pressure during the treatment period; and mean systolic blood pressure during the treatment period. Authors calculated risk ratios with 95% confidence intervals for dichotomous data and mean differences with 95% confidence intervals for continuous outcomes. They assessed heterogeneity with the I^2 statistic. Two authors assessed risk of bias according to the *Cochrane Handbook for Systemic Reviews of Interventions* and used the Grading of Recommendations Assessment, Development and

Authors included 34 randomized controlled trials comprising 7,731 patients. Twenty-six trials evaluated nimodipine, 3 trials studied flunarizine, and 1 trial assessed each of the following: isradipine, nicardipine, fasudil, and lifarizine. Most trials used a placebo control arm and had follow-up at greater than or equal to 3 months. The majority of trials reported that both treatment and control groups received antiplatelet and anticoagulation therapy. Data from 22 published trials (6,684 patients) suggested no difference in all-cause mortality or dependency with calcium antagonists (Table). There were no differences in adverse events during treatment, including hypotension during treatment. Although published trials did not show an overall effect of active treatment on the primary outcome, unpublished trials demonstrated a deleterious effect between treatment with a calcium antagonist and the primary outcome, suggesting publication bias.

Commentary

Stroke is the leading cause of disability worldwide and the second most common cause of mortality.[2] Ischemic cerebrovascular accidents account for 87% of strokes.[3] Massive calcium influx into cells is the final common pathway for cell demise, and calcium antagonist therapy may be neuroprotective by decreasing calcium influx through voltage-gated channels.[4] Indeed, previous studies have shown calcium antagonists to decrease mortality and disability in aneurysmal subarachnoid hemorrhage.[4,5] Prompt administration of calcium antagonism may improve perfusion of this ischemic penumbra. Although stroke teams typically admit these patients and may administer calcium antagonists, in settings that are resource limited or with prolonged emergency department boarding, the emergency physician may manage these aspects of care.

This Cochrane review demonstrated no benefit in regard to either mortality or long-term dependency with calcium antagonists in patients experiencing ischemic stroke. Subgroup analyses suggested an increase in mortality with the use of flunarizine, and the largest trial studying this agent also showed increased risk of adverse events, including superficial thrombophlebitis (risk ratio 3.16; 95% confidence interval 1.91 to 5.21).[6] Subgroup analyses of studies on nimodipine showed no effect of this agent on primary or secondary outcomes. This contrasts to the meta-analysis by Mohr et al[7] that demonstrated decreased mortality with prompt administration of oral nimodipine. The present meta-analysis comprises a larger number of patients, suggesting its conclusions are more robust. Unfortunately, data limitations in the meta-analysis by Mohr et al[7] precluded direct comparisons of the 2 meta-analyses, leaving open the possibility of a different effect size in regard to the primary outcome based on routine of administration of nimodipine.

Limitations of this Cochrane review include 5 trials without blinding and 1 trial that did not report whether blinding occurred. Attrition bias because of incomplete outcome data introduced a high risk of bias in 20 of 34 studies. The meta-analysis authors'

Evaluation criteria to assess evidence quality.[1] Authors analyzed all outcomes and included analyses stratified by route of administration, dose, and interval. They conducted subgroup analyses on drug administration route, dose, and interval to the start of treatment. They planned to conduct sensitivity analysis with the inclusion of only multicenter studies or published trials.

sensitivity analyses suggested a high likelihood of publication bias, with published studies demonstrating no overall effect of calcium antagonists on the primary outcome, whereas unpublished trials demonstrated a deleterious effect between calcium antagonists and the primary outcome. Moreover, pharmaceutical manufacturers funded 20 of 34 trials, offering another potential source of bias. Many trials included only patients with strokes involving the middle cerebral artery territory or supratentorial region. Finally, a majority of these studies predate the use of neuroprotective and advanced care strategies and thrombolytics in stroke management, which may not necessarily reflect the current standards of stroke care.

According to these results, patients with acute ischemic stroke who receive calcium antagonists by any route do not have decreased mortality or long-term dependency in activities of daily living, and therefore calcium antagonists have a limited role in the acute setting.

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