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Original Study

Does Low Dose Angiotensin Converting Enzyme Inhibitor Prevent Pneumonia in Older People With Neurologic Dysphagia—A Randomized Placebo-Controlled Trial

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A B S T R A C T

Objective: To examine if angiotensin converting enzyme inhibitor reduces the risk of pneumonia in older patients on tube-feeding because of dysphagia from cerebrovascular diseases.
Design: Randomized placebo-controlled trial.
Setting: Acute and subacute geriatrics units, speech therapists' clinic, and nursing home.
Participants: Older patients on tube-feeding for >2 weeks because of dysphagia secondary to cerebrovascular diseases.
Intervention: Participants were randomized to lisinopril 2.5 mg or placebo once daily for 26 weeks.
Measurements: Participants were followed up at weeks 12 and 26. The primary outcome was the incidence rate of pneumonia as determined by pneumonic changes on x-ray and clinical criteria. The secondary outcomes were mortality rate and swallowing ability as defined by the Royal Brisbane Hospital Outcome Measure for Swallowing at week 12.
Results: A total of 93 older patients were randomized. In interim analysis, 71 completed the trial, whereas 15 had dropped out. Among those who had completed the trial, odds ratio (OR) for death was significantly higher in the intervention group (unadjusted OR 2.94, $P = .030$; fully adjusted OR 7.79, $P = .018$). There was no difference in the incidence of pneumonia or fatal pneumonia in the 2 groups. The intervention group had a marginally better swallowing function at week 12 (Royal Brisbane Hospital Outcome Measure for Swallowing score: 4.2 ± 1.5 in intervention group, 3.5 ± 1.5 in placebo group, $P = .053$). As a result of the interim finding on mortality, the trial was prematurely terminated with 7 participants still in the trial.
Conclusions: Low dose lisinopril given to older tube-fed patients with neurologic dysphagia resulted in increased mortality, although swallowing function showed marginal improvement. ACE inhibitors did not prevent pneumonia in older patients with neurologic dysphagia and might increase mortality.

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Tube feeding is increasingly used in frail older people with dysphagia for the prevention of aspiration pneumonia and the maintenance of nutrition. This practice is particularly common in nursing home settings. However, despite tube-feeding, these patients still have high recurrence rates of pneumonia resulting in hospitalizations and mortality. Contrary to common belief, there is no evidence that tube-feeding prevents aspiration pneumonia in patients with dysphagia.[1]

Angiotensin enzyme converting (ACE) inhibitor is a commonly used antihypertensive drug that can cause a dry cough as a side effect. One of the mechanisms for this side effect is the decreased degradation of substance P, which is released from sensory nerve terminals in the nasopharynx. It has been found that substance P level in sputum is low in aspiration pneumonia patients.[2] Previous randomized trials have shown that ACE inhibitor could significantly improve swallowing reflex and reduce silent aspirations without lowering blood pressure in at-risk patients.[3,4] Observational studies have also found that ACE inhibitor use was associated with lower incidence of pneumonia in older stroke patients with hypertension.[5] A meta-analysis found that ACE inhibitor may have a protective role in pneumonia, especially in stroke patients and among Asian populations.[6,7] ACE inhibitors may, therefore, have a role in preventing pneumonia in frail patients with dysphagia by improving their swallowing and cough reflexes. Two recent case-control studies, however, have failed to find any association between ACE inhibitor use and pneumonia among a general Asian population[8] and in the older general population.[9] Its effect in patients with very high risk of aspirations and pneumonia were yet uncertain.

We hypothesized that ACE inhibitors may reduce the incidence of pneumonia in tube-fed patients with neurologic dysphagia related to cerebrovascular disease and conducted a randomized controlled trial (RCT) to examine the effectiveness and safety of an ACE inhibitor in preventing pneumonia in this high-risk group of patients. A lower dose was used because of the risk of hypotension and electrolyte disturbances with ACE inhibitors in frail older people.

Methods

Participants

Tube-fed patients aged 60 years or older were recruited from the medical wards of an acute university, 2 subacute hospitals, affiliated geriatric outpatient clinics, and speech therapy clinics in Hong Kong. All had a history of recent hospitalization in the previous 3 months. They had been on tube-feeding for more than 2 weeks because of neurologic dysphagia as recommended by a trained speech therapist. The clinical diagnosis of cerebrovascular diseases was confirmed by computerized axial tomography of the brain. Exclusion criteria included the following: life expectancy less than 6 months, baseline systolic blood pressure less than 100 mm Hg, known intolerance to ACE inhibitors, current use of ACE inhibitor or angiotensin receptor blockers, symptomatic chronic lung disease or cardiac failure, frequent withdrawal of enteral tube by patients, serum creatinine >150 μmol/L, and serum potassium >5.1 mmol/L. The study was approved by the combined Ethics Committee of the Hospital Authority New Territories East Cluster and the Chinese University of Hong Kong. It was registered in ClinicalTrials.gov under the trial number of NCT02358642.

Measurements

After obtaining written informed consent from participants or family caregivers (if participants were incapable of giving informed consent), the following measurements were made.

Dysphagia Assessment

All participants were assessed by designated speech therapists who rated the participants' swallowing ability by the Royal Brisbane Hospital Outcome Measure for Swallowing (RBHOMS).[10] It is a clinically assessment scale for swallowing ability graded from levels of 1 to 10. Stage A comprises of level 1–3 and indicates the need to be kept nil by mouth; stage B comprises of level 4 and indicates fitness for commencing oral intake; stage C comprises of levels 5–7 and indicates the establishment of oral intake; and stage D comprises of levels 8–10 and indicates maintaining oral intake.

Demographics

Information regarding the following were collected: place of residence (home or nursing home), history of medical diseases (including history and time of stroke, history of recent pneumonia in recent hospitalization, diabetes, hypertension, dementia, Parkinson disease, chronic obstructive pulmonary diseases, and congestive heart failure), and concurrent use of antihypertensives. Duration of dysphagia and tube-feeding, information about the formula, and feeding regime were also recorded.

Blood Tests and Clinical Characteristics

All participants had a nonfasting blood test for baseline renal function prior to the start of the trial. Another renal function test was performed within 1 week after the start of the trial to ensure tolerance to the study drug.

On the day prior to the start of the trial, sitting blood pressure at rest was taken on 2 consecutive occasions, and the average was used for analysis. Mid-arm circumference was measured to estimate nutritional status.[11] Modified Barthel index was used to measure basic functional status (maximum score of 20).[12] Abbreviated mental test score was administered to screen for dementia.[13] A local validation study showed that cut-off values of 4 and 6 out of 10 in illiterate and educated people respectively suggested dementia.

Intervention

The intervention group participants were given lisinopril 2.5 mg once daily at bedtime. A low dose regime was chosen as it was less likely to cause hypotension, electrolyte disturbances, and impair renal function. A similar low dose ACE inhibitor regime had been shown to be effective in preventing silent aspiration.[4] The control group participants were given identical placebo once daily at bedtime.

Randomization

Participants were randomized according to a computer-generated random sequence. The manufacturer of the trial tablets was responsible for generating the group assignment and packaged the drug bottles accordingly. Consecutive participants were assigned a participant number. They were given 4 weekly supplies of trial drugs in bottles labeled by their participant numbers. The coding file was kept by the manufacturer and a research assistant not involved in the trial. The coding was kept confidential to all other parties until the end of the trial.

Safety Monitoring

Sitting blood pressure was measured at least 3 times in the first 24 hours after the first dose of trial drug in all participants. Blood pressure was measured at week 12 follow-up. Renal function test was