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# The preventive effect of captopril on aspiration pneumonia in stroke patients: A Single-Blind Randomized Controlled Clinical Trial

**Nima Rahimi Petrudi [1], Parviz Amri Maleh [2], Amin Ataie [3], Khadijeh Ezoji [4], Shahrbanoo Latifi [5], kayvan Latifi [6], Shahram Seyfi [7]***

1. Cardiovascular Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran. Petrudi.nima@gmail.com.
2. Clinical Research Development Unit of Ayatollah Rouhani Hospital, Babol University of Medical Sciences, Babol, Iran. pamrimaleh@yahoo.com.
3. Neuroscience Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran. ataieamin@yahoo.com.
4. Social Determinants of Health Research Center, Health Research Institute, Babol University of Medical Sciences, Babal, Iran. dr.kh.ezoji@gmail.com.
5. Master of Medical Education, Babol University of Medical Sciences, Babal, Iran Latifinursing@yahoo.com.
6. Assistant Professor of Critical Care Medicine, Department of Anesthesiology, Operating Room and Emergencies, School of Allied Medical Sciences, Mazandaran University of Medical Science, Sari, Iran. latifikayvan@gmail.comlatifikayvan@gmail.com.
7. Clinical Research Development Unit of Ayatollah Rouhani Hospital, Babol University of Medical Sciences, Babol, Iran. Ficu-ss@yahoo.com.

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**ABSTRACT**

**Background:** In patients with stroke, alongside diminished level of consciousness, impaired swallowing and aspiration pneumonia are also common. In some studies, angiotensin-converting enzyme inhibitors (ACEIs) have caused improved swallowing and reduced incidence of aspiration pneumonia in some patients. This study has examined the effects of captopril on reducing the extent of aspiration pneumonia in stroke patients.

**Methods:** A total of 68 patients with brain stroke and diminished level of consciousness hospitalized in Ayatollah Rouhani Hospital, Babol were chosen and randomly assigned into captopril and placebo groups. In the captopril group, in case of blood pressure above 100/70 mmHg, captopril was prescribed with a dose of 6.25 mg three times per day. In the placebo group, vitamin C was given, and in both groups in the case of hypertension, an antihypertensive drug other than ACEI was used. Age, gender, blood pressure, potassium level, and primary underlying diseases were recorded. The two groups were compared with each other daily for 14 days in terms of severity of incidence of pneumonia as well as hemodynamic changes in potassium.

**Results:** A total of 68 patients with brain stroke were included in the study in two equal 34-subject groups. The two groups had no difference in terms of age, gender, systolic and diastolic blood pressure, initial potassium level, and underlying diseases. In the captopril group, 1 (2.9%) and in the placebo group 6 (17.6%) suffered pneumonia ($P < 0.046$). The two groups had no significant difference in terms of systolic and diastolic blood pressure, heart rate, and serum potassium.

**Conclusion:** The results of this study indicated that captopril is effective in reducing the extent of incidence of aspiration pneumonia in brain stroke patients.

**Keywords:** Captopril, Aspiration Pneumonia, Cerebral Stroke.

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* **Corresponding Author:** Shahram Seyfi
**Address:** Clinical Research Development Unit of Ayatollah Rouhani Hospital, Babol University of Medical Sciences, Babol, Iran.
**Tel:** +989111139348 **E-mail:** Ficu-ss@yahoo.com

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## Introduction

Infections are among the common causes of mortality among patients hospitalized in intensive care units (ICU). Aspiration pneumonia is common in patients with diminished consciousness levels with swallowing disorders or dysphagia. The common causes of aspiration pneumonia include intubation and mechanical ventilation, causing impaired swallowing and discharge of secretions (1-6). Other causes of aspiration pneumonia are oral feeding as well as nasogastric tube (NGT). Healthy individuals aspirate some amount of oropharynx secretions during sleep, but due to strong cough mechanisms and healthy swallowing, as well as healthy cellular plus humoral immunity, no special event occurs (5,7).

Swallowing is a complex and coordinated neuromuscular process that is impaired in neurological diseases such as Parkinson's, cerebrovascular accidents (stroke), and dementia. Swallowing disorder and dysphagia due to reduced clearance of secretions is a serious risk factor for aspiration pneumonia. In acute stroke, impaired swallowing and dysphagia occur in most patients, and mostly improve. However, in some cases, dysphagia persists and results in pneumonia. Pathogenic agents colonized in the oropharynx of the elderly alongside dysphagia often include Staphylococcus aureus, anaerobic bacteria, and gram-negative bacteria (E. Coli and Klebsiella) (8-12).

Diagnosis of pneumonia is based on fever, increased pulmonary secretions (inside the tracheal tube), increased white blood cells, and radiographic signs. Sampling for culture and diagnosis from preliminary secretions as tracheal aspiration bronchoalveolar lavage is helpful. The complications of pulmonary infection include increased duration of hospitalization, mortality, and hospital costs (8-9). Thus, its prevention is very important. To control and improve dysphagia of neurological diseases, a coordinated plan is required in terms of nutrition and controlling the Gag reflex as well as cough by the medical team. P substance is a neurotransmitter effective in maintaining the sensory pathway of cough, swallowing, and dysphagia. Angiotensin-converting enzyme inhibitors, as antihypertensive drugs, prevent the breakdown of this substance, and thus they have been reported to prevent aspiration pneumonia (13-19).

The side effects of these drugs include cough, hypotension alongside vertigo, as well as weakness, especially in patients with sodium deficiency or dehydration. Subcutaneous lesions with or without itching, fever, and joint pain are other side effects of these drugs. Eosinophilia may be observed in some patients. Angioedema in hands and feet, face, lips, mucous membranes, tongue, larynx, and chest cavity are among the side effects of the drugs. Other side effects include hyperkalemia, agranulocytosis, presence of glucose in the urine, pancreatitis, dry as well as persistent coughs, and headache (20, 21).

The first drug of this group introduced into the market is captopril. This drug is a potent Angiotensin-converting-enzyme inhibitor (ACE inhibitor) and is rapidly absorbed orally. Its maximum plasma concentration emerges within one hour. Its half-life is two hours and its metabolites are cleared through the urine, with 50% of the drug cleared intact in the urine. The oral dose of captopril is 6.25-150 mg 2-3 three times a day. Since food reduces the drug absorption, it should be consumed one hour before meal (17-21).

Pneumonia and respiratory infections are very important in mortality caused by stroke, and they should be prevented. There are studies on the effect of ACEI in reducing the incidence of aspiration pneumonia in stroke patients. We planned to conduct a study on the effect of captopril on the rate of aspiration pneumonia in stroke patients with reduced consciousness in our hospital.

## Methods

The present research is a single-blind randomized clinical trial. Adult patients with stroke hospitalized in the ICU or neurology ward of Ayatollah Rouhani Hospital were introduced in the study in case they

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met the criteria. The inclusion criteria were stroke for the first time, diminished level of consciousness (Glasgow coma degree of equal to or greater than 8), dysphagia, prediction of hospitalization for at least 14 days, and stable hemodynamic status after 24 hours.

The exclusion criteria were history of taking captopril, respiratory diseases such as asthma, and bronchitis, pulmonary infections, diagnostic and therapeutic measures on the respiratory system, re-intubation, severe organ failure, chemotherapeutic drugs, and immunodeficiency, drug side effects, contraindications for taking captopril, mortality, and early recovery before two weeks. The initial information of patients was collected including age, gender, systolic and diastolic blood pressure, history of hypertension as well as underlying diseases such as Alzheimer's, diabetes, kidney diseases, as well as chronic pulmonary disease, and heart failure.

A total of 68 envelopes including 34 envelopes containing 42 Captopril tablets (6.25 mg, 1/4 tablets of Captopril 25 Exir Pharmaceutical Company) and 34 envelopes containing 42 tablets (1/4 of vitamin C tablet as placebo) were prepared, and provided to the ICU or neurology ward. They were then randomly assigned to each of the patients in the intervention and control groups. During the two weeks of treatment, the drug present in the envelope of each patient was used. The subjects did not know which group they were in.

For the patient in the first group, 24 hours after starting the hospitalization, captopril (6.25 mg) was initiated three times per day by the ward nurse with no information about the plan. In the second group, the placebo drug, vitamin C, was administered. In both groups, in the case of hypertension above 140.95, antihypertensive drugs other than ACEIs were employed. The patients were visited daily by the ICU specialist. The patients who showed fever at 48 hours post-hospitalization, were monitored in terms of purulent secretions in the tracheal tube or purulent coughs, leukocytosis, and progressive infiltration in the chest X-ray. The concurrent presence of the above criteria was regarded as a pneumonia diagnosis.

In both groups, the severity of the incidence of pneumonia based on the pneumonia severity index (PSI) or PORT Score (26) was examined for two weeks. Systolic and diastolic blood pressure, heart rate, and serum potassium level were controlled and recorded seven times (odd days for two weeks). Changes in systolic and diastolic blood pressure as well as heart rate more than 20% of the baseline level were considered positive. The two groups were compared with each other in terms of demographics including age, gender, history of hypertension, and underlying diseases.

After obtaining informed consent from the patients' companions and acquiring permission from the ethics committee of Babol University of Medical Sciences, the patients were enrolled. The patients with a Glasgow score of less than 11 and greater than 8 took the swallowing test. To assist the swallowing, the Royal Brisbane Hospital Outcome Measure for Swallowing (RBHOMS) was used, where the physician scores the patient's swallowing from 1 to 10. Score 1-3 means NPO (Nothing by mouth) and complete dependence on feeding through a tube, 4-5 represents little oral feeding and requiring supplementary tube feeding, 6-7 shows modified diet with no need to tube feeding supplement, and the possibility of applying normal feeding through the mouth at scores above 8 (25).In case the patients had no swallowing reflects or weak reflects (score equal to or less than 5), and blood pressure equal to or higher than 100/70 mmHg, they were included in the study.

This study has been registered in irct. ir with the code of IRCT20141121020020N6. This study was approved by the university research ethics committee with the code of ethics of IR.MUBABOL.REC.1391.014. The data were analyzed by SPSS 22. Chi-square, t-test, and Fisher exact test were applied for quantitative and qualitative variables. P-value less than 0.05 was considered significant.

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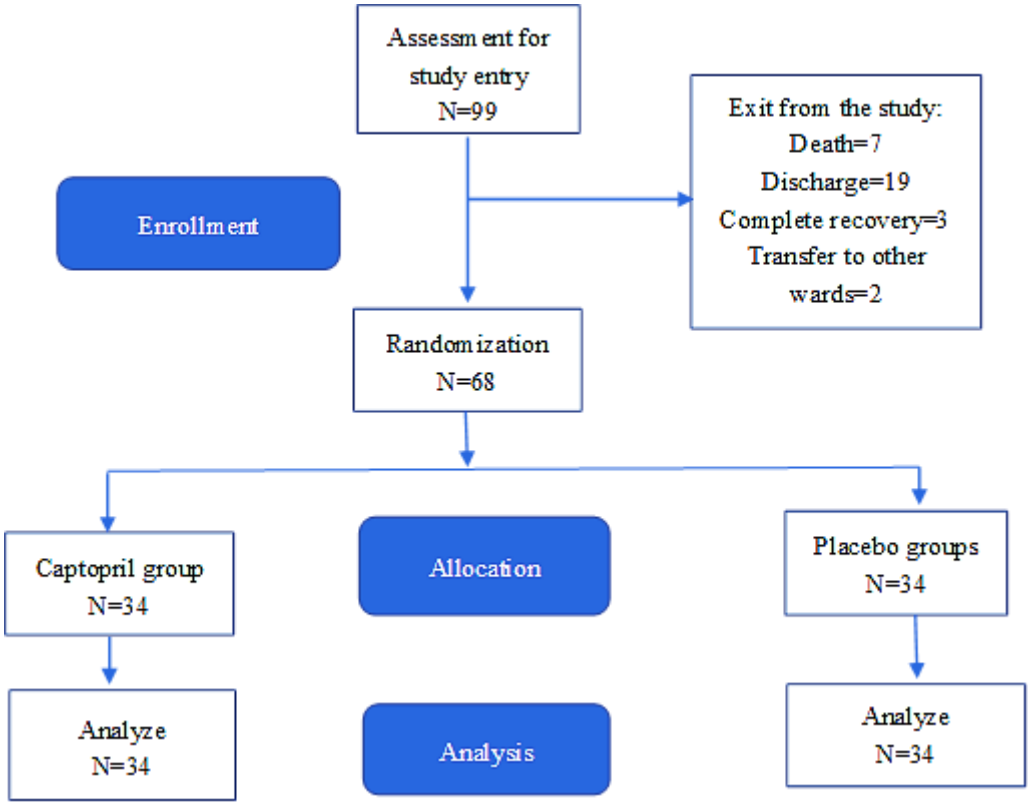


**Flowchart No. 1. Flowchart of the participants during the study**

## Results

A total of 99 patients hospitalized at the baseline were examined in terms of inclusion and exclusion criteria, with 31 being excluded due to the following reasons: death (n=7, 10.2%), discharge from hospital before beginning the study (n=19, 27.9%), complete recovery (n=3, 4.4%), transfer to other wards (n=2, 5.2%). Eventually, the data related to 68 patients, 34 in the drug and 34 in the placebo groups, were analyzed.

Out of all of the patients studied (n=68), 31 (45.58%) were in the ICU, with 17 of them receiving captopril and 14 receiving placebo. Also, 37 (54.41%) were in the neurology ward, with 17 and 20 cases receiving captopril and placebo respectively. According to Table 1, the two groups did not differ significantly in terms of demographics including age, gender, systolic and diastolic blood pressure, history of hypertension, and underlying diseases.

The rate of pneumonia in all patients was 7 cases (10.3%), 1 case (2.9%) in the captopril group and 6 cases (17.6%) in the placebo group had pneumonia ($P < 0.046$). Out of all patients, 22 (32.4%) were intubated, and 46 had no tracheal tube. In the captopril and placebo groups, 11 and 11 patients received tracheal tubes. The extent of pneumonia in all patients was 7 (10.3%): 1 case in captopril (2.9%) and 6 (17.6%) in the placebo.

The average serum potassium level in all patients was 3.8 meq. g/dL. variations in serum potassium were minor, and the range of changes in the captopril group was greater than in the placebo group, though it was not significant.

Diagrame 3 shows the average number of heart rate per minute in two groups. The difference in heart rate changes in two groups was not significant (p-value > 0.05).

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**Table 1. Comparison of demographic and clinical characteristics of patients in two groups**

| Variables | captopril group(n=34) | Placebo group (n=34) | P value |
|---|---|---|---|
| **n(%) Men,** | 12(35.2) | 16(47) | 0.46 |
| **Age (yrs), mean ±SD** | 69.24±14.27 | 73.26±11.52 | 0.20 |
| **Underlying disease, n(%)** | 21(61.8) | 24(70.6) | 0.61 |
| **history of hypertension (%)** | 13(38.2) | 17(50) | 0.46 |
| **Systolic blood pressure (mm Hg)** | 148.09±78/10 | 147.85±26.08 | 0.99 |
| **Diastolic blood pressure (mm Hg)** | 82.32±23.88 | 84.35±13.69 | 0.67 |
| **potassium mEq / L** | 4.13±0.74 | 3.99±0.75 | 0.25 |

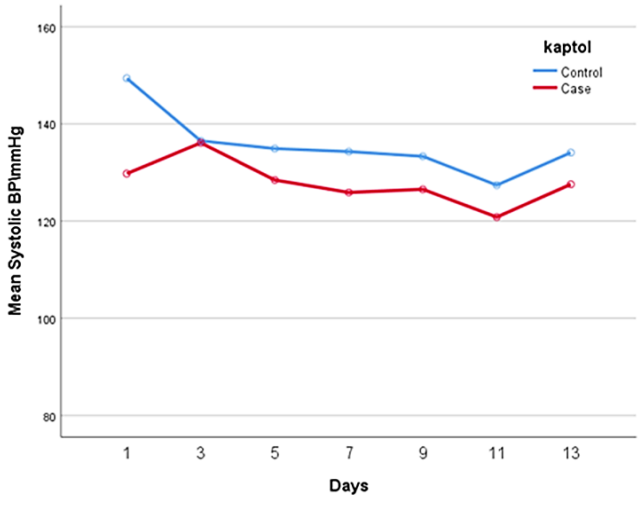


**Diagram 1. Displays the average systolic blood pressure in both groups. The reduction of systolic blood pressure was greater in the captopril than in the placebo group, but it was not significant**

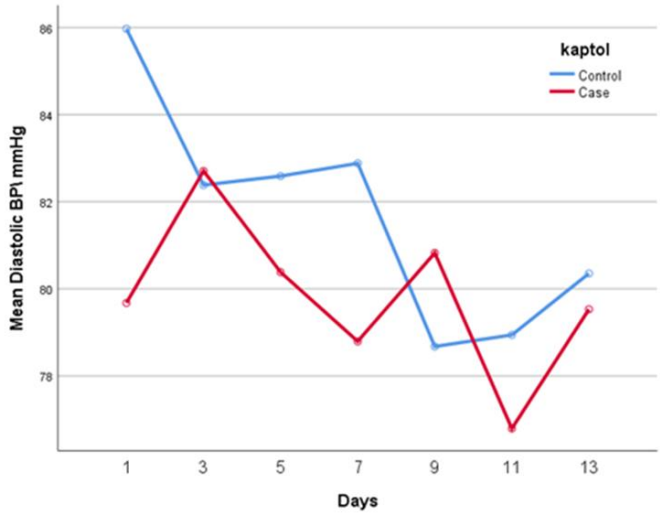


**Diagram 2. Reveals the average diastolic blood pressure in both groups. The reduction of diastolic blood pressure was greater in the captopril than in the placebo group, but it was not significant**

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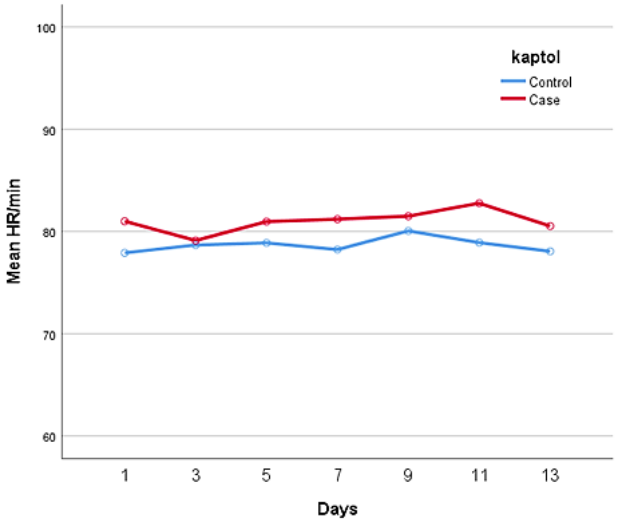


**Diagram 3. Indicates the average heart rate per minute for both groups. The difference between the two groups regarding heart rate changes was not significant**

## Discussion

Our study indicated that captopril can lower the incidence of pneumonia in stroke patients with reduced consciousness. This was confirmed in some studies (27), while others have found different results. Since captopril is an ACE inhibitor, by inhibiting lysis of substance P it leads to improved swallowing and less dysphagia, and hence lowered incidence of aspiration pneumonia, which is one of the common complications of stroke due to dysphagia (24).

The intravenous injection of imidapril, which is an ACE inhibitor in rats, resulted in stimulation of activity of the cervical, phrenic, and hypoglossal vagus nerve and increased motor activity of swallowing muscles, which has been associated with increased substance P level (18). Substance P is an 11-amino acid peptide. This substance is present in special neurons of the brain especially sensory neurons as well as reticular neurons in the digestive tract wall. In other words, substance P is a neurotransmitter that specifically participates in contracting the lower sphincter reflex of the esophagus (30).

Lee et al. conducted a study investigating the effect of low doses of ACE inhibitors on the incidence of pneumonia in patients with stroke plus dysphagia. They applied a low dose of lisinopril in their study. They concluded that dysphagia improved in those receiving lisinopril, but mortality increased. Despite the similarity between the method and this study, different results were found, which can be due to the type of drug or racial differences (17).

Extensive studies have confirmed the effect of ACE inhibitors on reducing the incidence of aspiration pneumonia in all among hospitalized patients due to stroke (13,27), where conducting this study in patients hospitalized for different reasons yielded different results (28, 29, 31). ACE inhibitors also caused improved dysphagia in asymptomatic patients and the elderly (22-23), in which cases the elevation of the P substance has been expressed as the reason for this improvement.

Changes in systolic and diastolic blood pressure were greater in the captopril group compared to the placebo, though the changes were not statistically significant. By inhibiting ACE, captopril inhibits the version of angiotensin I to angiotensin II, with angiotensin II causing contraction of vessels as well as sodium plus water retention. By preventing vascular contraction and fluid retention, captopril in turn causes reduced blood pressure. In this study, a low dose of captopril was used, and in another study which had also used a low dose of an ACE inhibitor, no change of blood pressure was observed in the captopril group and placebo group (17). Lowering the blood pressure without changing the heart rate is

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one of the advantages of captopril (33). In our study, variations in heart rate in the captopril and placebo groups were not statistically significant.

The average serum potassium was higher in the captopril than in the placebo group, though again this difference was not significant. Hyperkalemia is one of the possible complications of treatment with ACE inhibitors, due to its impact on aldosterone. Suppressing angiotensin II leads to reduced levels of aldosterone. Since aldosterone is responsible for increasing potassium excretion, ACE inhibitors can cause potassium retention (34). In the study by Lee et al., again changes in potassium were evaluated in two groups receiving low-dose ACE inhibitor and placebo, with no significant changes.

The results of this study showed that captopril, which is an ACE inhibitor, can reduce the incidence of aspiration pneumonia in brain stroke patients, without significantly altering the blood pressure, heart rate, and serum potassium. Thus, administering captopril is recommended for reducing aspiration pneumonia in all patients with brain stroke whether with hypertension or normal blood pressure. Hereby, the research deputy of Babol University of Medical Sciences, the unit of development of clinical research at Babol Ayatollah Rouhani Hospital, the personnel of the neurology ward, and the ICU ward of Ayatollah Rouhani Hospital are highly appreciated.

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**Authors' Contributions:** Conceptualization: SH.S, N.R.P; Methodology: K.L,P.A.M.; Statistical analysis and investigation: KH.E, SH.L.; Writing - original draft preparation: SH.S, A.A.; Writing, review and editing: KH.E, N.R.P, SH.S.

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**Conflicts of interest:** The authors declare no conflicts of interest.

**Data availability:** The data that supports the findings of this study are available from the corresponding author upon reasonable request.

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