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Systematic Review

Comparison Of Reduction In Blood Pressure Between Sublingual and Oral Captopril

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Abstract

Background: Hypertensive crisis poses a high risk for long-term cardiovascular complications, and management focuses on controlled blood pressure (BP) reduction rather than immediate normalization. **Objective:** To compare the effectiveness of sublingual and oral captopril in reducing BP among patients with hypertensive urgency. **Methods:** A literature review was conducted using English-language studies published after 2012 that evaluated BP reduction outcomes of sublingual versus oral captopril. **Results:** Three relevant studies met the inclusion criteria, comparing both administration routes in hypertensive urgency management. All studies demonstrated that sublingual and oral captopril were similarly effective in lowering systolic and diastolic BP within the first few hours after administration. Sublingual captopril consistently produced a faster onset of action, with BP reduction observed within 15–30 minutes, whereas oral administration required 30–60 minutes to achieve comparable effects. None of the studies reported significant differences in adverse effects between the two routes. These findings suggest that while overall efficacy is comparable, the sublingual route provides more rapid BP control, which may be crucial in acute care settings. **Conclusion:** Both sublingual and oral captopril are effective options for hypertensive urgency, with the sublingual form offering a faster therapeutic response suitable for rapid BP reduction in emergency situations.

Keywords: *Angiotensin converting enzyme (ACE); Captopril; Hypertensive urgency*

Introduction

Hypertensive crisis is a condition characterized by an increase in systolic blood pressure >180 mmHg or diastolic blood pressure >120 mmHg, with or without organ damage[1]. Hypertension is one of the most common degenerative diseases encountered in healthcare facilities, particularly among the elderly. The prevalence of hypertension increases with age. Estimates indicate that 31.1% of adults (1.39 billion people) worldwide suffer from hypertension. The prevalence of hypertension among adults is higher in low- and middle-income countries (31.5%, 1.04 billion people) than in high-income countries (28.5%, 349 million people)[2].

The majority (two-thirds) of hypertensive patients reside in low- and middle-income countries. Approximately 1 in 4 men and 1 in 5 women worldwide suffer from hypertension. Less than 1 in 5 individuals with hypertension have their condition under control. Hypertension is a leading cause of premature death globally. A global target for non-communicable diseases is to reduce hypertension prevalence by 25% by 2025[3]. In America, the prevalence of hypertension is 23.4% among adults aged 18–39 years, 52.5% for those aged 40–59 years, and 71.6% for individuals over 60 years old. The prevalence is higher in men than in women for those under

60 years old. However, there is no significant difference in prevalence between men and women aged 60 years and above[4]. Basic Health Research (Riskesdas) in Indonesia shows that the prevalence of hypertension diagnosed by a doctor in the adult population is 8.36%, which is significantly lower than the prevalence identified through blood pressure measurements (34.11%). These data indicate that hypertension remains underdiagnosed in Indonesian society. Furthermore, adherence to routine medication among diagnosed hypertensive patients is only 54.40%[5].

There are two types of hypertensive crises: hypertensive urgency and hypertensive emergency, distinguished by symptoms involving target organs[6]. Management of hypertensive crisis focuses on lowering blood pressure (BP), though not necessarily to normal BP levels. Common organ damage associated with hypertensive crises includes hypertensive encephalopathy, intracranial hemorrhage, acute ischemic stroke, acute myocardial infarction, left heart failure with pulmonary edema, unstable angina pectoris, aortic dissection, acute renal failure, and eclampsia. This condition is often referred to as a "silent killer"[7]. Epidemiological studies in North America show that 1-2% of hypertensive patients experience hypertensive crises, including both urgency and emergency. Acute pulmonary edema, myocardial ischemia, and neurological emergencies are the most commonly observed acute target organ dysfunctions. The availability of antihypertensive medications has reduced hypertensive emergencies and improved survival rates for hypertensive patients[8]. Hypertensive crises are associated with a higher long-term cardiovascular incidence, making blood pressure control, reduction of hypertension triggers, and consistent follow-up with primary healthcare facilities essential[6,9,10].

The goal of hypertensive urgency therapy is to gradually lower BP within 24-48 hours. Guidelines generally recommend intravenous antihypertensive drugs for patients with hypertensive crises. However, certain conditions make this approach unfeasible. Oral antihypertensive medications are considered a good initial step to prevent overly aggressive BP reduction[11,12]. Nifedipine was initially the most commonly used oral therapy. However, side effects such as hypotension, tachycardia, and palpitations have made its effects increasingly unpredictable[11,12]. Consequently, oral or sublingual nifedipine is no longer recommended for hypertensive urgency and has been replaced by captopril[13,14]. Angiotensin-converting enzyme inhibitors (ACE inhibitors) are widely used in hypertension management[15]. Captopril is commonly used in hypertensive management due to its minimal side effects and satisfactory therapeutic effects[13]. Captopril is an effective antihypertensive agent for hypertensive crisis management. When administered orally, captopril has a slow onset of action, which is why it is often given sublingually (SL) in hypertensive crisis treatment[11,16].

Captopril is frequently used as an antihypertensive agent for patients with hypertensive urgency in emergency settings, including in primary healthcare services and resource-limited facilities. This article aims to assess the effectiveness of sublingual and oral captopril in reducing blood pressure in patients with hypertensive urgency. Additionally, we analyze the side effects of these treatments in patients with hypertensive urgency.

Material and Method

Study Design

This study employs a systematic review and meta-analysis design following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines.

The study aims to analyze the effectiveness of sublingual versus oral captopril administration in reducing blood pressure in cases of hypertensive urgency. This design was chosen as it allows for a comprehensive synthesis of existing evidence to assess intervention efficacy in clinical settings.

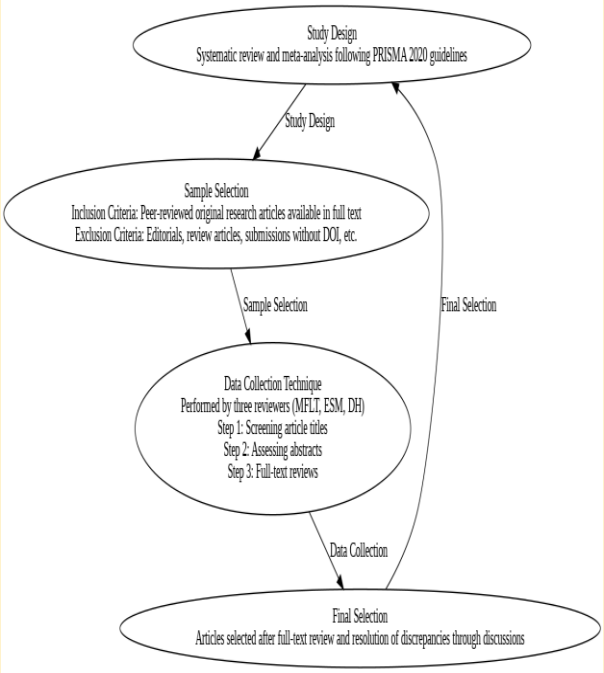

Figure 1. PRISMA Flowchart Effectiveness of Sublingual vs Oral Captopril in Hypertensive Urgency

Sample

The study population consists of research articles published in English after 2012 that examine the effectiveness of sublingual versus oral captopril in hypertensive urgency. The selection process includes: Inclusion criteria: Peer-reviewed original research articles available in full text; Exclusion criteria: Editorials, review articles, submissions without a Digital Object Identifier (DOI), and other similar publications. The literature search was conducted on January 17, 2025, using the PubMed and SagePub databases. The keywords used were: "sublingual," "oral," "captopril," "blood pressure reduction," and "hypertension urgency."

Data Collection Technique

The study selection was performed by three reviewers (MFLT, ESM, and DH) through a three-step process: (1) screening article titles for relevance, (2) assessing research abstracts, and (3) performing full-text reviews of selected articles. Discrepancies among reviewers were resolved through discussions with all five authors.

Data Analysis Technique

Data extracted from the included studies were analyzed using descriptive statistics and meta-analytic techniques where applicable. Statistical analysis was performed using appropriate software (e.g., R or STATA) to ensure accuracy. The significance level was set at $p < 0.05$. Heterogeneity among studies was assessed using I^2 statistics, and results were presented through forest plots and summary effect measures. Sensitivity analyses were also conducted to evaluate the robustness of pooled estimates and identify potential sources of heterogeneity among the included studies.

Ethical Consideration

As this study is a systematic review and meta-analysis, it does not involve direct human participants and does not require ethical clearance. However, all included studies were screened to ensure they adhered to ethical research standards, including informed consent and institutional review board approval where applicable.

Result

We found three studies that discuss the impact of oral and sublingual captopril administration on blood pressure reduction. Kaya et al. (2016) showed that the reduction in systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) was more pronounced in the sublingual group within the first 10 minutes ($p < 0.001$). At the 30-minute

mark, this reduction remained significant only for SBP and MAP ($p < 0.001$). However, blood pressure changes were not significant at the 60-minute mark ($p > 0.05$)[16].

Table 1. Literature Included in This Study

Author	Country	Method	Sample Size	Results
Kaya, 2016[16]	Turkey	Cross-sectional	212 patients	Sublingual captopril reduced SBP, DBP, and MAP more significantly than oral captopril within the first 10 minutes ($p < 0.001$).
Karakilic, 2012[17]	Turkey	Retrospective observational study	28 patients in the oral captopril group and 43 patients in the sublingual captopril group	Oral and sublingual captopril did not affect blood pressure at 0, 5, 15, 30, 45, and 60 minutes.
Mousavi, 2018[18]	Iran	Retrospective observational study	35 patients	SBP and MAP in patients receiving sublingual captopril decreased significantly more after 10, 20, and 30 minutes of administration ($p < 0.05$). After 60 and 90 minutes, the blood pressure reduction effect was almost the same between the two groups.

Karakilic (2012) did not show a clear difference in blood pressure between oral and sublingual captopril administration at 0, 5, 15, 30, 45, and 60 minutes after drug administration[17]. Another study found that systolic blood pressure (SBP) and mean arterial pressure (MAP) in both groups significantly decreased after 10, 20, and 30 minutes of sublingual administration, whereas diastolic blood pressure (DBP) did not. The difference in blood pressure reduction became less apparent after 60 and 90 minutes. Two patients in the sublingual group reported experiencing headaches as a side effect. The comfort and satisfaction scores for the sublingual group were significantly lower than those for the oral group[18].

Discussion

Hypertensive urgency is a common condition encountered in emergency care. This condition is characterized by a sudden and severe increase in blood pressure without evidence of target organ damage, such as pulmonary edema, myocardial ischemia, neurological deficits, or acute kidney failure. Specific thresholds for hypertensive urgency have been proposed, such as a systolic blood pressure greater than 180 mmHg or a diastolic blood pressure greater than 110 mmHg. Some experts suggest the term "hypertensive urgency" for patients with extremely high blood pressure and significant risk factors for progressive end-organ damage, such as congestive heart failure or chronic kidney disease. However, hypertensive urgency is associated with a higher long-term incidence of cardiovascular disease and requires a focused approach to ensure better blood pressure control, reduce triggers for blood pressure spikes, and facilitate follow-up at primary healthcare facilities (PHC)[4,19,20].

Patients with hypertensive urgency face an increased risk of long-term morbidity and mortality. The one-year mortality rate for those experiencing an episode of hypertensive urgency is approximately 9%. Untreated hypertension can elevate the risk of death and is often described as a "silent killer." The long-term prognosis for patients with hypertensive urgency or emergency is poor. A retrospective study conducted on 670 adults with severe blood pressure elevation found that 57.5% suffered from hypertensive emergency[21].

Medications can be administered intravenously, orally, or sublingually as alternative methods in emergency care. If the patient is unconscious and the drug can be absorbed sublingually, rapid and safe treatment can be achieved through the sublingual route. Many alternative antihypertensive drugs are used in cases of hypertensive urgency, but captopril has been utilized for over 20 years in emergency care. This is supported by the fact that captopril can be administered sublingually and is recommended in many studies for patients with hypertensive crises[22,23].

The overall therapeutic goal for patients in a hypertensive crisis is a controlled reduction of blood pressure (BP) to a safer level to prevent or limit further damage caused by hypertension while avoiding hypotension and related complications. Randomized controlled trial data are still lacking to provide clear guidance on blood pressure targets and the time required to achieve them. Most recommendations are based on expert consensus. The type of acute target organ damage is the primary determinant of the chosen treatment approach[1].

Management of blood pressure reduction in patients with hypertensive urgency does not require parenteral medications. The administration of oral medications with rapid action will be beneficial in lowering blood pressure within 24 hours, where the mean arterial pressure (MAP) can be reduced by no more than 25%. In the initial phase, the standard goal of blood pressure reduction is to bring it down to 160/110 mmHg. The use of both parenteral and oral antihypertensive medications is not without risks in lowering blood pressure[24].

Angiotensin converting enzyme inhibitor (ACEi) is a medication used in the management of hypertension[15]. The therapeutic effect of captopril is considered better and safer. Captopril 25 mg has been proven to have the same effectiveness in lowering blood pressure with fewer side effects compared to nifedipine 10 mg. The onset of action of captopril takes 1-2 hours longer, so it is often administered sublingually to accelerate its absorption. Sublingual administration of captopril is not included in the recommended guidelines for managing hypertensive crises. However, many studies state that sublingual captopril is highly beneficial in lowering blood pressure rapidly without the side effects associated with nifedipine[13,14]. Captopril suppresses the renin-angiotensin-aldosterone system (RAAS)[25].

ACE inhibitors prevent ACE from performing its normal function, which is converting angiotensin I into angiotensin II. Angiotensin (AT)-II increases blood pressure by binding to AT-1 receptors on smooth muscle, causing vasoconstriction of pre-capillary arterioles and post-capillary venules[26–28]. Captopril inhibits the reuptake of norepinephrine, leading to the release of catecholamines from the adrenal glands. The production of aldosterone by the adrenal cortex is stimulated by AT-II[26]. Aldosterone works by causing the distal tubules and collecting ducts of the kidneys to reabsorb water and salt to make room for potassium. This results in increased extracellular volume and elevated blood pressure[22,23].

ACE inhibitors lower plasma levels of AT-II, leading to vasodilation and reduced aldosterone production. The decrease in aldosterone secretion causes several side effects, including increased serum potassium and sodium levels, as well as fluid loss. Hypertensive patients taking captopril experience a reduction in peripheral arterial resistance[22]. ACE inhibitors reduce the preload of the circulatory system by inducing vasodilation and natriuresis, and reduce the afterload by decreasing AT-II synthesis. The end result is an increased cardiac output along with a reduction in blood pressure. Cough is a

major side effect of captopril due to bradykinin metabolism[23].

The sublingual route of administration is preferred because the oral mucosa is well-vascularized. This can lead to bypassing the absorption of the drug in the small intestine and the first-pass absorption in the liver, resulting in a rapid therapeutic effect. Medications administered sublingually often have a bitter taste and can cause adverse effects on the tongue, even with short-term use. Sublingual administration can also lead to unexpected effects, such as hypersensitivity and chemical burns on the oral mucosa. Some earlier studies have shown that sublingual captopril lowers blood pressure more effectively than oral administration[17]. However, Dess-Fulgeri et al. reported no difference between oral and sublingual captopril in lowering blood pressure and inhibiting plasma renin and ACE activity[29].

Paroxysmal cough, proteinuria, and skin rashes are potential side effects of captopril use. Drug interactions between captopril and nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin can lead to nephrotoxicity[22]. Neutropenia, hyperkalemia, and thrombocytopenia are some of the hematological side effects. Some potential gastrointestinal side effects include nausea, vomiting, diarrhea, constipation, dry mouth, and irritation of the oral mucosa. There have been several documented cases where the use of captopril led to the development of hepatitis, cholestasis, and pancreatitis[12,30].

Conclusion

Both oral and sublingual captopril are effective in reducing blood pressure and can be used as alternative treatments for hypertensive urgency. However, sublingual captopril generally has a faster onset of action compared to oral administration, making it a preferred choice in urgent situations requiring rapid blood pressure control.

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