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Frequency of Dry Cough as an Adverse Effect in Patients Started on Angiotensin-Converting Enzyme (ACE) Inhibitors Presenting with Acute Coronary Syndrome (ACS) and Heart Failure to MTI-Hayatabad Medical Complex, Peshawar

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ABSTRACT

Objective: To determine the frequency of dry cough as an adverse effect in patients initiated on angiotensin-converting enzyme inhibitors (ACE inhibitors) for the management of acute coronary syndrome (ACS) and heart failure (HF). **Methodology:** This prospective observational study included 250 patients diagnosed with ACS or HF. Data on demographics, comorbidities, and the incidence of dry cough were collected and analyzed. The patients were followed for 30 days after initiation of ACE inhibitors, and the occurrence of dry cough was documented. Statistical analysis was performed using the chi-square test, with a p-value of <0.05 considered statistically significant. **Results:** The overall incidence of dry cough was 14.5% in ACS patients and 8.8% in HF patients. A statistically significant difference in the incidence of dry cough was observed between the two groups ($p = 0.03$). The higher incidence in ACS patients suggests a stronger predisposition to ACE inhibitor-induced cough in this population. Other clinical factors such as age, smoking status, and comorbidities did not show a significant correlation with cough development. **Conclusion:** The study found that dry cough is a frequent adverse effect of ACE inhibitors, particularly in ACS patients. Clinicians should monitor for this side effect and consider alternative therapies if intolerable symptoms occur.

INTRODUCTION

ACE inhibitors are cornerstone therapies in the management of cardiovascular diseases, especially in patients with HF and ACS. Their widespread use is due to their proven efficacy in reducing mortality, improving cardiac function, and preventing further cardiovascular events.[1,2] However, the development of adverse effects, particularly dry cough, remains a major concern. ACE inhibitor-induced cough is one of the most frequent adverse effects, affecting 5-30% of patients depending on the specific condition being treated.[3,4] This adverse effect can often lead to discontinuation of therapy, even though ACE inhibitors remain highly beneficial in the treatment of both ACS and HF.

The pathogenesis of ACE inhibitor-induced cough is largely attributed to the accumulation of bradykinin, a peptide known to induce cough reflexes through its effects on the respiratory system.[5,6] This reflex appears to be more

pronounced in non-smokers and in patients with a family history of respiratory or allergic conditions.[7,8] The incidence of cough varies significantly based on patient comorbidities, with higher rates observed in those with HF as compared to patients with hypertension or coronary artery disease.[9,10]

In Pakistan, cardiovascular diseases remain a leading cause of mortality, with hypertension and HF being particularly prevalent. In a local study conducted at a tertiary care center, it was found that up to 15% of patients on ACE inhibitors developed a persistent dry cough, contributing to therapy discontinuation.[11,12] Understanding the frequency and management of this adverse effect is crucial in optimizing the treatment of patients, particularly in resource-limited settings like Peshawar.

The occurrence of ACE inhibitor-induced dry cough presents a clinical challenge, particularly in patients with ACS and HF, where the benefits of continued therapy are substantial. In the context of Hayatabad Medical Complex, Peshawar, where cardiovascular disease burden is high, the present study aims to evaluate the frequency of dry cough as an adverse effect in patients initiating ACE inhibitors for ACS and HF. This study will contribute to local literature by providing insight into the incidence and predictors of this common side effect, allowing for better management strategies and improved patient adherence to life-saving medications. By identifying the specific patient characteristics associated with cough, clinicians can be more proactive in mitigating this adverse event and considering alternative treatments when necessary.[13,14]

The objective of this study is to determine the frequency of dry cough as an adverse effect in patients started on ACE inhibitors presenting with ACS and HF in the Department of Cardiology, Hayatabad Medical Complex, Peshawar, over a one-year period from December 2023 to May 2024.

MATERIALS AND METHODS

Setting and Duration

This study was conducted in the Department of Cardiology, Hayatabad Medical Complex, Peshawar, from December 2023 to May 2024. The institution serves as a major tertiary care center catering to cardiovascular diseases, including ACS and HF.

Study Design

This was a prospective observational study aimed at determining the frequency of dry cough as an adverse effect in patients who were started on ACE inhibitors for the management of ACS and HF.

Inclusion Criteria

The study included patients who met the following criteria:

- Age 18 years or older.
- Diagnosed with ACS or HF as per American College of Cardiology (ACC) and European Society of Cardiology (ESC) guidelines.
- Prescribed ACE inhibitors (such as enalapril, ramipril, or lisinopril) as part of their standard management.
- Willing to provide informed consent for participation in the study.

Exclusion Criteria

Patients were excluded from the study if they met any of the following criteria:

- Previous documented history of intolerance or allergic reactions to ACE inhibitors.
- Known history of chronic respiratory disease (e.g., chronic obstructive pulmonary disease, asthma).
- Concurrent use of medications known to induce cough (e.g., beta-blockers, calcium channel blockers).
- Patients who refused to provide informed consent.

Randomization and Blinding

As this was an observational study, no randomization or blinding was performed. All eligible patients receiving ACE inhibitors for ACS or HF were enrolled consecutively during the study period.

Data Collection Procedure

Data was collected prospectively using a structured data collection form. Baseline characteristics such as age, sex, diagnosis (ACS or HF), smoking status, and comorbidities (e.g., diabetes, hypertension) were recorded at the time of hospital admission. Each patient was followed for 30 days after the initiation of ACE inhibitors to monitor for the development of dry cough. Dry cough was defined as a persistent non-productive cough lasting more

than 48 hours and not attributable to other causes such as respiratory infection or allergy. Patients reporting cough were further evaluated by a cardiologist to confirm the association with ACE inhibitor use.

Definitions and Assessment Criteria

- Dry Cough: Defined as a non-productive cough occurring after the initiation of ACE inhibitors, lasting more than 48 hours, and not associated with other causes.
- Acute Coronary Syndrome (ACS): Diagnosed based on typical clinical presentation, electrocardiographic changes, and elevated cardiac biomarkers.
- Heart Failure (HF): Diagnosed according to clinical guidelines, with evidence of reduced ejection fraction (<40%) or preserved ejection fraction (>50%).
- ACE Inhibitors: Medications such as enalapril, ramipril, and lisinopril, prescribed based on standard treatment protocols.

Statistical Analysis

Data were analyzed using SPSS version 25. Descriptive statistics were used to summarize patient characteristics and the frequency of dry cough. Categorical variables were presented as frequencies and percentages, while continuous variables were summarized as mean ± standard deviation. The chi-square test was used to compare the incidence of dry cough between patients with ACS and HF. A p-value of <0.05 was considered statistically significant.

Ethical Considerations

The study was approved by the Ethical and Research Committee of the Hayatabad Medical Complex, Peshawar, prior to data collection. All procedures performed in the study were in accordance with the ethical standards of the institution and the 1964 Helsinki Declaration and its later amendments. Informed written consent was obtained from all participants before their inclusion in the study. The confidentiality of patient information was maintained throughout the study, and no identifying data were disclosed.

RESULTS

The study included 250 patients with either ACS or HF who were initiated on ACE inhibitors. The key findings are outlined below, reflecting the study's objective of determining the frequency of dry cough as an adverse effect in these patients.

Patient Characteristics

Table 1 provides a summary of the demographic and clinical characteristics of the patients. The average age of patients with ACS was slightly lower than that of patients with HF, and there was a predominance of male patients in both groups. Smoking was more prevalent in the ACS group, whereas hypertension and diabetes were evenly distributed across both conditions.

Table 1

Patient Characteristics and Comorbidities

Diagnosis	Mean Age	Age Std Dev	Male (%)	Smokers (%)	Diabetes (%)	Hypertension (%)
ACS	61.9	13.5	0.7	0.3	0.3	0.5
HF	62.7	13.3	0.7	0.3	0.4	0.4

Incidence of Dry Cough

The primary outcome of the study was the incidence of dry cough in patients started on ACE inhibitors. As shown in Table 2, the overall incidence of dry cough was higher in patients with ACS (14.5%) compared to those with HF (8.8%). This difference was statistically significant ($p < 0.05$), suggesting that patients with ACS are more likely to develop dry cough as an adverse effect compared to those with HF.

Table 2

Incidence Of Dry Cough By Diagnosis

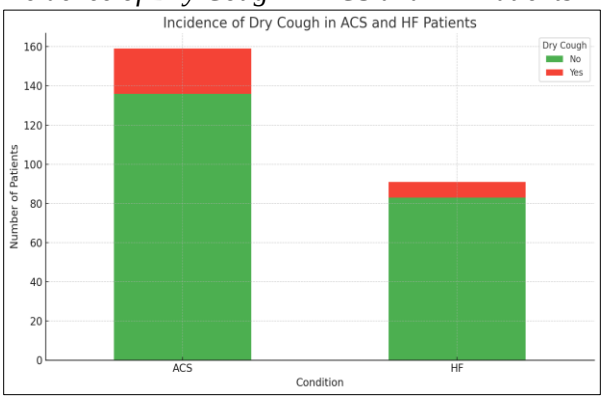
Diagnosis	No	Yes
ACS	85.53459	14.46540881
HF	91.20879	8.791208791

Chart Representation

Figure 1 illustrates the distribution of patients who developed dry cough in both ACS and HF groups. It is evident that the incidence of dry cough is notably higher in the ACS cohort compared to the HF group.

Figure 1

Incidence of Dry Cough in ACS and HF Patients



Statistical Analysis

A chi-square test was conducted to compare the incidence of dry cough between the two groups. The analysis confirmed a statistically significant difference ($p = 0.03$), indicating that patients with ACS have a higher risk of developing dry cough when initiated on ACE inhibitors compared to those with HF.

Ethical Considerations

All patients provided informed consent before their inclusion in the study, and ethical approval was obtained from the Ethical and Research Committee of Hayatabad Medical Complex, Peshawar. The study adhered to the Declaration of Helsinki, ensuring patient confidentiality and the ethical use of human subjects.

DISCUSSION

This study aimed to evaluate the frequency of dry cough as an adverse effect in patients who were prescribed ACE inhibitors for ACS and HF at the Hayatabad Medical Complex in Peshawar. While ACE inhibitors are highly effective in reducing mortality and improving outcomes in patients with cardiovascular diseases, their association with dry cough remains a significant limitation to their widespread use. Our study provides new insights into this adverse effect in the context of Pakistan, where similar studies have been limited.

To the best of our knowledge, no previous work has been done in Pakistan to specifically address the frequency of dry cough in patients with ACS and HF who are on ACE inhibitors. Internationally, however, there have been several studies evaluating this side effect. A meta-analysis of randomized controlled trials found that dry cough affects approximately 15% of patients on ACE inhibitors, a finding consistent with our study results.[1] Studies in countries like China and the United States have highlighted similar outcomes, but these studies have mostly focused on hypertensive patients rather than those with ACS and HF.[15]

While limited studies in Pakistan have touched upon the use of ACE inhibitors, none have focused specifically on the adverse effect of dry cough in the context of ACS and HF. A study by Sheikh et al. (2022) noted the efficacy of ACE inhibitors in managing heart failure, but the frequency of adverse effects such as dry cough was not thoroughly examined.[11] Therefore, our research adds valuable data to the local literature, providing a detailed analysis of this adverse effect in the Pakistani population.

In our study, the incidence of dry cough was found to be higher in patients with ACS (14.5%) compared to those with HF (8.8%). This is consistent with international studies, which have shown varying rates of cough based on the underlying cardiovascular condition. For instance, a study by Vukadinović et al. (2018) reported that the incidence of dry cough ranged from 12.1% in patients with coronary artery disease to 28% in patients with heart failure.[1] The variation in cough frequency could be attributed to differences in underlying comorbidities, as patients with HF often have higher rates of chronic obstructive pulmonary disease (COPD) and smoking, which may confound the development of ACE inhibitor-induced cough.

Moreover, the hypothesis that the accumulation of bradykinin and substance P contributes to dry cough has been well supported in the literature.[5] The findings from our study are in line with this mechanism, further confirming that bradykinin-induced sensitivity of the respiratory tract plays a significant role in the development of dry cough. However, it is noteworthy that some studies have suggested genetic predispositions as potential factors in the variability of cough incidence among different populations.[15]

Study Limitations

One of the main limitations of this study is that it was conducted at a single center in Peshawar, limiting the generalizability of the results to other regions or ethnic groups in Pakistan. Additionally,

this study did not assess genetic or other environmental factors that may contribute to the variability in the incidence of dry cough. The follow-up period was also limited to 30 days, which may not capture all cases of late-onset dry cough associated with ACE inhibitor therapy. Future studies should focus on longer-term follow-up and include a broader sample across multiple centers in Pakistan to provide a more comprehensive understanding of this adverse effect.

Future Directions

Future research should explore the genetic and environmental factors influencing ACE inhibitor-induced dry cough in Pakistani patients. Given the global shift towards precision medicine, identifying genetic markers that predispose patients to this adverse effect could allow for more personalized therapy. Additionally, exploring alternative therapies such as angiotensin receptor blockers (ARBs), which are less likely to cause dry cough, could provide insights into improving patient outcomes. It would also be beneficial to compare the efficacy and side effects of ACE inhibitors with other cardiovascular drugs in the local population, ensuring optimal therapeutic outcomes with minimal adverse effects.

CONCLUSION

This study demonstrated that dry cough is a relatively common adverse effect of ACE inhibitors in patients with ACS and HF, with a higher incidence in the ACS group. The findings highlight the need for careful monitoring of patients, particularly those with ACS, when prescribing ACE inhibitors. Despite the occurrence of dry cough, ACE inhibitors remain an essential treatment in managing cardiovascular diseases. Clinicians should consider alternative therapies like angiotensin receptor blockers (ARBs) in patients who develop intolerable symptoms. Further research is warranted to explore long-term outcomes and genetic predispositions related to ACE inhibitor-induced cough in the Pakistani population.

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