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Management of Persistent Postnasal Drip Without Sinus Affection

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ABSTRACT

Persistent postnasal drip (PPND), characterized by chronic mucus sensation in the throat without evident sinus involvement, poses challenges in otolaryngology. This study aimed to evaluate low dose, long duration Clarithromycin's efficacy in managing PPND symptoms, addressing the limitations of existing therapies. A prospective, randomized, controlled trial was conducted with 50 participants (18-65 years) diagnosed with PPND but without sinus pathology (proved by sinus clear CT Paranasal sinus scans). They received either Clarithromycin (250 mg daily) or a placebo for 12 weeks. Validated assessment tools, such as the nasal symptom score (NSS), visual analog scale (VAS), and Sino-nasal outcome test-22 (SNOT-22), measured treatment outcomes. Current therapies addressing associated symptoms exhibit limited efficacy, prompting the need for novel treatment strategies. The study revealed a significant improvement in PPND symptoms with low-dose, long-duration Clarithromycin treatment. Participants exhibited reduced throat-clearing frequency, cough episodes, and subjective mucus sensation. Objective assessments showed enhanced nasal pathology and mucociliary clearance post-treatment. Low-dose, long-duration Clarithromycin treatment demonstrated promising efficacy in ameliorating PPND symptoms and improving quality of life without sinus involvement. These findings emphasize the potential therapeutic role of macrolides in addressing PPND's underlying pathophysiology. Further research, including larger trials, is essential to validate these outcomes and establish effective clinical guidelines for managing PPND.

INTRODUCTION

Background on PPND and its Impact on Quality of Life

Persistent postnasal drip (PPND), also known as chronic mucus sensation in the throat without clear involvement of the sinuses, remains a challenging condition in otolaryngology (RATHI DS, 2022). PPND manifests as the chronic accumulation of mucus in the throat, originating from the nasal cavity or throat, without direct sinus pathology. It presents psychological distress and physical discomfort, significantly impacting daily routines, social interactions, and sleep patterns of affected individuals. The continuous sensation of mucus accumulation, accompanied by throat clearing, coughing, and occasional hoarseness, profoundly affects patients' overall well-being, necessitating effective management strategies (Morice, 2004).

Review of Existing Treatments and Their Limitations

Current therapeutic approaches for PPND primarily aim at symptom relief, targeting associated manifestations rather than addressing the root cause. Treatments such as antihistamines, intranasal corticosteroids, saline nasal irrigation, and mucolytics focus on alleviating nasal congestion, reducing mucus production, and easing discomfort (Richards *et al.*, 2014). However, the efficacy of these interventions in managing PPND remains modest, often yielding suboptimal results. Moreover, these treatments may not fully address the unique pathophysiological mechanisms driving PPND in cases without apparent sinus involvement. Hence, the limitations of current therapies underscore the pressing need for novel, targeted approaches to address this perplexing clinical scenario (Rosenfeld *et al.*, 2015).

Rationale for Exploring Macrolides as a Potential Therapeutic Option

Amidst the various treatment modalities used for PPND, macrolide antibiotics have gained attention due to their distinct properties beyond their antimicrobial effects (Bandyopadhyay & Samanta, 2020). Studies indicate that macrolides possess immunomodulatory, anti-inflammatory, and immunoregulatory properties, rendering them potential candidates for managing chronic airway diseases characterized by excessive mucus production, including PPND (Rosenfeld *et al.*, 2015). The rationale for exploring macrolides as a therapeutic option for PPND stems from their capacity to modulate inflammatory pathways, reduce mucus hypersecretion, and modify mucus viscoelastic properties. However, it's important to note potential side effects or limitations associated with macrolide use in PPND, which will be addressed further in this study.

Challenges in Diagnosing and Delineating PPND from Other Conditions

A significant challenge in managing PPND lies in its diagnosis, especially in distinguishing it from conditions

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with overlapping symptoms (Liu *et al.*, 2023). The absence of universally accepted diagnostic criteria for PPND contributes to diagnostic difficulties, often leading to misdiagnosis or overlapping treatments for conditions like chronic rhinosinusitis, allergic rhinitis, or gastroesophageal reflux disease (GERD) (Tan *et al.*, 2013). Precise clinical guidelines are lacking, emphasizing the need for a careful differential diagnosis to tailor appropriate therapeutic strategies for patients presenting solely with PPND symptoms (Pratter, 2006).

Need for Targeted Therapies and the Scope of Current Research

Recognizing PPND as a distinct clinical entity, separate from sinus-involved conditions, necessitates tailored therapeutic strategies addressing its underlying pathophysiology (Zarbo *et al.*, 2001). Current research aims to elucidate the mechanisms driving PPND and explore novel therapeutic avenues that could revolutionize its management. This study contributes to the growing body of evidence aimed at delineating PPND from related conditions, highlighting the necessity for tailored therapies to improve the quality of life for affected individuals.

LITERATURE REVIEW

Studies on Macrolides in Respiratory Conditions

Macrolide antibiotics, including azithromycin and clarithromycin, have undergone extensive exploration beyond their antimicrobial roles in various respiratory conditions. Investigations into their use have indicated potential efficacy in treating chronic airway diseases. Research focusing on macrolides in bronchiectasis, chronic obstructive pulmonary disease (COPD), and cystic fibrosis has demonstrated their ability to reduce exacerbations, improve lung function, and modulate airway inflammation. These studies provide insights into the broad-spectrum effects of macrolides beyond their conventional antibacterial actions and lay a foundation for considering their application in managing PPND without sinus involvement (Pollock & Chalmers, 2021).

Mechanisms of Action of Macrolides in Reducing Inflammation

Understanding the mechanisms underpinning the anti-inflammatory properties of macrolides is crucial in exploring their therapeutic potential for respiratory conditions (Min & Jang, 2012). These antibiotics exhibit multifaceted actions beyond their direct antimicrobial effects: they interfere with various inflammatory pathways by inhibiting pro-inflammatory cytokine production, suppressing neutrophil recruitment, and modulating immune responses. These mechanisms contribute to their ability to mitigate airway inflammation, mucus hypersecretion, and tissue damage (Kanoh & Rubin, 2010).

Previous Research on Macrolides in Treating PPND

The absence of standardized diagnostic criteria for PPND poses significant challenges in accurately identifying and differentiating it from other conditions with similar symptoms. Differential diagnoses may include chronic rhinosinusitis, allergic rhinitis, gastroesophageal reflux disease (GERD), and upper airway cough syndrome (UACS) (Pratter, 2006). Distinguishing PPND from these conditions is crucial due to differences in management approaches and underlying pathophysiology. Clinical evaluation, encompassing detailed history-taking, physical examination, and, in some cases, diagnostic tests like nasal endoscopy or imaging, aids in narrowing down the differential diagnosis (Ryan, 2010).

Novel Therapeutic Approaches beyond Antibiotics

Emerging research delves into alternative therapeutic approaches for managing PPND. Investigations into targeted therapies involving immunomodulators, mucoregulatory agents, and receptor antagonists offer potential alternatives or adjuncts to conventional treatments (Casale & Stokes, 2008). Innovative strategies that modulate mucin expression, regulate neural pathways involved in mucus production, and disrupt biofilm formation in the upper airways present promising avenues for potential therapeutic interventions in PPND. These approaches aim to target specific pathophysiological mechanisms underlying PPND, indicating a shift towards precision medicine tailored to individual patient profiles (Rouillard *et al.*, 2022).

Patient-Centered Care and Psychological Interventions

In addition to pharmacological interventions, recognizing the psychological impact of PPND and implementing patient-centered care approaches is gaining attention. Psychological distress associated with chronic symptoms like persistent throat clearing and coughing warrants attention to holistic management strategies. Integrating psychological interventions such as cognitive-behavioral therapy (CBT) or mindfulness-based stress reduction (MBSR) programs could complement pharmacotherapy, improving overall patient well-being and treatment outcomes. For instance, CBT techniques might involve identifying and challenging unhelpful thoughts related to throat sensations, while MBSR practices could include mindfulness meditation to manage distress associated with PPND symptoms (Qamar *et al.*, 2011).

Innovations in Diagnostic Technologies

Advancements in diagnostic technologies offer promising prospects for accurate diagnosis and targeted treatment of PPND. Emerging diagnostic tools, including high-resolution nasal endoscopy, acoustic rhinometry, and nasal cytology, enable precise assessment of nasal and pharyngeal mucosa, aiding in the differential diagnosis of PPND from other conditions with similar presentations (Scadding *et al.*, 2011). Moreover, innovative imaging techniques like optical coherence tomography (OCT) and magnetic resonance imaging (MRI) provide detailed

anatomical insights, facilitating better characterization and differentiation of PPND from sinus-involved pathologies. Integration of these novel diagnostic modalities into clinical practice holds the potential for more accurate and personalized management strategies for PPND (Bliss & Muntz, 2015).

This study aims to investigate and delineate the effectiveness of macrolide antibiotics as a potential therapeutic option for managing PPND without sinus involvement. This research aims to bridge the existing gap in understanding and treating PPND, which often presents as a challenging clinical entity in otolaryngology. The study intends to explore the specific mechanisms of macrolides in reducing inflammation, modifying mucus properties, and potentially ameliorating the bothersome symptomatology associated with PPND. By elucidating the role of macrolides in addressing the underlying pathophysiological mechanisms of PPND, the research strives to contribute to the development of more targeted and effective treatment strategies, thereby improving the quality of life for individuals affected by this chronic condition.

METHODOLOGY

Inclusion and Exclusion Criteria for Study Participants

A prospective, randomized, controlled trial was conducted at Mediclinic UAE to evaluate the efficacy of low-dose, long-duration Clarithromycin in managing PPND without sinus involvement. Fifty participants aged between 18 to 65 years, experiencing PPND persisting for at least 12 weeks without clinical and radiological evidence of sinusitis (clear sinuses in CT paranasal sinus), were recruited. Inclusion criteria encompassed absence of acute or chronic sinusitis, no recent history of macrolide use, and persistent PPND despite conventional treatments. Exclusion criteria included pregnant or lactating women, known macrolide allergies, concurrent medication that could interact with macrolides, and patients with chronic systemic diseases.

Dosage and Duration Considerations for Macrolide Treatment

Participants were randomly assigned to receive either low-dose, long-duration Clarithromycin or a placebo. Clarithromycin was administered orally at a dosage of 250 mg once daily for a specific duration of 12 weeks. The choice of this low-dose, long-duration regimen aimed to assess sustained treatment effects while minimizing potential adverse effects associated with prolonged antibiotic use.

Study Design

The severity and frequency of PPND symptoms were measured using validated assessment tools including the Nasal Symptom Score (NSS), Visual Analog Scale (VAS) for symptom intensity, and Sino-Nasal Outcome Test-22 (SNOT-22) questionnaire. These tools were employed to assess changes in PPND severity, throat-clearing frequency, cough episodes, and subjective mucus sensation. Quality of life indicators were assessed using the Pittsburgh Sleep Quality Index (PSQI) to evaluate sleep quality and the Short Form Health Survey (SF-36) to assess physical and mental health parameters.

Outcome Measures and Assessment Tools

The primary outcome measure encompassed changes in the severity and frequency of PPND symptoms, assessed using validated instruments such as the Nasal Symptom Score (NSS), Visual Analog Scale (VAS) for symptom intensity, and Sino-Nasal Outcome Test-22 (SNOT-22) questionnaire. Secondary outcome measures included improvements in quality of life indicators, such as sleep quality assessed by the Pittsburgh Sleep Quality Index (PSQI), physical and mental health parameters evaluated through the Short Form Health Survey (SF-36), and patient-reported treatment satisfaction. Assessment tools were administered at baseline, week 4, week 8, and week 12 to monitor treatment response and potential adverse effects.

Assessment tools were administered at baseline and at weeks 4, 8, and 12 to monitor treatment response and potential adverse effects. The timeline of assessments aimed to track the progression of treatment effects and provide insights into any changes in symptoms or quality of life throughout the 12-week duration.

Statistical Analysis

The study used Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 20.0 for data analysis. Appropriate statistical methods (ANOVA, t-tests) were employed to assess the effectiveness of low dose, long duration Clarithromycin compared to placebo in ameliorating PPND symptoms and improving quality of life indicators while considering any adverse events or dropouts during the trial period.

Ethical Approval

The study obtained written informed consent from all participants and strictly adhered to Good Clinical Practice (GCP) guidelines and ethical standards as per the Declaration of Helsinki throughout the investigation.

RESULTS AND DISCUSSIONS

Demographic Characteristics of Study Participants

The study included 50 participants recruited from Mediclinic UAE. Of these, 28 were male (56%) and 22 were female (44%). The age distribution ranged from 18 to 65 years, with a mean age of 42.6 years (±8.9). Table 1 provides a detailed breakdown of the demographic characteristics, including gender distribution, age range, ethnicity, employment status, and socioeconomic status.

The treatment involved a low-dose regimen of

Table 1: Demographic Characteristics of Study Participants

Characteristics	Frequency (n=50)
Gender	
Male	28
Female	22
Age (years)	Mean: 42.6 ± 8.9
Ethnicity	
Middle Eastern	20
South Asian	11
White	15
African	4
Employment	
Full-time	30
Part-time	10
Unemployed	10
Socioeconomic Status	
Low-income	07
Middle-income	30
High-income	13

Clarithromycin (250 mg orally, once daily) administered for 8 weeks. Participants were regularly monitored for potential side effects throughout the treatment period.

Subjective Assessment of Treatment Outcomes

Table 2 demonstrates the pre-treatment (baseline) and post-treatment subjective assessments. The results showed a significant reduction in PPND severity as measured by the Visual Analog Scale (VAS), frequency of throat clearing per day, cough episodes per day, and improvements in Quality of Life (QoL) scores using the SF-36 assessment tool after treatment.

Table 2: Subjective Assessment of Treatment Outcomes

Outcome Measure	Pre-treatment (Baseline)	Post-treatment
Visual Analog Scale (VAS) for PPND severity	Mean: 7.9 ± 1.2	Mean: 3.2 ± 1.5
Frequency of throat clearing per day	Mean: 18.5 ± 4.6	Mean: 8.2 ± 3.9
Cough episodes per day	Mean: 6.7 ± 2.1	Mean: 2.4 ± 1.2
Quality of Life (QoL) assessment (SF-36)	Mean: 48.2 ± 5.9	Mean: 68.7 ± 7.3

Objective Assessment of Treatment Outcomes

Table 3 presents objective measures showing improvements post-treatment. Nasal endoscopy findings displayed a reduction in the grade of nasal pathology, while mucociliary clearance exhibited enhancement.

Table 3: Objective Assessment of Treatment Outcomes

Outcome Measure	Pre-treatment (Baseline)	Post-treatment
Nasal endoscopy findings (Grade)	Mean: 2.6 ± 0.8	Mean: 1.2 ± 0.5
Mucociliary clearance (mm/min)	Mean: 6.8 ± 1.5	Mean: 10.3 ± 2.1

Adverse Effects of Clarithromycin Treatment

Table 4 summarises the adverse effects reported during the study. Common adverse events included gastrointestinal upset, palpitation and headache, while fewer cases of allergic reactions were noted. The incidence of these effects remained relatively low, suggesting the tolerability of the low-dose Clarithromycin regimen among participants.

Table 4: Adverse Effects of Clarithromycin Treatment

Adverse Effects	Frequency (n=50)
Gastrointestinal Upset	4
Headache	3
Palpitation	3
Allergic Reactions	2

DISCUSSION

The present study aimed to investigate the efficacy of low-dose, long-duration macrolide treatment in managing PPND without sinus involvement. The findings of this study provide valuable insights into the potential therapeutic role of macrolides in alleviating PPND symptoms and enhancing the quality of life for affected individuals.

Comparative analysis with existing literature reveals a paucity of studies specifically focusing on PPND management without overt sinus involvement (Tomazic *et al.*, 2020). Previous research has predominantly emphasised treatments targeting sinus-related conditions, often overlooking PPND as an independent entity (Vaezeafshar *et al.*, 2017). However, studies exploring macrolide therapy in chronic airway diseases, such as chronic rhinosinusitis (CRS) and non-CF bronchiectasis, have exhibited promising outcomes showcasing the multifaceted benefits of macrolides beyond their antimicrobial effects (Sun & Li, 2022).

The current investigation demonstrated encouraging outcomes in PPND management using Clarithromycin (250 mg orally, once daily) for an extended duration (12 weeks). Participants exhibited a significant reduction in the frequency of throat clearing, coughing episodes, and subjective perception of mucus accumulation, indicating symptomatic improvement. These findings align with previous studies suggesting macrolides' potential to modulate inflammatory pathways, reducing mucus

hypersecretion and altering mucus properties, thereby alleviating bothersome symptoms associated with PPND (Berkhof *et al.*, 2013).

The mechanisms underlying macrolides' efficacy in PPND warrant attention. Macrolides possess anti-inflammatory properties, inhibiting pro-inflammatory cytokines and downregulating neutrophil activation, which are implicated in airway inflammation (Majima, 2004). Additionally, these agents exhibit immunomodulatory effects by suppressing inflammatory cell recruitment and mitigating excessive mucus production, further supporting their potential in managing chronic airway diseases, including PPND (Kricker *et al.*, 2021).

The outcomes of this study have notable implications for clinical practice in managing PPND without sinus involvement. The observed symptomatic improvement with low-dose, long-duration macrolide therapy suggests a potential therapeutic avenue for otolaryngologists and healthcare providers when encountering patients solely presenting with PPND symptoms (Ryu *et al.*, 2023). Understanding the role of macrolides in PPND management could aid in devising tailored treatment strategies, thereby enhancing patient care and quality of life.

Assessing the impact of low-dose, long-duration macrolide therapy on healthcare resource utilisation is imperative. Evaluating factors such as healthcare costs, hospital visits, and medication adherence associated with this treatment regimen could elucidate its cost-effectiveness and feasibility within healthcare systems. Understanding the economic implications of adopting macrolides as part of PPND management could aid healthcare policymakers and providers in decision-making processes.

Incorporating patient-reported outcomes and perspectives regarding the impact of macrolide therapy on their daily lives and well-being is crucial. Qualitative assessments exploring patients' experiences, symptom relief, and changes in quality of life due to macrolide treatment could offer valuable insights beyond clinical measures. Understanding the holistic impact of treatment interventions on patients' perceptions and satisfaction levels contributes significantly to enhancing patient-centred care.

While this study sheds light on the efficacy of macrolides in PPND management, several avenues remain unexplored. Future investigations could delve deeper into elucidating the precise mechanisms by which macrolides alleviate PPND symptoms. Additionally, large-scale randomised controlled trials (RCTs) with extended follow-up periods are warranted to establish the long-term safety and efficacy of macrolide treatment in PPND. Furthermore, studies comparing the effectiveness of macrolides against other conventional treatments in PPND management would provide valuable insights into the most optimal therapeutic approach.

CONCLUSION

In conclusion, the study highlights the efficacy of low-dose, long-duration macrolide treatment, particularly Clarithromycin, in alleviating symptoms and improving the quality of life in individuals experiencing PPND without sinus involvement. These findings suggest a promising therapeutic avenue for PPND management and emphasise the potential of macrolides in addressing its underlying pathophysiology. Further exploration through extended trials and assessments of patient-centred outcomes is crucial to solidify these findings and better guide clinical practice.

LIMITATIONS

The strength of this study is its rigorous design as a randomised controlled trial (RCT) employing a placebo group, enhancing the reliability of the findings. Moreover, the use of validated assessment tools, such as the Nasal Symptom Score (NSS), Visual Analog Scale (VAS), and Sino-Nasal Outcome Test-22 (SNOT-22), ensured a comprehensive evaluation of treatment outcomes. At the same time, the limitation of this study is the small sample size and lack of long-term follow-up data.

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Ethical Approval

Informed consent was obtained from all participants before their inclusion in the study. This study was conducted according to the protocol of Good Clinical Practice (GCP) guidelines and ethical standards set forth by the Declaration of Helsinki throughout all phases of the investigation.

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