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Combination of Turmeric and Vitamin B_6 in Burning Mouth Syndrome: A Retrospective Single-Arm Study

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Abstract: Background: Burning mouth syndrome (BMS) is a chronic condition characterized by an intractable burning sensation in the oral cavity without visible mucosal lesions. Current treatment options are diverse but often limited by variable efficacy and patient tolerance. This study aimed to evaluate the efficacy of turmeric combined with vitamin B_6 (pyridoxine HCl) in treating BMS. Methods: In this retrospective, single-arm study, 28 non-smoking female patients with BMS were treated with a daily regimen of turmeric and vitamin B_6 for 60 days. The pain intensity was assessed using the visual analog scale (VAS) before treatment initiation (baseline VAS, BVAS) and after the treatment period (final VAS, FVAS). The Wilcoxon signed-rank test was utilized to analyze changes in the VAS scores. Results: The mean BVAS score was 5.61 (SD = 1.87), indicating moderate pain at baseline. Post-treatment, the mean FVAS score significantly decreased to 2.14 (SD = 1.35). The median delta in the VAS scores demonstrated a substantial reduction in pain intensity (median delta = 4.0; mean delta = 3.46; SD = 2.05). Statistical analyses revealed a significant reduction in the VAS scores ($W = 0.0$, $p < 0.0001$). Conclusions: The combination of turmeric and vitamin B_6 was found to significantly reduce pain scores in patients with BMS, indicating this therapeutic approach may be a promising alternative for BMS management. Larger-scale clinical trials are warranted to further validate these findings.

Keywords: burning mouth syndrome; curcumin; pyridoxine HCl; turmeric; visual analog scale (VAS); vitamin B_6

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1. Introduction

Burning mouth syndrome (BMS) is a chronic pain condition characterized by a persistent intraoral burning sensation without identifiable objective findings or a known cause, predominantly affecting elderly females. It is officially recognized in the latest *International Classification for Headache Disorders (ICHD-III beta)* as an intraoral burning or dysesthetic sensation, recurring daily for more than two hours over a period exceeding three months in the absence of clinically evident causative lesions [1]. The oral mucosa is typically normal in appearance, and sensory testing does not reveal abnormalities [2,3].

Patients afflicted with BMS often report a range of symptoms, including a burning, prickling, tingling, itching, or numbness sensation affecting various regions of the oral mucosa, such as the tongue, lips, palate, and gums. Accompanying symptoms frequently encompass dysgeusia, xerostomia, and an altered oral mucosa sensation, alongside potential psychological comorbidities, notably anxiety and depression [4].

The etiology of BMS remains elusive, though current research suggests a potential linkage with psychological disorders. The prevalence of BMS is reported to range from 0.1% to 3.9%, predominantly manifesting in postmenopausal women aged between 50 and 70 years. The emerging evidence points towards the involvement of peripheral and central neuropathy, possibly mediated through neurotrophic signaling pathways [5,6].

The management of BMS primarily involves a comprehensive approach that includes pharmacological treatments. This strategy covers a wide range of medications, such as antidepressants and antiepileptic drugs, and the topical application of various agents, including curcumin, capsaicin, and retinoic acid. Each of these has been supported by studies indicating their potential efficacy in treating BMS [4,7–9]. Among these options, clonazepam stands out due to its extensive study and widespread recognition as a commonly used drug for BMS, highlighting its importance in treatment protocols [10–13]. However, it is crucial to note that while clonazepam is effective, it may also be associated with serious side effects, underscoring the need for careful consideration and monitoring when prescribing it as part of a BMS treatment regimen.

Additionally, the role of dietary supplements, specifically B vitamins, zinc, and folic acid, along with hormone replacement therapies, has been explored, revealing their potential in the array of therapeutic modalities available for BMS management [7,14–21]. The literature indicates that imbalances in vitamin B_6 (pyridoxine HCl) levels may contribute to the mouth pain experienced by BMS patients, suggesting the significance of vitamin B_6 in BMS and a potential causal relationship [22]. Emphasizing the advancements in treatment, photobiomodulation therapy has emerged as a notable non-invasive option, garnering support from several studies, which highlights its growing acceptance and application in treating BMS [3,10,23,24].

Curcumin, also known as diferuloylmethane, is a polyphenolic compound found in the rhizome of Curcuma longa, commonly known as turmeric. Turmeric has been widely used in traditional medicine for its anti-inflammatory, antioxidant, and antimicrobial properties. The rhizome is rich in bioactive compounds called curcuminoids, with curcumin being the most notable for its therapeutic benefits. Curcumin has been recognized for its efficacy in alleviating symptoms of neuropathy across various patient groups, largely due to its ability to reduce inflammatory cytokines while enhancing antioxidative mechanisms [25,26]. Specifically, in the context of BMS, curcumin has been identified as a beneficial agent in mitigating the condition's characteristic burning sensation [27]. Moreover, a study has indicated that a combination of curcumin and honey can yield positive outcomes in reducing the burning sensation associated with potentially malignant disorders in the oral cavity [8]. The widespread use of turmeric supplements, standardized for curcumin content, is supported by the U.S. Food and Drug Administration's (FDA) designation of these products as being generally recognized as safe (GRAS), which underscores their safety profile and therapeutic potential [28].

Despite this broad spectrum of treatments, achieving satisfactory outcomes remains a challenge, reflecting the complexity of BMS and the need for established treatment guidelines [29,30]. This underlines the importance of personalized treatment plans that consider the unique circumstances and needs of each patient, leveraging the growing body of research to inform more effective and targeted therapeutic strategies.

The objective of this investigation is to evaluate the therapeutic effectiveness of turmeric in conjunction with vitamin B_6 in the treatment of BMS.

2. Materials and Methods

2.1. Ethical Approval and Study Design

This study received approval from the Ethics, Research, and Innovation Committee of Oman Dental College Ref (ODC-2022-AE-180). In this retrospective, single-arm study, patient records were consecutively accessed from a dental school hospital over the period from September 2021 to February 2022. The study design, including patient selection, treatment data extraction, and pain assessment, is summarized in the flowchart presented in Figure 1.

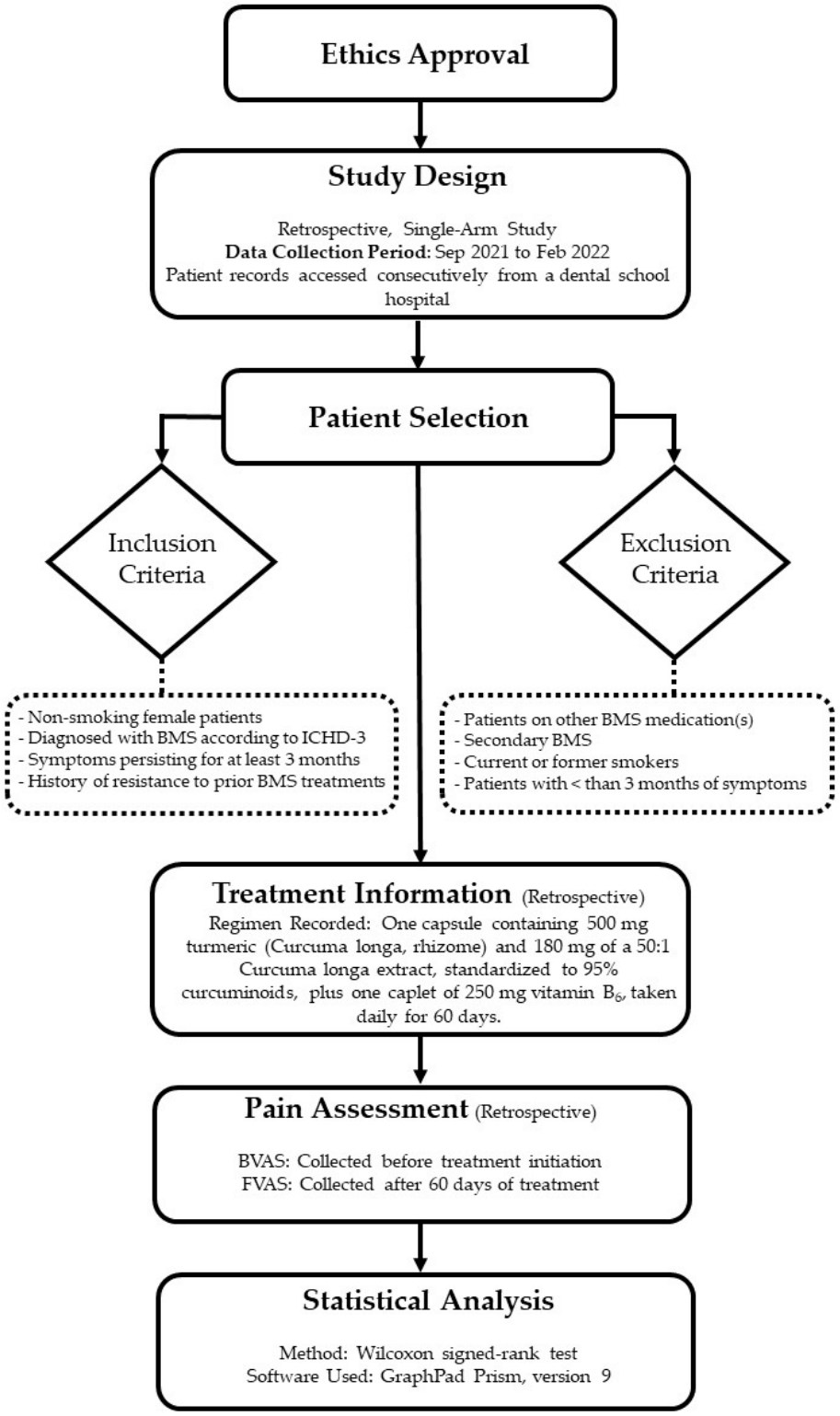

Figure 1. Flowchart of the retrospective, single-arm study design. The process involves patient selection and data extraction, followed by a review of treatment information and pain assessments, leading to a statistical analysis of the collected data.

2.2. Patient Selection

A total of 28 female patients were selected for the study based on specific inclusion and exclusion criteria to ensure the accuracy and relevance of the findings. Patients were included if they were diagnosed with BMS according to the *International Classification of*

Headache Disorders (ICHD-3), had been experiencing symptoms for a minimum duration of three months, were female, had never smoked in their lifetime, and had a history of resistance to or non-compliance with prior treatments for BMS. Patients were excluded from the study if they were currently taking any other medications at the time of presentation, had secondary BMS resulting from identifiable local or systemic causes, were male, were current or former smokers, or if their BMS symptoms had been present for less than three months. The records provided comprehensive demographic information, including occupation, age, and detailed accounts of pain characteristics such as onset, triggers, location, frequency, prior treatments, and instances of xerostomia accompanying the pain.

2.3. Treatment Regimen

The treatment regimen for the study involved administering a capsule containing a total of 680 mg of turmeric (Curcuma longa, rhizome), which includes 500 mg of turmeric rhizome and 180 mg of a 50:1 turmeric extract standardized to 95% curcuminoids, along with a caplet of 250 mg of vitamin B_6 (both sourced from Jamieson Laboratories, Toronto, ON, Canada) daily for a period of 60 days. Both the capsule and caplet were taken orally once daily. The patients were instructed to take the capsule and caplet together with a meal and a large amount of water to enhance absorption and minimize any potential gastrointestinal discomfort. The 60-day treatment period was chosen to prevent any potential peripheral neuropathy that might arise from prolonged use of vitamin B_6.

2.4. Pain Assessment

The severity of pain was quantitatively evaluated using the visual analog scale (VAS) at two points: the baseline VAS (BVAS), measured before initiating the treatment, and the final VAS (FVAS), assessed upon the completion of the 60-day treatment period.

2.5. Statistical Analysis

Statistical analysis was carried out using the Wilcoxon signed-rank test, a non-parametric method suitable for paired data, to evaluate the change in VAS scores pre- and post-treatment. All statistical analyses were performed with a two-tailed approach, considering p-values of 0.05 or lower as indicative of statistical significance. Data processing and analysis were facilitated using GraphPad Prism software, version 9.

3. Results

The data presented herein encompasses the treatment outcomes and observations from 28 patients. The age range of the female patients included in the study was between 37 and 65 years, with a mean age of approximately 51 years and a standard deviation of 7.5 years.

The BVAS had a mean of 5.61 (SD = 1.87), indicating moderate pain levels among the patients. After the intervention, the mean of the FVAS scores was 2.14 (SD = 1.35), indicating a decrease in the pain levels after treatment. The median VAS scores also reflected this improvement, dropping from 5.0 at baseline to 2.0 post-treatment.

The change in pain scores (quantified as the delta numerical rating score) revealed a median improvement of 4.0 points. The mean delta difference was 3.46 points (SD = 2.05), further supporting the noticeable decrease in pain experienced by the patients. To visualize the distribution of the pain scores before and after the treatment, boxplots were generated (Figure 2). These plots illustrate the central tendency and variability of the data and clearly show a reduction in pain intensity post-treatment.

A Wilcoxon signed-rank test was conducted to determine the statistical significance of the observed reduction in pain scores. The test results showed that the decrease in VAS scores was statistically significant ($W = 0.0$, $p < 0.0001$).

The demographic characteristics of the study population, along with the baseline and final VAS scores, are summarized in Table 1.

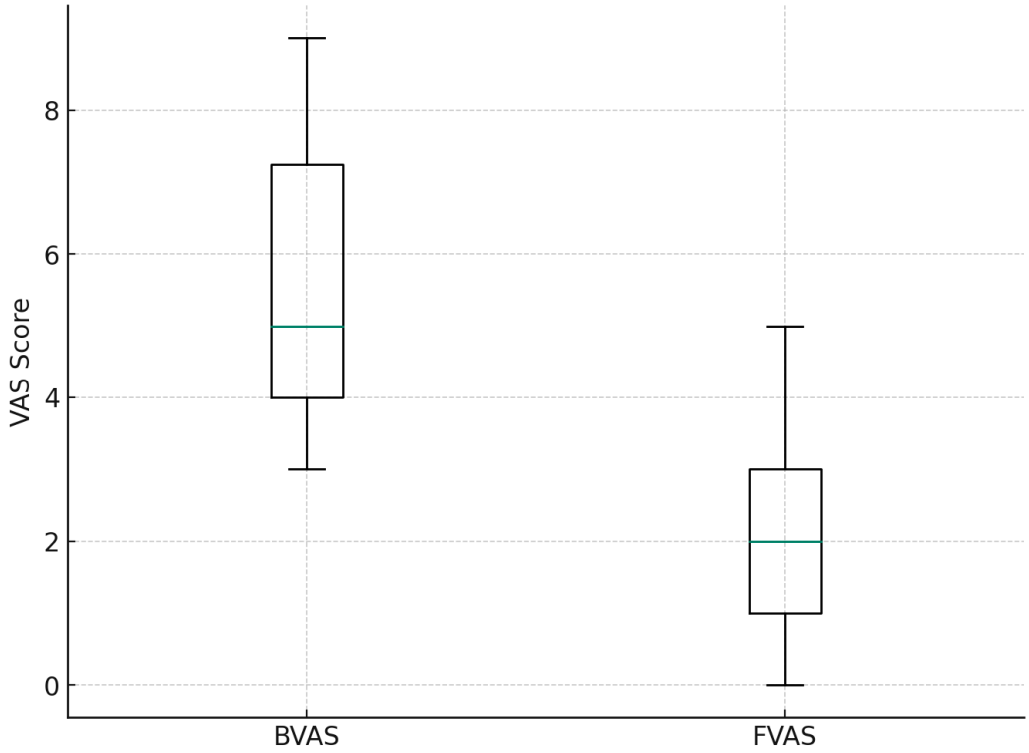

Figure 2. Boxplot of VAS scores before treatment (BVAS) and after treatment (FVAS) for patients with BMS. The boxplots display the distribution of pain scores, with the central line representing the median, the box encompassing the interquartile range (IQR), and the whiskers extending to the minimum and maximum values within 1.5 times the IQR. The boxplot illustrates a clear reduction in pain intensity post-treatment, with the median and overall range of VAS scores decreasing significantly after the administration of turmeric and vitamin B_6.

Table 1. Summary of the demographic characteristics, baseline, and final VAS scores, and statistical analysis of the study population undergoing treatment for BMS with turmeric and vitamin B_6.

Measure	Value
Number of patients	28
Age range (years)	37–65
Mean age ± standard deviation (years)	51 ± 7.5
Baseline VAS (BVAS) mean ± standard deviation	5.61 ± 1.87
Standard deviation ± standard deviation	2.14 ± 1.35
Median delta VAS (ΔVAS)	4.0
Mean delta VAS (ΔVAS) ± standard deviation	3.46 ± 2.05
Statistical significance (Wilcoxon signed-rank test)	W = 0.0, $p < 0.0001$

4. Discussion

Before discussing the outcomes of this study, it is essential to recognize the clinical observations that have motivated this research. An increase in the number of patients, especially females, reporting symptoms of BMS post-COVID-19 has been noted by the authors of this study. This observation aligns with the existing literature, including a systematic review and meta-analysis that linked COVID-19 severity with a heightened risk of BMS, with a higher incidence reported among female patients [31]. In addition, a comprehensive analysis conducted across 32 European countries found a connection between females, mRNA-based vaccines, and a greater prevalence of oral side effects, BMS

included [32]. The authors believe that this increase may also be influenced by heightened public health vigilance following the pandemic, resulting in a greater tendency among individuals to seek medical advice for symptoms that may have been underreported before COVID-19.

The results of this study demonstrate a significant reduction in pain intensity among patients with BMS following a 60-day treatment regimen with turmeric and vitamin B_6. The mean VAS scores decreased from 5.61 at baseline to 2.14 post-treatment, indicating a marked improvement in patients' symptoms. This reduction in pain scores highlights the potential effectiveness of the combination therapy in managing BMS, particularly in a population that has been resistant to or non-compliant with previous treatments.

In recent years, there has been a growing interest in the role of curcumin in modulating neuroplasticity, with an accumulating body of evidence highlighting its positive impact [33–35]. Additionally, curcumin's efficacy extends to the treatment of various neuropathies, as demonstrated in several studies published over the last five years [30,36–40]. This collective research underscores curcumin's potential as a versatile therapeutic agent, particularly in conditions related to neuropathic pain and dysfunction.

Recent studies have underscored a potential immune component in the pathogenesis of BMS, highlighted by alterations in key inflammatory mediators. Specifically, an upregulation of salivary interleukins, such as IL-2, IL-6, and IL-18, has been observed, alongside a decrease in tumor necrosis factor (TNF)-α and alterations in sCD14 and sTLR-2 levels [41,42]. TNF-α is a critical cytokine involved in systemic inflammation, and its modulation is of particular interest due to its central role in the inflammatory process. Concurrently, high-dose vitamin B_6 has demonstrated an anti-inflammatory effect, partly by modulating TNF-α activity and influencing other immune mediators like sCD14 and sTLR-2 [43,44]. The findings from our study suggest that vitamin B_6 may help manage BMS by normalizing these immune functions, a notion supported by previous research. However, further investigation is needed to elucidate the specific mechanisms by which vitamin B_6 influences the complex immune interactions involved in BMS.

The combination of turmeric and vitamin B_6 has exhibited both additive and synergistic effects, significantly enhancing the suppression of specific cell signaling pathways, as highlighted in recent research [45,46]. This dual approach not only promises targeted action on multiple pathways but also offers the advantage of reducing potential side effects. The rationale is that the effective dose of each component in the combination therapy can often be lowered, owing to the increased efficacy of the combined action [47,48]. Further elaborating on this, Wu et al. (2021) have shown that the co-administration of turmeric and vitamin B_6 effectively downregulates various key pro-cancerous and pro-inflammatory signaling pathways, with the combined therapy outperforming the individual effects of either agent [45]. These insights, in conjunction with the outcomes of our study, highlight the potential of leveraging the turmeric and vitamin B_6 combination for treating conditions linked to aberrant or dysregulated cell signaling pathways, including those involving neuroplasticity and neuropathic cascades.

Over four decades ago, Lamey (1986) discovered a significant prevalence of vitamin B deficiencies among BMS patients, noting that the symptoms could be significantly alleviated with vitamin B replacement therapy [19]. This observation was later contradicted by Hugoson and Thorstensson (1991), who, upon studying 16 BMS patients, reported no instances of vitamin B_6 deficiency [49]. Contrarily, Dieb, and Boucher (2017) re-evaluated this cohort and identified three patients with elevated B_6 levels [50]. Following up, Dieb et al. (2017) conducted their own study, revealing high B_6 levels in seven female patients and associating a reduction in pain severity with decreased vitamin B_6 levels in two cases [51]. Compounding the confusion, Verenzuela et al. (2017) analyzed the vitamin B_6 levels in 350 BMS patients, finding a 6% deficiency rate but no elevated levels [52].

A recent report by Andersen et al. (2023) directly addresses these conflicting findings, suggesting that BMS might, in some instances, indicate hypophosphatasia [22]. This condition is characterized by the accumulation of pyridoxal phosphate (PLP), the active form of

vitamin B_6, in the bloodstream, with concurrently low intracellular levels in the brain [53], a state referred to as neuronal PLP deficiency [54]. Such dynamics could result in an apparent vitamin B_6 deficiency despite high serum levels, underscoring the necessity of a precise vitamin B_6 vitamer measurement in BMS assessments. This consideration of hypophosphatasia, along with the neuronal effects of vitamin B_6, further underscores the complex interplay between vitamin B_6, neuropathy, and BMS. It advocates for a better approach to the diagnosis and management of BMS, emphasizing the importance of understanding vitamin B_6 metabolism within this context.

While this study offers valuable insights into the potential efficacy of combining turmeric and vitamin B_6 in treating BMS, it does have certain limitations. Firstly, the single-arm design inherently lacks a control group, which is a significant limitation when evaluating the true efficacy of the treatment. Without a randomized controlled trial (RCT) design, it is challenging to rule out placebo effects or to make definitive conclusions about the treatment's efficacy. The reliance on the VAS as the sole index for pain measurement also introduces subjectivity, potentially influencing the accuracy of the reported outcomes. The absence of comparison with other pain assessment tools, such as the numeric rating scale (NRS) or the McGill pain questionnaire (MPQ), further limits the comprehensiveness of the pain evaluation.

Moreover, the study's sample was exclusively composed of female non-smokers, which, while addressing a significant demographic of BMS sufferers, limits the generalizability of the findings to the broader population, including males and smokers. The relatively small sample size of 28 patients, while sufficient to demonstrate statistically significant results, may not fully represent the broader BMS population. Another limitation is that patients were treated as outpatients and were not directly monitored during the study period; compliance was assessed based on patient self-reports, which could introduce variability in adherence to the treatment regimen. Additionally, the 60-day treatment period and the follow-up may not fully capture the long-term outcomes and potential relapses.

Finally, while efforts were made to exclude secondary BMS through medical history reviews, the complex etiology of BMS means that not all potential contributing factors may have been accounted. Future studies should aim to overcome these limitations by incorporating a broader participant demographic, utilizing an RCT design to include a control group, extending the follow-up period, and considering additional objective measures to assess the treatment outcomes more accurately. Only through such rigorous methods can the true efficacy and efficiency of the treatment be fully understood.

5. Conclusions

This study has demonstrated the promising efficacy of a combined turmeric and vitamin B_6 treatment in alleviating symptoms of BMS, particularly among non-smoking female patients. Significant reductions in pain scores, as evidenced by both the VAS and statistical analysis, underscore the potential of this regimen as an effective treatment option for BMS, especially for patients who have shown resistance to or non-compliance with previous therapies. The findings suggest that the anti-inflammatory and neuroprotective properties of turmeric and vitamin B_6 may play a crucial role in managing the neuropathic and immune-related aspects of BMS. However, given the limitations of this study, including the lack of a control group and the relatively small sample size, further research is warranted to confirm these results in a more diverse patient population and to explore the long-term effects of this combination therapy.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data are available on request from the corresponding author due to data confidentiality restrictions.

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

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