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Eficacia clínica de la tetraciclina tópica en alvéolos post-extracción. Una revisión sistemática

Clinical Efficacy of Topical Tetracycline in Post-extraction Sockets. A Systematic Review

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SUMMARY

Introduction: *Dental extractions are frequent surgical procedures requiring effective management of pain and postoperative complications. Topical tetracycline has emerged as a promising therapeutic intervention.* **Objective:** *To evaluate the scientific evidence supporting the efficacy of local tetracycline treatment in post-extraction alveoli, focusing on its clinical and microbiological implications.* **Materials and Methods:** *A systematic review was conducted following the PRISMA 2020 protocol. Studies published between 2013 and 2023 in PubMed, EBSCOhost, Scopus, Science Direct, and Google Scholar were analyzed. Methodological quality was assessed using STROBE and ROB 2 criteria.* **Results:** *Five studies with various tetracycline administration methods were included.*

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Results showed a significant reduction in alveolar osteitis incidence (from 23 % to 5 %) and postoperative pain. No studies evaluated microbiological effects. **Conclusions:** *Topical tetracycline demonstrated clinical efficacy in post-extraction management, though research on its microbiological effects is needed.*

Keywords: *Tooth socket, tetracycline, tooth extraction, osteitis, pain, postoperative.*

RESUMEN

Introducción: *Las extracciones dentales son procedimientos quirúrgicos frecuentes que requieren un manejo efectivo del dolor y las complicaciones postoperatorias. La tetraciclina tópica ha emergido como una intervención terapéutica prometedora.* **Objetivo:** *Evaluar la evidencia científica sobre la eficacia del tratamiento con tetraciclina local en alvéolos pos-extracción, enfocándose en sus implicaciones clínicas y microbiológicas.* **Materiales y Métodos:** *Se realizó una revisión sistemática siguiendo el protocolo PRISMA 2020. Se analizaron estudios publicados entre 2013-2023 en bases de datos PubMed, EBSCOhost, Scopus, Science Direct y Google Scholar. Se evaluó la calidad metodológica mediante criterios STROBE y ROB 2.* **Resultados:** *Se incluyeron cinco estudios con diversos métodos de administración de tetraciclina. Los resultados mostraron reducción significativa en la incidencia de osteítis alveolar (del 23 % al 5 %) y dolor postoperatorio. Ningún estudio evaluó efectos microbiológicos.* **Conclusiones:** *La tetraciclina tópica demostró eficacia clínica en el manejo pos-extracción, aunque se requiere investigación sobre sus efectos microbiológicos.*

Palabras clave: *Alvéolo dental, tetraciclina, extracción dental, osteítis, dolor posoperatorio.*

INTRODUCTION

Dental extraction, a frequent surgical intervention in dental practice, significantly impacts patient satisfaction and oral surgeon performance (1,2). Most patients require dental extractions due to pain, making effective pain management crucial during the perioperative and postoperative periods (3-5). Pain, inflammation, and alveolitis are the most common complications that usually occur after tooth extraction (6-8).

To address these complications, various protocols have been developed to reduce post-extraction issues. These include asepsis and antisepsis measures (9,10), antibiotic therapy (11,12), attention to oral structures, and post-procedure care instructions (13,14). The diversity of these approaches reflects the complexity of post-extraction management and the need for comprehensive treatment strategies.

Building on these protocols, a landmark study by Bloomer (2000) demonstrated a significant reduction in post-extraction complications, including alveolitis, by 2 %-8 % through various therapeutic interventions. These included chlorhexidine rinses, intra-alveolar antiseptics, metronidazole, fibrinolytic agents, tetracyclines, clindamycin, and other intra-alveolar pharmaceutical preparations. While the intra-alveolar application of bioactive substances has shown promise in minimizing postoperative sequelae and controlling bacterial infections, systematic documentation remains incomplete (15).

Among these interventions, tetracyclines have emerged as particularly effective bacteriostatic antibiotics since they are a class of broad-spectrum antibiotics that effectively inhibit the growth of both Gram-positive and Gram-negative bacteria (16,17). Their mechanism of action involves interfering with bacterial protein synthesis by reversibly inhibiting the 30S bacterial ribosomal subunit. Additionally, some tetracyclines, like doxycycline, have non-antimicrobial effects that can contribute to reduced bone resorption by inhibiting collagenase activity and potentially demineralizing the alveolar surface (18-20). This makes them especially valuable in dentistry, where understanding infection patterns is crucial for appropriate antibiotic use and resistance prevention (21,22).

Within the tetracycline family, doxycycline has attracted particular attention as a promising therapeutic agent (23-25). Its multifaceted properties, including antibacterial, anti-inflammatory, anticollagenolytic, and immunosuppressive effects (26,27), make it particularly effective in treating various dental conditions. Studies have shown its efficacy in managing periodontitis and peri-implantitis

through local application, with its ability to inhibit osteoclastogenesis playing a crucial role in bone regeneration (28-32).

Further supporting the importance of tetracyclines in dental surgery is the report by Sanchis et al. (2004), which explored their role in preventing dry socket following impacted mandibular third molar extractions (33). This work, along with studies on local tetracycline application methods (34,35) has contributed to our understanding of optimal delivery mechanisms and treatment protocols, as noted by Sun et al. (36). Øyri et al. (37) and Fernandes and Hatton (38) have further advanced our knowledge of tetracycline's effectiveness in post-extraction care. The scientific significance of this research lies in its systematic evaluation of the evidence supporting the microbiological assessment of infected alveoli treated with tetracyclines. This comprehensive review bridges existing knowledge gaps and provides evidence-based guidance for clinical decision-making, have been consistently linked to improved quality of care, patient safety, and many positive clinical outcomes in isolated reports throughout the literature, ultimately improving treatment outcomes through scientifically validated approaches (39-41).

This work aimed to evaluate scientific literature supporting the efficacy of local tetracycline treatment in post-extraction alveoli, with a particular focus on its clinical and microbiological implications for improved patient care and surgical outcomes.

MATERIALS AND METHODS

This methodological synthesis study was rigorously developed following the excellence parameters established by the PRISMA 2020 protocol for systematic reviews (42).

Research Question

The research question was defined using PICO methodology (43): Patient/Population (P): Patients who received pharmacological therapy with tetracycline; Intervention (I): Pharmacological therapy with tetracycline in post-extraction dental alveoli; Comparison (C): Use of antiseptic solutions or no pharmacological therapy; Outcomes (O): Clinical and microbiological evaluation of pharmacological therapeutics from protocols described in scientific literature.

Study Scope

The bibliographic search encompassed multiple relevant scientific repositories, including PubMed, EBSCOhost, Scopus, Science Direct, and Google Scholar. A specific temporal framework was established for study selection, considering publications between January 1, 2013 and July 30, 2023. The Inclusion Criteria were Primary scientific evidence, reports, and other documents of academic interest related to the pharmacological therapy of post-extraction alveoli treated with topical tetracycline; experimental and analytical studies; scientific evidence published between January 1, 2013, and July 31, 2023; and publications in both Spanish and English languages. While the Exclusion Criteria were systematic reviews and meta-analyses, Research conducted on subjects other than humans.

Information Sources and Tools. Databases included PubMed, EBSCOhost, Scopus, Science Direct, and Google Scholar, with publications from January 1, 2013, to July 30, 2023. Data collection utilized an Excel matrix instrument.

Data Extraction. The search algorithm was executed in the corresponding databases, with two researchers independently selecting articles based on inclusion and exclusion criteria. The results were compared between researchers to reduce selection bias and reported in the article, along with the pre-selection matrix instrument (Table 1). The data collection instrument included the following: Study, Database, Study Type, Country, Sample Size, Population Demographics, Intervention, Control Group, Follow-up Duration, Primary Outcomes, Key Results, Clinical Effect, Microbiological Effect, and Overall Direction (STROBE/ROB 2) (44,45).

Data Processing and Analysis. Microsoft Excel 2010 was employed for data organization and processing. A descriptive analysis was implemented to examine qualitative information relevant to the research objective.

BIAS Control

Table 1. Bias Assessment Criteria.

Type of Bias	Criterion	Description
Selection Bias	Publication Sources	Publication bias may occur as search was limited to Western information sources (Spanish-English languages)
	Review Process	Two independent reviewers conducted the extraction and analysis with an expert judge for disagreements
Information Bias	Quality Analysis	A critical analysis of the evidence found was performed
	Observational Studies Assessment	STROBE methodology was used for studies including cohort studies, case series, case reports, case-control studies, and cross-sectional studies
	Clinical Trials Assessment	ROB 2 methodology was used for randomized and non-randomized clinical trials

Source: Authors.

Ethical Considerations

This study employs retrospective documentary research techniques and methods without intervention or modification of biological, physiological, psychological, or social variables in study participants. Therefore, it is considered a risk-free study according to Resolution 008430 of 1993 of the Colombian Ministry of Health (46).

RESULTS

Article Identification and Study Selection

Following a systematic literature review in academic repositories and adhering to previously specified methodological protocols, 411 articles were initially identified. After removing duplicates and full-text screening, 12 articles were assessed for eligibility criteria. Finally, 5 potentially eligible published articles were selected for review. The complete article selection process is illustrated in Figure 1.

Study Characteristics and Distribution

The systematic review analyzed five key studies across major medical databases, comprising two from PubMed (36,37), one from EBSCOhost (38), one from Scopus (6), and one from ScienceDirect (41). The methodological approaches varied, including two randomized controlled trials, a prospective cohort study, a comparative prospective study, and a case report. This diversity in study designs provided a comprehensive evaluation of tetracycline efficacy in post-extraction alveoli (Table 2).

Geographic Distribution

The studies represented five countries across three continents. In Europe, Øyri et al. (37) conducted their research in Norway with 200 participants. From North America, Fernandes and Hatton (38) contributed with a single case study from the USA. Asian studies were represented by Sun et al. (36) from China with 46 participants, Patil et al. (6) from India with 90 participants, and Ibrahem and Al Hussaini (41) from Iraq with 50 participants.

Intervention Strategies and Delivery Methods

The studies evaluated diverse tetracycline administration approaches through five distinct delivery methods. Two studies focused on carrier-based delivery systems, as described by Øyri et al. (37) used oxytetracycline-impregnated drains

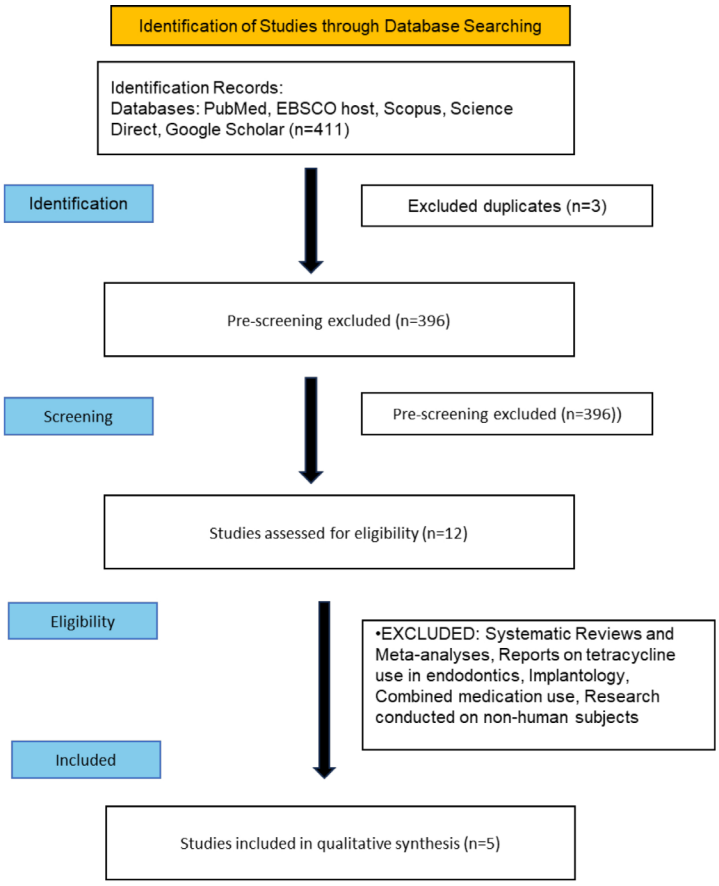

Figure 1. Flow diagram of the article identification and selection process.

compared to simulated placement, which allowed for controlled release of the antibiotic directly into the extraction socket. Fernandes and Hatton (38) utilized doxycycline-soaked Gelfoam, leveraging the absorbable gelatin sponge's ability to serve as both a drug carrier and a scaffold for healing.

Different formulations were also tested to evaluate optimal delivery mechanisms. Sun et al. (36) investigated the effectiveness of minocycline ointment versus iodoform gauze, providing insights into the effectiveness of semi-solid preparations compared to traditional dressing materials. Patil et al. (6) examined a combined approach using tetracycline with saline/gelatin sponge compared to no medication, exploring how the addition of a carrier material might enhance drug delivery and retention at the extraction site.

A unique comparative approach was taken by Ibrahem and Al Hussaini (41) who investigated the differential effects of local versus systemic doxycycline administration. This study specifically addressed whether targeted local delivery could provide comparable or superior results to traditional systemic administration, with implications for reducing overall antibiotic exposure.

The diversity in delivery methods across these studies, from impregnated drains (37) and gelatin sponges (38) to ointments (36) and local applications (6,41) - provides a comprehensive evaluation of various approaches to optimize

Table 2. Characteristics and Outcomes of Clinical Studies Evaluating Topical Tetracycline Applications in Post-Extraction Alveoli: A Systematic Review Summary.

Study Characteristics	**Øyri et al. (2019) (37)**	**Fernandes & Hatton (2016) (38)**	**Sun et al. (2022)(36)**	**Patil et al. (2021) (6)**	**Ibrahem & Al Hussaini (2022) (41)**
Database	PubMed	EBSCOhost	PubMed	Scopus	Science Direct
Study Type	Single-blind RCT	Case Report	Prospective Cohort	Comparative Prospective	Randomized Clinical Trial
Country	Norway	USA	China	India	Iraq
Sample Size	200	1	46	90	50
Population Demographics	127F/73M, Age >18 (mean 25)	M, Age 44	Mixed, Age >18	Mixed, Age 18-45	Mixed, Age 18-35
Intervention	Oxytetracycline-impregnated drain	Doxycycline-soaked Gelfoam	Minocycline ointment	Tetracycline + saline/ gelatin sponge	Local doxycycline
Control Group	Simulated drain placement	N/A	Iodoform gauze	No medication	Systemic doxycycline
Follow-up Duration	7 days	7 days	7 days	7 days	7 days
Primary Outcomes	AO incidence & pain scores	Pain & healing assessment	Pain scores & dressing changes	VAS pain scores	AO incidence
Key Results	AO: 5 % vs. 23% control	No pain reported	Pain relief by day 3	Significant pain reduction	Reduced AO incidence
	Pain reduction significant	70% flap approximation	25% needed redressing	P=0.024, 0.003, 0.018	Better coagulation
Clinical Effect	Positive	Positive	Positive	Positive	Positive
Microbiological Effect	Not studied	Not studied	Not studied	Not studied	Not studied
Overall Direction	Supports use	Supports use	Supports use	Supports use	Supports use

tetracycline delivery in post-extraction alveoli. Each method presented distinct advantages in terms of ease of application, drug retention, and delivery control, contributing to our understanding of optimal therapeutic strategies.

Clinical Outcomes and Follow-up Results

All studies maintained a standardized 7-day follow-up period, revealing significant clinical benefits: Reduction in alveolar osteitis incidence from 23 % to 5 % (37); Complete pain resolution with 70 % flap approximation (38); Early pain relief by day 3, with only 25 % requiring redressing (36); Statistically significant pain reduction (P=0.024, 0.003, 0.018) (6);

Improved coagulation and reduced alveolar osteitis incidence (41).

Microbiological Effects Assessment

A significant finding of this review was the complete absence of microbiological evaluation across all studies. Despite tetracyclines' known antimicrobial properties, none of the included studies assessed: Bacterial load changes in post-extraction sockets; Antimicrobial resistance patterns; Microbiome alterations following tetracycline application; Bacterial species identification pre- and post-treatment. This represents a critical gap in understanding the complete mechanism of action of topical tetracycline in post-extraction healing.

Quality Assessment and Methodological Analysis

The methodological quality evaluation revealed varying levels of rigor across the included studies, utilizing both STROBE

criteria for observational studies and ROB 2 for randomized clinical trials. This comprehensive assessment demonstrated strong evidence supporting tetracycline's clinical efficacy while highlighting areas requiring additional research.

STROBE Assessment

The prospective cohort studies by Sun et al. (36) and Patil et al. (6) achieved maximum STROBE scores (22/22 points), indicating excellent methodological quality. In contrast, Fernandes and Hatton's (38) case report scored lower (12/22 points), reflecting the inherent limitations of single-case studies (Table 3).

Risk of Bias Assessment

The ROB 2 evaluation for the randomized clinical trials showed predominantly favorable results. Ibrahem et al. (41) and Øyri et al. (37) demonstrated generally low risk of bias across most domains, with some notable distinctions (Figure 2).

Table 3. Quality Assessment Tool Scores summary.

Study	Quality Assessment Tool	Score/Result
Fernandes & Hatton (38)	STROBE	12/22
Sun et al. (36)	STROBE	22/22
Patil et al. (6)	STROBE	22/22

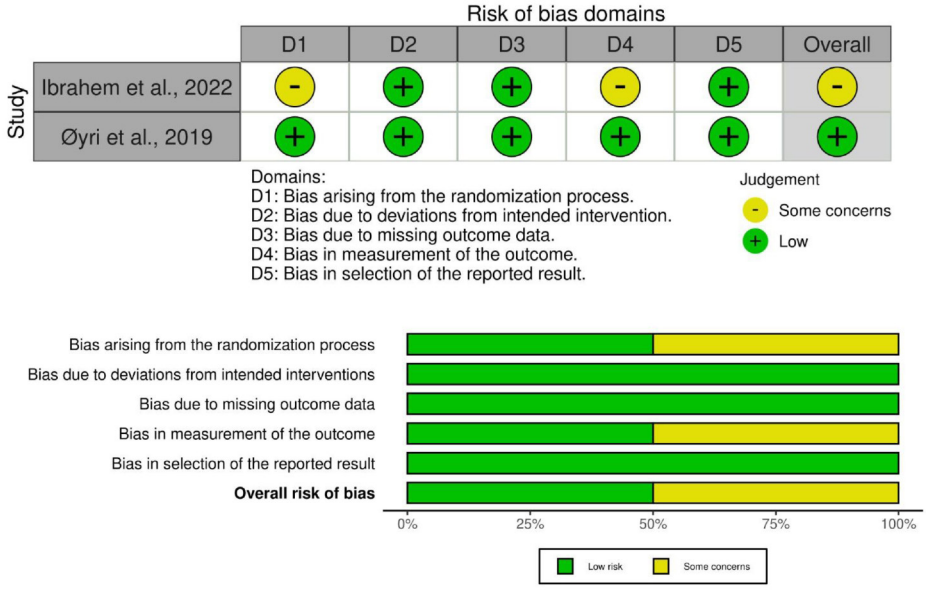

Figure 2. ROB 2 methodological quality assessment results.

- Ibrahem et al. (41): Showed "some concerns" in the randomization process (D1); Maintained low risk in intervention deviations (D2); Demonstrated low risk in missing outcome data (D3); Achieved low risk in outcome measurement (D4); Exhibited low risk in selective reporting (D5).
- Øyri et al. (37): Maintained consistent low risk across all domains (D1-D5).

This comprehensive analysis revealed strong evidence supporting the clinical efficacy of topical tetracycline in the treatment of post-extraction alveoli, while highlighting the need for further research into its microbiological implications.

Research Implications

The findings collectively demonstrated strong evidence for tetracycline's clinical efficacy across different delivery methods and patient populations. However, the assessment also highlighted the need for further research, particularly in understanding the microbiological implications of tetracycline use in post-extraction alveoli. Future studies should address these gaps while maintaining the high methodological standards observed in the higher-scoring studies.

DISCUSSION

The evaluation of topical tetracyclines in post-extraction alveoli treatment reveals several important dimensions. The literature demonstrates that tetracyclines have been widely used due to their antimicrobial and anti-inflammatory properties. As mentioned by Pal et al. (47) the application of topical tetracycline in the alveolus after dental extraction reduces postoperative pain compared to patients who do not receive this additional treatment.

Studies such as Sun et al. (36) have demonstrated that topical tetracycline application can significantly reduce the incidence of dry socket, a common post-extraction complication. Patil et al. (6) support the intra-alveolar placement of tetracycline and gelatin sponge, as their study showed that this combination is a good substitute for prolonged analgesic use and acts as an effective adjuvant in reducing pain during the first days following routine dental extraction. Similarly, Øyri et al. (37) advocate for the use of intra-alveolar tetracycline, demonstrating that an oxytetracycline-impregnated drain significantly reduces the incidence of dry socket following third molar extractions (37). This aligns with Fernandes et al. (38), who conclude that the combination of doxycycline, local anesthetic, and Gelfoam appears to be an effective technique for preventing dry socket.

However, it is important to consider the variations in results reported across different studies. For instance, some researchers, such as Vuylsteke et al. (40) recommend avoiding lipid-based antibiotic ointments in extraction sockets due to their negative influence on the post-extraction socket healing process observed in their study. This disparity suggests the need for standardized protocols and further research to optimize the use of topical tetracyclines in the post-extraction context.

Regarding the clinical effect of topical tetracyclines, our findings align with existing literature supporting their efficacy. Clinical studies, such as Krishna et al. (39), report that the use of hydrocortisone and oxytetracycline-soaked gauze resulted in a significant reduction of postoperative pain and swelling. Ibrahem et al. (41) conclude that local application of doxycycline-saturated Gelfoam significantly reduces the incidence of alveolar osteitis. Patil et al. (6) indicate that patients treated with topical tetracycline experience a reduction in postoperative pain and inflammation compared to those who did not receive this treatment.

Furthermore, Fernandes et al. (38) note that the combination of doxycycline, local anesthetic, and Gelfoam appears to be a promising strategy for preventing dry sockets. Additionally, Sorensen in 1987 achieved a significant reduction in alveolar osteitis incidence, from 28.7 % to 14.6 %, by placing intra-alveolar tetracycline powder immediately after tooth extraction. These results are consistent with the fact that tetracyclines have anti-inflammatory properties and have been shown to exhibit several intracellular and extracellular biologic effects unrelated to antibiotic activity, which help minimize local inflammatory responses and, therefore, improve patient comfort during the recovery period.

Limitations and Adverse Effects

Nevertheless, it is crucial to note that clinical responses can vary, and some authors, such as Vuylsteke et al. (40), report that the topical application of Terra-Cortril (Hydrocortisone,

oxytetracycline, and polymyxin B) to post-extraction sockets has a negative influence on socket healing. Additionally, Sanchis et al. (33) found that intra-alveolar placement of tetracycline compound following surgical extraction of impacted mandibular third molars did not affect the incidence of dry socket. Studies, such as those by Fisher et al. (34), in which Terra-Cortril (a petroleum-based tetracycline/steroid ointment) was applied over Gelfoam in surgically extracted third molar sockets, revealed a diagnosis of myospherulosis. This finding highlights the need for caution when using lipid-based products in dental treatments, as they may have unexpected adverse effects and compromise the healing process.

Gaps in Current Research

The systematic review revealed a lack of studies on the microbiological effect of topical tetracyclines in post-extraction sockets despite their known antimicrobial potential. This absence of evidence underscores the need for well-designed research to evaluate the impact of these agents on bacterial load and resistance profiles in this specific context. Controlled clinical trials are required to compare the efficacy of tetracyclines with other antimicrobial treatments in post-extraction sockets.

CONCLUSIONS

Topical tetracycline application in post-extraction alveoli has emerged as an effective therapeutic intervention, as demonstrated across five key studies from different geographical locations. The evidence consistently shows significant clinical benefits, particularly in reducing the incidence of alveolar osteitis and post-operative pain, with positive outcomes observed across various delivery methods, including impregnated drains, gelatin sponges, and ointments.

Despite these promising clinical results, a critical gap exists in the current research regarding the microbiological assessment of these interventions. None of the reviewed studies evaluated changes in bacterial load or resistance patterns, highlighting the need for further research to understand the antimicrobial mechanisms and standardize treatment protocols. Future studies should focus on investigating the microbiological implications while optimizing delivery methods and dosing regimens to enhance therapeutic outcomes.

Conflicts of Interest: The manuscript was prepared and reviewed with the participation of all authors, who declare that there are no conflicts of interest that could compromise the validity of the presented results.

AUTHOR CONTRIBUTIONS

AD-C: Development of the original idea, draft development, manuscript revisions. SC-M: Draft development, manuscript revisions. GT-A: Draft development, manuscript revisions. LB-P: Draft development, manuscript revisions. JPR: Draft development, manuscript revisions. JH-R: Draft development, manuscript revisions. All the authors approved the final version of the document.

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