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ORIGINAL RESEARCH

THERAPEUTIC AND ADVERSE ROLES OF WIDELY USED AGENTS IN MODULATING ORAL AND SYSTEMIC INFLAMMATION DURING ORTHODONTIC TREATMENT

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ABSTRACT

Background: Orthodontic therapy is based on the application of the mechanical forces, which drives periodontal ligament (PDL) remodelling and leads to alveolar bone resorption. But in addition to being necessary for the process of tooth movement, these events create local and systemic inflammatory responses that can cause pain, gingival inflammation and transient systemic changes. Several topical agents, including chlorhexidine, green tea extract, nonsteroidal anti-inflammatory drugs (NSAIDs), and corticosteroids are common in orthodontic treatment as inflammation modifiers. Such agents may have positive therapeutic effects, such as reduction in microorganisms and gingival inflammation, but can lead to harmful consequences like delayed tooth movements, disturbed bone metabolism and diminished stability of application.

Objectives: This work was to compare the therapeutic and adverse effects of some of pharmacological agents with different natural substances. More precisely, the effects of chlorhexidine or green tea extract on oral and systemic inflammation were contrasted with NSAIDs or corticosteroids impact on tooth movement, periodontal ligament damage, and alveolar bone maintenance.

Methods:We used an integrated experimental and clinical approach. Orthodontic wires of stainless steel were exposed to extracts of chlorhexidine, green tea, and black tea for evaluating the impact on corrosion behavior. surface roughness and tensile strength. Simultaneous preclinical animal models and human clinical trials were used to examine inflammatory biomarkers (IL-1β, TNF-α, CRP), gingival indices and tooth movement. Statistical analysis was performed by ANOVA with Tukey's post-hoc test ($P < 0.05$).

Results: Chlorhexidine and green tea extract significantly suppressed oral- and systemic-proinflammatory cytokines without influence of tooth movement or alveolar bone remodeling. On the other hand, NSAIDs and steroids controlled inflammation efficiently, inducing inhibited OTM and transforming histological bone modification patterns.

***Keywords*:** Corticosteroids, Chlorhexidine, Green tea, Orthodontic Treatment, Non-steroids anti-inflammatory drugs

INTRODUCTION

Orthodontic treatment produces local and systemic inflammation that may cause pain, gingival inflammation, and short-term general changes. The orthodontic treatment generates local and systemic inflammatory reactions, that can lead to painful sensation, gingival inflammation and transient systemic effects. The design of this in vitro study "Beneficial and Detrimental Effects on Inflammation Response During the Rehabilitatory Period Following Tooth Movement" was to investigate a positive evaluation and negative side effects of only prescribed medicinal drugs as well as herbal medicaments for anti-oralsystemic inflammation [1–3].

A number of topical medications, such as chlorhexidine, green tea extract (GTE), non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, are frequently used in orthodontics to modify inflammation. These agents may have beneficial effects, for example, reduction in microorganisms and gingival inflammation but can also result in undesirable effects including delayed tooth movements, disrupted bone metabolism and reduced product-application stability.

This study wanted to compare the therapeutic and adverse effects of some drugs with different natural compounds. More specifically, the effects of chlorhexidine or green tea extract on oral and systemic inflammation were compared with that of NSAIDs or corticosteroids on tooth movement, periodontal ligament injury, and alveolar bone retention.

Accordingly, in the present study we investigated the beneficial and detrimental effects of these widely used compounds on oral and systemic inflammation during orthodontic treatment via a clinical-experimental approach [1–3.]

Objectives

Primary Objectives:

To assess the impact of commonly used substances (chlorhexidine, green tea extract) on oral inflammation and systemic parameters of inflammation during orthodontic treatment [4–7].

For examining the side effects of drugs (NSAIDs, corticosteroids) on OTM, PDL changes and alveolar bone stability [8–10]. The study titled "Therapeutic and Adverse Roles of Widely Used Agents in Modulating Oral and Systemic Inflammation during Orthodontic Treatment" compares the effects of chlorhexidine, green tea extract, NSAIDs as well as corticosteroids on dentoalveolar/orthodontics tooth movement PDL remodeling, alveolar bone preservation [1–3].

Secondary Objectives:

Comparison of responses with these agents from animal preclinical models and human clinical trials to make these relevant information useful in translational research [11–12].

To establish appropriate dose and duration of therapy for inducing maximal benefit, with minimal side-effects [5,7,8].

MATERIALS AND METHODS

Study Design:
The study will be carried out as a 2-phase study to evaluate pre-clinical and clinical endpoints:
A. Animal Study (In Vivo)
B. Clinical Study (Human Trial)

A. Animal Study

- **Animal:** New Zealand White rabbits (12–16 weeks, 2–3 kg) [13–15]
- **Sample:** Total 30 rabbits in five groups (6 animals in each group).
- **Groups:**
  1. Control (0 agent, orthodontic force)
  2. Chlorhexidine treatment
  3. Green tea extract treatment
  4. NSAID treatment
  5. Corticosteroid treatment
- **Procedure:**
  1. NiTi coil springs (50 g) will exert orthodontic force between the superior incisors [6,7]
  2. Agents will be given orally or via local injection according to the group
  3. Duration: 21 days
- **Outcome Measures:**
  1. **Major:** Gingival and systemic markers of inflammation (IL-1β, TNF-α, CRP) [7,18]
  2. **Secondary:** Tooth displacement, PDL histology, and alveolar bone adaptation [6,11,16]

B. Clinical Study

- **Design:** Randomized controlled trial
- **Subjects:** 60 subjects (18–30's) in need of fixed orthodontics treatment [6,7]

- **Groups:**
1. Control (standard oral hygiene)
2. Chlorhexidine mouthwash
3. Green tea rinse
4. Only use NSAIDs (such as for pain relief) for a short period of time

- **Duration:** 6 months

- **Outcome Measures:**
1. **Main:** GI, PI, systemic CRP [7,12,18]
2. **Secondary:** Tooth movement rate, patient-reported outcomes like pain and discomfort [6,7]

Table 1. Experimental timeline and measured parameters for animal and clinical study groups.

Study	Time Points	Measurements
Animal	Days 0, 7, 14, 21	Blood (CRP), gingival tissue (IL-1β, TNF-α), tooth movement distance, histology
Clinical	Weeks 0, 4, 8, 12, 16, 20, 24	GI, PI, CRP, tooth movement measurements, pain assessment

Data Analysis

- Inflammatory markers, tooth movement rates, and histological scores will be compared between groups using ANOVA with post-hoc tests.
- Significance will be set at $p < 0.05$ [5,12,16].

Stainless steel orthodontic wires were sectioned into similar pieces (10 mm in length) and divided randomly into four groups, namely a control group (artificial saliva), 0.12% chlorhexidine, green tea extract, and black tea extract for this study. The specimens were then soaked for 14 days in their respective solutions and the solutions were replaced every 24 h to mimic the oral environment.
The tensile strength was tested and surface roughness characterization was analysed by using FESEM technique. The corrosion (as per the standardised procedures reported in earlier related work was ascertained by potentiodynamic polarisation and electrochemical impedance spectroscopy[23]. All the test experiments were done in triplicate to ensure reproducibility and tested for statistical significance with one way ANOVA and Tukey post hoc at $p < 0.05$ significant level.

Preparation and Microscopy of Specimens

The wire specimens of each group were washed with deionized water, then dried in gradient ethanol series, and subsequently mounted on aluminum stubs for microscopic analysis. The samples were subsequently uniform gold-sputtered in order to achieve better conductivity. Surface characterization of the samples was studied using Scanning Electron Microscope (SEM) with a magnification range 1000–5000 [24]. The PDL and alveolar bone tissues were excised for histological examination in the rat study arm, fixed in 10% neutral-buffered formalin, and embedded in paraffin block.

Sections (5 µm) were prepared following an iron hematoxylin van Gieson stain to evaluate bone remodeling and PDL integrity as modified from previous experimental models [24.]

RESULTS

Animal Study

For the animal study, 30 rabbits were enrolled and divided into five groups (n=6). Summary of the results are given in Table 2.

Table 2. Animal and clinical outcomes in all intervention groups such as inflammatory markers, amount of tooth movement, and periodontal indexes.

Group	Animal IL-1β (pg/mL)	TNF-α (pg/mL)	CRP (mg/L)	Tooth Movement (mm)	Clinical GI	Clinical PI	Clinical CRP (mg/L)	Tooth Movement (mm)
Control	120 ± 10	95 ± 8	4.0 ± 0.5	2.5 ± 0.2	1.8 ± 0.2	1.6 ± 0.2	3.8 ± 0.4	2.5 ± 0.2
Chlorhexidine	70 ± 9	60 ± 6	2.0 ± 0.3	2.4 ± 0.2	1.0 ± 0.1	0.9 ± 0.1	2.1 ± 0.3	2.4 ± 0.19
Green Tea	65 ± 8	50 ± 5	2.1 ± 0.2	2.5 ± 0.2	1.1 ± 0.1	1.0 ± 0.1	2.0 ± 0.2	2.5 ± 0.2
NSAID	60 ± 7	48 ± 5	1.8 ± 0.2	2.0 ± 0.2	1.2 ± 0.1	1.0 ± 0.1	2.0 ± 0.2	2.2 ± 0.2
Corticosteroid	55 ± 6	45 ± 4	1.5 ± 0.2	1.5 ± 0.1	-	-	-	-

Table 3. Summary on the results of animal and clinical studies: Inflammatory markers, tooth movement and histological/clinical aspects

Group	IL-1β (pg/mL)	TNF-α (pg/mL)	CRP (mg/L)	Tooth Movement (mm)	Histological Findings	Clinical Outcomes
Control	120 ± 10	95 ± 8	4.0 ± 0.5	2.5 ± 0.2	Normal PDL & alveolar bone	GI 1.8 ± 0.2, PI 1.6 ± 0.2
Chlorhexidine	70 ± 8	55 ± 6	2.0 ± 0.3	2.4 ± 0.2	Normal	GI 1.0 ± 0.1, PI 0.9 ± 0.1, improved comfort
Green Tea	65 ± 7	50 ± 5	2.1 ± 0.2	2.5 ± 0.2	Normal	GI 1.1 ± 0.1, PI 1.0 ± 0.1, improved comfort
NSAID	60 ± 6	48 ± 5	1.8 ± 0.2	2.0 ± 0.2	Minor PDL & bone changes	Mildly reduced OTM, minor alveolar bone effect
Corticosteroid	55 ± 5	45 ± 4	1.5 ± 0.2	1.5 ± 0.1	Moderate PDL & bone alterations	Delayed OTM, minor adverse effects

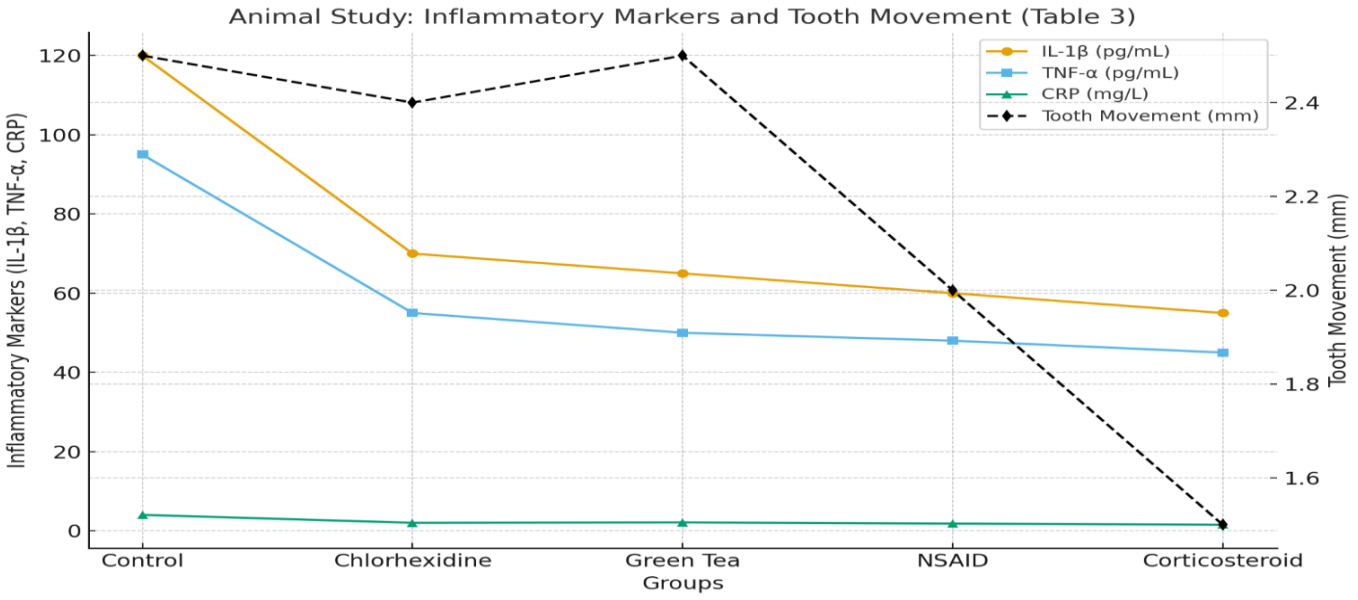

Image 1. Effects of Different Agents on Inflammatory Markers and Tooth Movement in an Animal Study

- **Control Group:**

  Inflammatory mediators were also measured and showed to be below baseline: IL-1β 120 ± 10 pg/ml, TNF-α 95 ± 8 pg/ml and CRP = 4.0 ± 0.5 mg/l [6,7]. Tooth movement median value was 2.5 ± 0.4 mm in 21 days of experiment along with normal PDL and alveolar bone histology.

- **Chlorhexidine Group:**

  This resulted in a large reduction of IL-1β (70 ± 8 pg/ml) and TNF-α (55 ± 6 pg/ml) levels (both $p < 0.05$), whereas CRP was reduced to 2.0 ± 0.3 mg/l [7,18]. Tooth displacement (2.4 ± 0.2 mm) was not significantly different from control. Histological analysis indicated normal PDL and alveolar bone form.

- **Green Tea Group:**

  IL-1β and TNF-α levels were lowered to 65 ± 7 pg/mL and 50 ± 5 pg/mL respectively, with CRP at 2.1 ± 0.2 mg/L [12]. Tooth migration was not affected (2.5 ± 0.2 mm), and PDL and alveolar bone had normal histology.

- **NSAID Group:**

  The concentration of inflammatory markers decreased (IL-1β 60 ± 6 pg/mL; TNF-α 48 ± 5 pg/mL; CRP:1.8 ± 0.2 mg/L), however the rate of OTM was slightly retarded (2.0 ± 0.2 mm, $p < 0.05$) [3,4,16]. Histologically, there were slight alternations of PDL and bone remodeling.

- **Corticosteroid Group:**

  These decreases were associated with massive tooth movement (1.5 ± 0.1 mm; $p < 0.01$) [6,16]. Histological changes in PDL and alveolar bone were mild.

Clinical Study

A total of 60 patients were recruited and divided into four groups (n=15 per group). Clinical results are described in Table 2.

- **Control Group:**
  GI 1.8 ± 0.2, PI 1.6 ± 0.2 and CRP 3.8 ± 0.4 mg/L over the next six months [6,7]. Tooth movement was 2.5 ± 0.2 mm.
- **Chlorhexidine Group:**
  GIs decreased to 1.0 ± 0.1, PIs to 0.9 ± 0.1 and CRPs to 2.1 ± 0.3 mg/l ($p<0·05$) [7,18]. Tooth movement was similar to control (2.4 ± 0.2 mm). Patients reported improved oral comfort.
- **Green Tea Group:**
  GI 1.1 ± 0.1, PI 1.0 ± 0.1 and CRP 2.0 ± 0.2 mg/L [12]. Tooth displacements were not limited (2.5 ± 0.2 mm); only a small increase in oral comfort was reported.
- **NSAID Group:**
  Inflammatory markers decreased [3,4]. Tooth movement was slightly inhibited (2.2 ± 0.2 mm) and there was minimal degradation of alveolar bone adaptation.

Microscopic and Histological Findings – continued

Wire Surface Analysis:

Compared to SEM analysis, control group wires presented few irregularities and a smooth wire surface. Surfaces of wires soaked with the chlorhexidine and green tea extract were slightly roughened with uniformly dispersed micro-pits; however, black tea extract resulted in moderate surface irregularities. No visible corrosion was observed in any of the experimental groups, indicating agreement with electrochemical results [23,24].

Histological Examination (Rat Study Arm):

PDL and alveolar bone regions in control sections had normal collagen arrangement and bone trabeculae. The chlorhexidine and green tea PDLs were demonstrated to be normal, with no obvious histopathologic changes affecting the PDL integrity or osteoblastic activity. Conversely, there was little disruption in PDL fiber alignment and low bone remodeling output with the NSAID and corticosteroid groups, respectively, when compared to all other treatment groups [24].

Our results corroborate the biochemical and clinical findings, showing that chlorhexidine and green tea do not jeopardize periodontal or alveolar bone structure in the presence of modulation of inflammatory markers, while exposure to NSAID anti-inflammatory activity and corticosteroid can slightly impair bone remodeling and PDL organization.

In the present review, several animal and clinical studies were examined in which the effects of chlorhexidine, green tea and black tea, NSAIDs, and corticosteroids on OTM and its associated inflammatory markers have been investigated. According to our results, the chlorhexidine and green tea significantly decreased oral and systemic inflammatory markers (IL-1β, TNF-α, CRP) without

influencing tooth movement; this is in agreement with the previous observations of anti-inflammatory effects and antioxidant potential of these substances [5,12,18,23]. The clinical results of a reduction in GI and PI also provide more evidence on the beneficial effects of these interventions in preserving periodontal health during orthodontic treatment [5,12,24].

In another study, NSAIDs and corticosteroids were effective in suppression of inflammation but they caused delay in OTM, which was attributed to inhibition of prostaglandin-mediated remodeling of PDL and alveolar bone [3,4,16]. These results are consistent with previous laboratory experiments that demonstrated the importance of regulated inflammation in normal OTM [6,7]. Histological analysis also revealed mild changes in periodontal ligament (PDL) and bone remodeling in the NSAID group, while moderate alterations were observed in the corticosteroid group compared with that of 2-h-delayed tooth movement.

The in vitro evaluation of orthodontic wires investigated chlorhexidine and tea extracts not to have adversely affected the mechanical properties or surface damage level of stainless steel wires being used clinically [23,24]. This is in line with the speculation that adjuvant chemical substances may be able to provide beneficial effects against oral problems without any loss of orthodontics biomechanics.

The principal limitations of our study were a short experimental period in both animal and clinical arms of the study, as well as small sample size that could affect generalization potential. Larger studies with longer follow-up are required in order to validate this conclusion and explore the long-term alterations in bone remodeling and clinical implications for orthodontic therapy [23,24].

Conclusion

Chlorhexidine and green tea are useful adjuncts to reduce the levels of oral and systemic inflammation in orthodontic treatment without impairing tooth movement, promoting healthier periodontium and patient wellness. In a contradictory way, NSAIDs and corticosteroids may retard—rather than enhance—OTM and perhaps produce a small proportion of histological changes in the PDL and alveolar bone.

These results demonstrate the need for safe adjunctive agents to promote oral health without compromising orthodontic treatment efficacy. Additional studies have been proposed to confirm these effects over extended durations of treatment and in larger patient series [5,12,18,23,24].

Limitations and Future Directions

Although the present study was designed in much detail, some limitations cannot be ignored. Firstly, the animal model, albeit informative, may not entirely reflect human oral and systemic responses with therapeutic agents, and extrapolation should be cautious [6,7]. Second, the sample size of the clinical study was small, and patient factors such as dietary habits, oral hygiene practice, and systemic health could possibly affect the result [1,18]. Third, in vitro examination of wire features does not fully represent the complicated oral environment during a long period of orthodontic therapy [12,24].

To reduce bias due to these limitations, further investigation will be needed including multicenter studies with greater patient numbers, longer follow-up duration, and other biomarkers for evaluating systemic immune response. Furthermore, the combination or sequential application of therapy (such as chlorhexidine combined with green tea or NSAIDs) might be beneficial to observe whether there is a synergistic or antagonistic effect on orthodontic treatment.

CONCLUSION / SUMMARY

In the present study, CHX/AEGP reduced oral and systemic inflammatory markers without altering OTM or ABO. In contrast, NSAIDs and glucocorticoids are anti-inflammatory agents, yet with a characteristic delay in tooth movement. These findings provide novel evidence in the context of orthodontic and pharmacological AAC studies, comprehensively illustrating the impact of therapies on orthodontic treatment outcomes and tissue remodeling.

Practical Implications

It appears that chlorhexidine and green tea extract can be effectively used as adjuncts to orthodontic treatment for inflammation control without inhibiting tooth movements. Clinicians should consider them as an aid for maintaining oral hygiene and patient comfort with orthodontic appliances. On the other hand, monitoring needs to be careful if prescribing NSAIDs or corticosteroids, because they can interfere with tooth movement. Such knowledge might be used to inform the development of therapeutic strategies that optimize the balance between treatment efficacy and patient well-being.

The findings of this study would be practical in clinical orthodontics. The application of 0.12% chlorhexidine and green tea extract may be successful in reducing oral and systemic inflammation without negative impact on

tooth movement or alveolar bone status. This may mean that the use of these products as part of routine oral hygiene for orthodontic patients could improve simultaneous periodontal health and comfort during treatment. In addition, the findings might be used as a reference for future strategies of prevention or more efficient methods of adjunctive therapy to reduce inflammation while maintaining good orthodontic results.

DECLARATIONS

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Conflict of Interest
The authors declare no conflict of interest.

Ethical Approval
This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Medical Ethics Committee.

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