The Effect of Local Pharmacological Agents in Acceleration of Orthodontic Tooth Movement: A Systematic Review

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Abstract

AIM: Acceleration of orthodontic tooth movement has gained a massive interest to decrease the total treatment time. Local pharmacological agents might be used for that purpose as a practical, effective and inexpensive alternative. A systematic review was achieved to evaluate the evidence in that topic.

METHODS: A search was conducted on electronic databases including PubMed, Lilacs, Web of Science (Thompson Reuters), EMBASE (OvidSP), and Cochrane Database of Systematic Reviews (Wiley) in addition to hand searching of relevant journals till June 2018. Only studies written in English were utilised. Publications were selected, assessed systematically and graded by two observers according to Bondemark grading system.

RESULTS: Only two human studies were found investigating the effect of Relaxin and Prostaglandins in the rate of orthodontic tooth movement. No obvious side effects were reported. Relaxin showed no increase in the rate of tooth movement while prostaglandin showed a marked increase in the rate of orthodontic tooth movement.

CONCLUSION: There is below moderate evidence showing no effect of relaxin on orthodontic tooth movement, while inconclusive evidence was found regarding Prostaglandin in the acceleration of orthodontic tooth movement. More prospective well-conducted clinical trials are needed to reach a proper conclusion regarding the local pharmacological agents which can be safely used to accelerate orthodontic tooth movement.

Introduction

Orthodontic tooth movement has been defined as the production of a biological reaction to an interruption in the physiological equilibrium related to the dentofacial complex by an externally applied force [1].

The lengthy duration of orthodontic treatment is considered a major disadvantage. This may lead to loss of patient compliance. This may be considered a problem especially for patients who require extraction of teeth as the treatment takes a relatively longer period than patients who don’t require extraction of teeth [2]. This may also lead to increasing the risk of caries [3] and periodontal breakdown [4]. Therefore, attention was paid to find methods to accelerate orthodontic tooth movement [5]. These methods were surgical, mechanical or physical. Examples of these methods are low-level laser therapy, corticotomy, electrical current, pulsed electromagnetic fields, and dentoalveolar or periodontal distraction. Evidence showed that corticotomy is effective and safe to accelerate orthodontic tooth movement [5]. Unluckily, very few patients can accept this surgical intervention to accelerate tooth movement due to its aggressive and invasive nature.

Another direction was focused on pharmacological approaches either locally or systemic administration to accelerate orthodontic tooth movement [6], [7].

Most of the previous systematic reviews concentrated on the physiological and surgical interventions with little concentration on the...
pharmacological interventions [5], [8], [9], [10].

This systematic review aims to investigate - in a systemic methodology and critical analysis - the available scientific literature discussing locally administrated pharmacological agents used in the acceleration of orthodontic tooth movement in humans.

**Material and Methods**

This section was written following the PRISMA 2009 checklist [11].

**Protocol and Registration**

There was neither a detailed protocol nor a systematic review registration done.

**Information Sources and Search strategy**

A search was conducted on electronic databases including PubMed, Lilacs, Web of Science (Thompson Reuters), EMBASE (OvidSP), and Cochrane Database of Systematic Reviews (Wiley) in addition to hand searching of relevant journals till June 2018. Only studies written in English were utilised.

The terms used in the search were shown in Table 1.

| PICOS item | Synonyms |
|------------|----------|
| P | Orthodontic patient OR Orthodontic therapy OR Orthodontic treatment OR Orthodontic* OR Tooth Movement (Mesh) OR tooth Pharmacological OR Drug OR Local Factor OR Pharmacol* OR vitamin D OR Prostaglandin OR Cholecalciferol |
| I | Accelerate tooth movement OR Fast treatment OR Treatment time OR Accelerate* movement OR Rapid tooth movement OR Quick treatment |
| C | Control OR Regular Orthodontic treatment |
| O | Rate of tooth movement |
| S | Randomized controlled studies and non-randomized controlled studies |

**Eligibility Criteria**

The PICOS format (P = Population, I = Intervention, C = Comparison, O = Outcome, S = Study design) was constructed in order to state a clinical question with particular inclusion criteria.

**P** - Patients at any age undergoing orthodontic tooth movement

**I** - Local pharmacological interventions to accelerate tooth movement

**C** - Conventional orthodontic therapy without local pharmacological intervention.

**O** - Rate of tooth movement

**S** - Randomized controlled studies and non-randomized controlled studies

**Inclusion criteria:** - Local intervention; - Injectable; - Clinical trials; - Trial aiming to accelerate tooth movement.

**Exclusion Criteria:** - Animal study; - Systemic drug; - Histological study; - Trial comparing drugs decelerating tooth movement; - Subcutaneous, Intramuscular, Intravenous administration.

**Review question**

Are the local pharmacological interventions able to accelerate tooth movement compared to conventional orthodontic treatment without local pharmacological intervention?

**Study selection**

Two independent reviewers examined the article titles and abstracts. Full-text articles were retrieved when the articles were either potentially eligible or when the eligibility criteria couldn’t be determined. Full-text articles were assessed following the inclusion and exclusion criteria. Reviewers’ results were compared. Discussion of the data was done to resolve any disagreement.

**Data Items**

From the studies that met our inclusion criteria, specific data items were extracted including (drug, frequency, dose, site, duration, total, dose, control, appliance, outcome, Risk Ratio, Mean Defence and side effects).

**Data collection**

The data items were extracted independently by 2 reviewers. The results were compared for accuracy and reassessment of the extracted data was done in case of any discrepancy until resolving the disagreement.

**Bias Assessment**

A quality assessment was performed based on the method described by Bondemark et al. [12, [13]. Following this method, studies were assigned to the grading of A, B, & C. A was considered high-quality evidence, B was a moderate value of evidence and C was considered the low value of evidence. In case of disagreement between the two reviewers or inadequately described criteria, the study was discussed thoroughly until reaching a consensus (Table 2).

https://www.id-press.eu/mjms/index
Summary measures and synthesis of the results

The final level of evidence was determined based on Bondemark et al., [12] The protocol divided evidence level to 1 (strong), 2 (moderate), 3 (limited) and 4 (inconclusive) (Table 3).

Approach to Data synthesis

A meta-analysis was considered if the available collected data was adequate.

Results

Study selection

A flowchart showed the selection process in each stage of the systematic review. (Figure 1) Five hundred seventy-eight articles were excluded by title and abstract while 4 articles were selected for full review. Two of these articles weren’t written in English [14], [15].

Two articles were included in our review utilising relaxin [16] and prostaglandin [17] as local pharmacological interventions aiming to accelerate tooth movement.

Study characteristics

Methods. One study was a randomised controlled study while the other study was a prospective study which was divided into 3 phases. Subjects. Total of 65 patients was involved in both studies. Intervention. Relaxin hormone and prostaglandin were used in selected studies.

Quality assessment

One study was graded A (High value of evidence) [16], while the other was graded B (moderate level of evidence) [17].

Results of Individual Studies

The primary outcome assessed in both studies was the effect of the local agent in the acceleration of orthodontic tooth movement. Secondary outcome included side effects resulted from using prostaglandin and effect of Relaxin on relapse (Table 4). The effect of prostaglandin was investigated both macroscopically and using radiographic images. There was no side effect observed on the gingiva or bones. Relaxin showed no effect on short-term stability.

Table 2 : Bondemark grading system

| Grade A | Grade B | Grade C |
|---------|---------|---------|
| All criteria should be met: A randomised clinical study or a prospective study | All criteria should be met: Cohort study or retrospective case series with defined control or reference group | Not more or of the conditions below:
| Diagnostic reliability tests and reproducibility tests described | Diagnostic reliability tests and reproducibility tests described | The high rate of attrition (1/3)
| Defined diagnosis and endpoints | Defined diagnosis and endpoints | or more of subjects lost during the study
| Blinded outcome assessment | Blinded outcome assessment | Poorly defined patient material

Table 3: Evidence level

| Level | Evidence | Definition |
|-------|----------|------------|
| 1 | Strong | Minimum of 2 studies level A |
| 2 | Moderate | At least 1 study level A and two studies level B |
| 3 | Limited | Minimum of 2 studies level B |
| 4 | Inconclusive | Less than 2 studies level B |

Table 4: Results of individual data

| Title | Author | Year | Design of the study | Number of Groups | Split mouth |
|-------|--------|------|---------------------|------------------|-------------|
| A randomized, placebo-controlled clinical trial on the effects of recombinant human relaxin on tooth movement and short-term stability | Eltimamy, et al., [12] | 2012 | RCT | 40 | 2 | no |
| Clinical application of prostaglandin E1 (PGE1) upon orthodontic tooth movement. | Fukuhara, T. et al., [13] | 1994 | 3 phases | 25 | 3 | yes |

| Title | Drug | Sample size | Dose | Site | Duration | Control | Apparent side effect |
|-------|------|-------------|------|------|----------|---------|---------------------|
| A randomized, placebo-controlled clinical trial on the effects of recombinant human relaxin on tooth movement and short-term stability | Human relaxin | 40 | 0.9g/7 days | 2 sites buccal and lingual of the target teeth | 56 | 49 | Vehicle ±1.5 g |
| Clinical application of prostaglandin E1 (PGE1) upon orthodontic tooth movement. | PGE1 | Phase I | 9 | 3 to 5 times | Injection of the submucosal area of the buccal side of the first premolar | Up to 21 days | Lidoca ine |
| | | Phase II | 8 | 3 to 4 times | Injection of the submucosal area distal to the canine | Up to 5 months | Lidoca ine |
| | | Phase III | 8 | 5 to 13 times | Injection of the submucosal area distal to the canine | Up to 5 months | Lidoca ine |
| A randomized, placebo-controlled clinical trial on the effects of recombinant human relaxin on tooth movement and short-term stability | Rate of tooth movement, rate of relapse | /7 | 56 | 25µg/0.1 ml | 1 | No |
| Clinical application of prostaglandin E1 (PGE1) upon orthodontic tooth movement. | Orm and side effect was examined macroscopically | 3 to 5 times | 15-20 | No | 2.1±0.33 |
| | | 3 to 4 times | 10-21 | No | not mentioned |
| | | 5 to 13 times | 40-144 | No | 1.6±0.09 |

Risk of bias

The study investigating Prostaglandin effect was found to be of high risk of bias as it was not a randomised controlled trial, while some concerns...
regarding the allocation concealment were detected in the other study investigating Relaxin effect.

Evidence level was below moderate regarding Relaxin and inconclusive regarding Prostaglandin according to Bondemark grading system [12]. Only 1 study was found which was graded A for Relaxin. While for Prostaglandin, only one study which was graded B was found.

The RCT investigating Relaxin showed that there was no significant difference and was considered of low risk of bias. Yet they used aligners which might not have delivered a consistent force that couldn’t be measured-necessary for proper comparison. Both studies were based on submucosal injection in the areas adjacent to OTM.

This study showed the need for further studies investigating the use of local pharmacological agents in the acceleration of orthodontic tooth movement.

**Strength and limitations**

Previous studies investigated different approaches with no concentration on the pharmacological approaches [23]. This study, however, focused on the local pharmacological agents used in orthodontic treatment to accelerate tooth movement.

There were not enough studies to conduct a meta-analysis. There were only a few heterogenous human studies. The quality of evidence was poor in that topic indicating the need for further studies to reach a proper conclusion.

**Conclusion**

There is below moderate evidence showing no effect of relaxin on orthodontic tooth movement, while inconclusive evidence was found regarding Prostaglandin in the acceleration of orthodontic tooth movement. More prospective well-conducted clinical trials are needed to reach a proper conclusion regarding the local pharmacological agents which can be safely used to accelerate orthodontic tooth movement.

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