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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.

Table 1: Terms used in the search strategy of the systematic review

PICO item	Synonyms
P	Orthodontic patient OR Orthodontic therapy OR Orthodontic treatment Or Orthodox* Or Tooth Movement (Mesh) OR teeth
I	Pharmacological OR Drug Or Local Factor OR Pharmacol* OR vitamin D OR Prostaglandin OR Cholecalciferol
C	Control OR Regular Orthodontic treatment
O	Accelerate tooth movement OR Fast treatment OR Treatment time OR Accelerate* movement OR Rapid tooth movement OR Quick treatment

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 Deference 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).

Table 2 : Bondemark grading system

Grade A	Grade B	Grade C
All criteria should be met: A randomised clinical study or a prospective study Diagnostic reliability tests and reproducibility tests described Defined diagnosis and endpoints Blinded outcome assessment	All criteria should be met: Cohort study or retrospective case series with defined control or reference group Diagnostic reliability tests and reproducibility tests described Defined diagnosis and endpoints	One or more of the conditions below: The high rate of attrition (1/3 or more of subjects lost during the study) Poorly defined patient material Unclear diagnosis and endpoints

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) (Table3).

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

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 4: Results of individual data

Title	Author	Year	Design of the study	Number	Groups	Split-mouth
A randomized, placebo-controlled clinical trial on the effects of recombinant human relaxin on tooth movement and short-term stability	Susan P. McGorray, a Calogero Dolce,b Susan Kramer,c Dennis Stewart,d and Timothy T. Wheelere	2012	RCT	40	2	no
Clinical application of prostaglandin E1 (PGE1) upon orthodontic tooth movement.	Yamasaki, K Shibata, Y.Imai, STani, Y.Shibasaki, Y Fukuhara, T	1984	3 phases	25	3	yes

Title	Drug		Sample	Frequency	Dose	Site	Duration	Total dose	Control	Appliance and force
A randomized, placebo-controlled clinical trial on the effects of recombinant human relaxin on tooth movement and short-term stability	Human relaxin		40	/7 days	25µg/site/0.1 ml	2 sites buccal and lingual of the target teeth	56	400µg	Vehicle 1.6 ml	Invisalign vacuum aligners
Clinical application of prostaglandin E_1 (PGE_1) upon orthodontic tooth movement.	PGE_1	Phase I	9	3 to 5 times	10 µg PGE_1	Injection of the submucosal area of the buccal side of the first premolar	Up to 26 days		Lidocaine	Double spring soldered on lingual arch(100 gm)
		Phase II	8	3 to 4 times	10 µg PGE_1	Injection of the submucosal area distal to the canine	Up to 21 days		Lidocaine	Sectional contraction loop (150 gm)
		Phase III	8	5 to 13 times	10 µg PGE_1	Injection of the submucosal area distal to the canine	Up to 5 months		Lidocaine	Compressed open-coil springs or ringlets (150 grams)

	Outcome	Frequency days	Duration (days)	Dose	Mean difference (intervention/control) (ratio)	Side effects
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/site/0.1 ml	1	No
Clinical application of prostaglandin e_1 (pge_1) upon orthodontic tooth movement.	Otm and side effect was examined macroscopically	3 to 5 times in 26 days 3 to 4 times in 14 days 5 to 13 times	15-28 10-21 45-144	10 µg pge_1	2.14±0.33 Not mentioned 1.6 ±0.09	No

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.

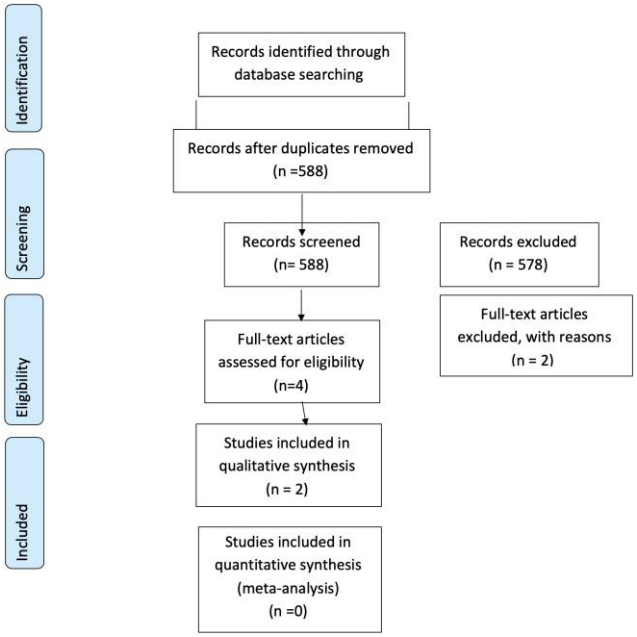

Figure 1: Prisma flow chart

Synthesis of Data

A meta-analysis was not possible due to the presence of insufficient studies.

Discussion

This study aimed to investigate the ability of the local pharmacological agent to accelerate orthodontic tooth movement. Surgical interventions have shown potential in the acceleration of orthodontic movement [8]. Its side effects had always been a barrier in the generalisation of these interventions. Local pharmacological interventions would be an excellent replacement if proven their efficiency, especially if not accompanied by any side effects. In spite of the huge focus on the acceleration of orthodontic tooth movement, there were only 2 human studies investigating the effect of local pharmacological agents on the acceleration of OTM. There were much more animal studies [18], [19], [20], [21] on the same topic. The obvious reason was the risk of side effects that accompany the tested interventions [22].

From the current systematic review, Relaxin [16] and Prostaglandin [17] were tested on humans. Prostaglandin showed a marked increase in OTM. The study was divided into 3 phases in which all phases showed acceleration of OTM in intervention sides, yet the study was considered having a high risk of bias. The study wasn't a randomised controlled study, and the sample size wasn't enough for each phase.

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 heterogynous 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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