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The Effect of Stem Cells on the Rate of Canine Retraction

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ABSTRACT

Purpose: This study was done to evaluate the effect of mandibular stem cells (MMSCs) on the rate of canine retraction. **Materials and methods:** The participants were twelve female patients with a bimaxillary dentoalveolar protrusion and age range from 15-21 (mean±SD 18.2 ±1.7). Bone marrow stem cells (BMSCs) were injected to one side, either right or left, while the other side served as a control group. Both upper and lower canines were retracted. Canines retraction were done under 150 gm of force using a 9 mm nickel-titanium TAD closed-coil spring between miniscrew and power arm welded to canines' bracket. Alginate impressions were taken every month until all canines had reached the second premolars, and study casts were fabricated and then scanned with a 3D scanner. **Results:** stem cells significantly increased the rate of tooth movement, particularly at T1. Anchorage loss was negligible and insignificant between the two groups. The pain was lower in the stem cells group, and patients were almost satisfied with the procedure. **Conclusion:** Non-cultured stem cell injection is a safe procedure that could be an effective method to accelerate tooth movement and significantly reduce the duration of orthodontic treatment.

KEYWORDS

Stem Cells,
Canine retraction,
Acceleration

INTRODUCTION

Accelerating orthodontic tooth movement, and subsequently decreasing treatment time, is an area of intense interest in the orthodontic field. It has a high demand for both patients and clinicians. Unfortunately, as orthodontic treatment time lengthens, many risks may

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arise. This includes white spot lesions and dental caries[1] root resorption[2], pain and discomfort[3] plaque accumulation and subsequent periodontal problems[4], improper patient compliance[5], and treatment fee[6]. Because of these risks, the demand for shortening of the treatment duration has increased and led researchers to focus on finding an effective method for accelerating tooth movement with minimum disadvantages. Thus, decreasing the time required for orthodontic treatment, while achieving optimum results, would be beneficial for patients and clinicians alike.

The Attempts of accelerating orthodontic tooth movement (AOTM) could be dated back to the 1890s when Cunningham made vertical interdental bone cuts as an "Immediate Method in Treatment of Irregular Teeth".[7] Up to now, different clinical and experimental techniques have been studied in accelerating the orthodontic tooth movement either surgical or non-surgical procedure.

Because the orthodontic tooth movement is directly related to the tissues and cells surrounding it, cell therapies were suggested to be examined as a method for acceleration orthodontic tooth movement.

Stem cells (SCs) therapy has been flourished lately, and it is one of the most important subjects of debate in different fields. Using of the SCs technology in orthodontics can bring a revolutionary change. With the successful evidence of stem cells in various medical treatments, maxillofacial surgeons and orthodontists have been eager to apply these cells for different purposes. This includes hard and soft tissues, engineering, temporomandibular joint disorders, distraction osteogenesis, rapid maxillary expansion, periodontal regeneration, treatment of external root resorption, and accelerated orthodontic tooth movement.

The role of stem cells in the OTM has been investigated in several studies. Zhang et al[8] established an OTM rat model and used some receptors to track the response of the PDLSCs. They found that the number of positive cells increased on both of the compression and the tension sides after three days of orthodontic treatment. Then the cells dropped after seven days. They suggested that the PDLSCs play a role in OTM, and they might be reactivated during orthodontic force treatment. Another study examined the role of the gingival mesenchymal stem cells (GMSCs) cultured in platelet rich fibrin in the bone remodeling process.[9] It was concluded that GMSCs cultured in PRF have potential osteogenic differentiation ability, which is capable of stimulating bone remodeling. In addition, One Recent study has been done to MSCs transfer to the periodontal ligament (PDL) on the rate of OTM of the rats' maxillary first molar teeth. It was found that the Injection of MSC into PDL may increase the amount of OTM.[10] So, it was concluded from the previous studies that stem cells could be a promising approach in accelerating orthodontic tooth movement. Thus, the purpose of this study was to investigate the effect of stem cells on the rate of orthodontic tooth movement.

SUBJECTS AND METHODS

The study was a randomized split-mouth, controlled clinical trial. It was ethically approved by the research ethics committee (REC) of the Faculty of Dental Medicine for girls, Al-Azhar University in Cairo. The participants were twelve female patients with a bimaxillary dentoalveolar protrusion and age range from 15-21 (mean±SD 18.2±1.7). All participants underwent a careful examination to ensure the compatibility of the inclusion criteria. The orthodontic appliance was bonded up to first molars for both the upper and lower arches. After leveling and alignment achieved until reaching a passive 0.020-inch stainless steel wire, the participants were ready for anchorage preparation and extraction of all first premolars. A self-drilling miniscrews were inserted on all upper and lower quadrants into the buccal alveolar bone between the second premolar and the first molar (1.6mm-diameter and 6mm-length). Subsequently, the extraction of first premolars was done for each side, either right or left, on a separate day.

Stem Cells aspiration, isolation, and injection:

Aspiration of Bone marrow was autologous; bone marrow was taken from the same patient. The ramus of the mandible was the site for the bone marrow aspiration in this study. Before starting any procedure, the internal and external oral areas were disinfected with using 10% povidone-iodine, and blocking of the inferior alveolar nerve was obtained with 0.1% lidocaine. 20 ml of bone marrow was manually aspirated with a 20 ml syringe preloaded with 1 ml of heparin (5000 IU) as an anticoagulant and 4 ml of 0.9% NaCl as a dilution. The collected bone marrow was immediately undergone MSCs isolation. Bone marrow underwent a chairside isolation procedure. A total of 10ml of bone marrow stem cells (BMSCs) was collected from each patient using two syringes of 5ml. BMSCs Injection was done submucosally into the buccal gingiva of the canine and the first premolar area and also inside the socket of the extracted first premolar (5ml for the upper quadrant and 5ml for the lower). The injections were applied only once on the day of the first retraction force application.

Canine retraction:

The canine retraction was achieved under 150 gm of force using a nickel-titanium 9 mm closed-coil spring connected between the miniscrew and laser-welded power arm of the canine bracket. The retraction force was reactivated every month (30days). Alginate impressions were taken immediately before canine retraction started, and then every month until all canines had reached the second premolars. Study casts were fabricated and then scanned with a three-dimensional scanner. Rate of canine retraction, loss of anchorage, pain, and satisfaction were evaluated. For the rate of upper canines, the anteroposterior linear distances between the right and left canine lines & the rugae lines, lines passing through the medial points of the right and left third rugae, and perpendicular to the mid-palatal line were measured. For lower canines, the anteroposterior distances between the right and left canine lines and the central fossae line -a line passing through the central fossa of the right and left second molars- were measured. The patients were given a questionnaire and asked to assess the level of pain after 1 hour, 12 hours, 24 hours, and at days 3, 5 and7 following the intervention procedure and after the first canine retraction with a numeric rating scale (NRS). The NRS was also used to rate the satisfaction of the BMSCs' aspiration and injections procedures and their easiness, fig (1).

Figure (1): Canine retraction mechanics

Statistical Analysis:

Statistical analysis was performed with IBM-SPSS software (IBM Corp. Released in 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. Qualitative data were expressed as frequency and percentage. Quantitative data were initially tested for normality using a z-score of skewness and kurtosis, as well as Shapiro-Wilk's test. Data are considered as normally distributed if two of the following three criteria are fulfilled (Z-scores are ± 2.58 and Shapiro test ($p>0.050$). The presence of significant outliers (extreme values) was tested by examining boxplots. Quantitative data were expressed as mean ± standard deviation (SD) if normally distributed or median and interquartile range (IQR) if not. For quantitative data, Independent-Samples t-Test was used for normally distributed data in both groups with no significant outliers, and the Chi-square test was used to study the differences by the time between the two groups.

For quantitative repeatedly-measure non-parametric data, Friedman's test was used. A linear mixed model was used to test if a statistically significant difference of a quantitative parameter (pain score) between two groups after adjustment for the repeated measurements. Results were considered statistically significant if the p-value ≤ 0.050.

RESULTS

Statistical analysis was carried out on twelve female patients who had a bimaxillary dental protrusion with no loss to follow up. The mean and standard deviation values for age were 18.2±1.7, with a minimum of 15 and a maximum of 20 years old.

Statistics showed a higher rate of canine retraction in stem cell groups for the maxillary and mandibular arches (P-value = 0.001) (P-value = 0.048), respectively tab (1).

Upper canine: From T0-T1, a significantly greater decrease was noted in the stem cell group (p=0.01). At T1 to T2, both groups recorded the same mean value. At T2-T3, T3-T4, T4-T5, a non-significant greater decrease was noted in the stem cell group.

Lower canine: From T0-T1, a greater decrease was noted in the stem cell group with no statistically significant difference. At T1 to T2, a greater decrease was noted in control. At T2-T3, T3-T4, T4-T5, a non-significant greater decrease was noted in the stem cell group with no significant difference.

Table (1): *Comparisons of the rate of canine retraction (SCs vs control) groups;*

Site	Stem (n=12)	Control (n=12)	t-value	P- value
Upper	1.3823 ± 0.109	1.1995 ± 0.127	3.784	0.001
Lower	1.2026 ± 0.222	1.0470 ± 0.119	2.135	0.048

Data expression: Mean ± SD.

Independent-Samples t-Test.

P value: Significant at P ≤ 0.05

There was no statistically significant difference in the anchorage loss between the two groups in the upper and lower arches (P-value= 0.923) (P-value= 0.651), respectively.

Pain at the aspiration site, injection site, and the feeling of discomfort significantly decreased at 12 hours, while the pain during eating and mouth opening decreased at 24 hours. None of the patients reported that they were awakened at night by pain. Pain-related to canine retraction was statistically significantly lower in stem vs. control in both arches (fig2).

The median and range values for satisfaction with bone marrow procedures, injection procedure, and easiness of the procedure were 2 (0 – 5), 1 (0 – 3), and 3.5 (0 – 5), respectively. About 66.7% of the participants recommended the procedure to others, while the majority of participants (83.3%) were willing to repeat the procedure. None of our cases was fully unsatisfied with any procedure (score = 10).

There was no statistically significant difference in the anchorage loss between the two groups in the upper and lower arches (*P*-value= 0.923), (*P*-value= 0.651), respectively.

Pain at the aspiration site, injection site, and the feeling of discomfort significantly decreased at 12 hours, while the pain during eating and mouth opening significantly decreased at 24 hours. None of the patients reported that they were awakened at night by pain. pain related to canine retraction was statistically significantly lower in stem vs control both at upper and lower sites (fig. 2).

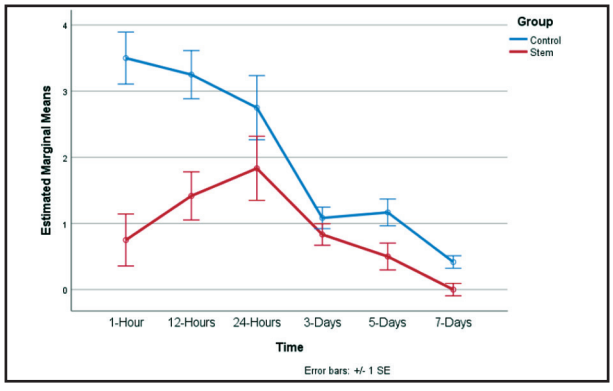

Figure (2): Profile plot of pain related to canine retraction

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DISCUSSION

Fourteen patients were enrolled in this study. A two-sided paired t-test showed that a number of twelve subjects (48 quadrants) were needed to achieve a power of 95%. All patients had a bimaxillary dentoalveolar protrusion. Two patients had been excluded from the research for different reasons. One of them was excluded because of his rejection of the BMSCs injection. The patient changed his mind and decided to withdraw at the same appointment of the stem cells application, although all procedures were explained to him & consent was signed before starting. The other patient was unable to maintain good oral hygiene, which resulted in the failure of the miniscrews in both sides. Thus, the final study sample was 13 patients; all were female.

Because of the fact that age affects the rate of tooth movement[11], the age was confined between 15 and 20. the average age of the sample was 18.1 ±2.03. This age range was intended to minimize the anticipated effect related to age, so the sample is homogeneous. However, only one patient was 15 years old, while the age of other ranged from 18-20.

The split-mouth design was chosen to make the collection of sample size easier and to reduce the biologic variability between the individuals.[12] Split moth design was used by many researchers to compare between the intervention and the control side. The sample was randomly allocated to receive the intervention either on the right or the left side.[13-15]

Both the upper and lower arches were included in this study in order to facilitate sample collection in a short time period. Each arch has its intervention and control side. The results relied on each jaw separately and not on a comparison between the upper and lower jaw, Due to the differences in nature of the maxilla and mandible.[16,17]

The type of orthodontic movement also affecting the rate of tooth movement.[18,19] Bodily movement occurred faster than tipping. In this study, a power arm was welded to the distal side of the mesh of the canine bracket to achieve bodily movement. So the tipping that may occur due to the retraction on a 0.020-in stst archwire could be avoided. In addition, wire ligatures were loosely tied around the canine bracket to reduce the amount of friction. Two different studies used a power arm attached to the canine bracket during canine retraction. Both studies stated that there is some tipping occurred, but its amount was not significant. [20,21]

Concerning the delivery force, the suitable force for orthodontic tooth movement is the lightest force, which produces a maximum or near-maximum response. The ideal force to slide a canine distally along a continuous archwire is 150-200 grams.237 In this study, nickel-titanium coil spring delivering 150 g force was used. It connected between the miniscrew and the welded-arm of the canine brackets.20,21 The coil spring is superior to the elastomeric chain in maintaining a long-range of activation.[22]

Selecting a mandibular ramus as a source of stem cells was based on the experiment of Bu-Kyu Lee et al. in 2011. They introduced the mandibular ramus as a new source of mesenchymal cells. They compared MSCS from mandibular ramus marrow with the MSCs from iliac marrow aspirates of the same individual. They conclude that the ramus of the mandible could be an alternative source for the collection of autologous MSCs, especially for the maxillofacial surgeon, since they are familiar with the mandible anatomy more than iliac.[23] Also, it was suggested that ramus derived stem cells will be more acceptable by patients than the other sources,

so the possibility of their rejection to participate in the research would be minimal.

In this study, the uncultured BMSCs method was used because of its multiple advantages such as easiness, not expensive, require minimal manipulation and does not need a chemical addition. It has been widely used for bone regeneration, and vascularization enhancement and its success were reported by many investigators.[24-26] since one of the purposes of this study was to find a feasible and effective method for acceleration OTM, non-cultured BMSCs method was preferred over the cultured method.

The submucosal type of injection was carried out in this study rather than the PDL injection. It was reported that the PDL injection type is absorbed quickly into the systemic circulation.[27] Moreover, different studies used the submucosal injection to evaluate the effect of certain substances or autologous cells on the rate of OTM.[28,29]

Dental impressions were taken every month in order to evaluate the rates of canines retraction and the loss of anchorage. In the upper arch, medial points of the third rugae area were used as reference points bilaterally; it was found that the medial and lateral points of the third rugae area are fixed and reliable points.[30,31] Regarding the lower arch, the lower second molars used as a fixed point since there were not included in the orthodontic appliance.

It is difficult to compare our result of the rate of canine retraction with other studies since there is no clinical study was done to evaluate the effect of non-cultured BMSCs on the OTM. Despite there were three studies shown in the literature about the role of stem cells in OTM, these studies were animal studies, in vitro, short-term evaluation, and examined different types of stem cells than the one used in this research.

The mean of the rate of the upper canine retraction for the stem and control group was 1.38 and 1.19, respectively. Regarding the lower arch, the mean of the rate of canine retraction was 1.2 for the stem group and 1.04 for the control group. These findings regarding the rate of tooth movement are in agreement with two studies9,[32] that stated that stem cells could accelerate the OTM. However, both studies are short-term and used different types of stem cells and different modalities, which made the comparison hard to be achieved. Compared to PRP, these results were less effective, and this could be due to the application of stem cells only once in comparison to the repetition of the application of PRP to 3 times in the previous studies.[29,33]

There was not a significant difference in the anchorage loss between the stem cells and control sides before and after the fully achieved of canine retraction. The anchorage loss was (0.28 and 0.29 mm) in the upper arch and (0.21 and 0.24) in the lower arch of the stem and control sides, respectively. These results are within the insignificant anchorage loss values of using a miniscrew as an anchorage, which ranged from 0.06 to 0.78 mm, as studied in Cochrane review.[34]

The level of the pain related to the canine retraction was lower in the stem cell groups. This could be in accordance with other studies in orthopedic, which stated that stem cells reduce pain in different orthopedic disorders.[35] More specifically, the findings regarding pain in this study could be compared with the pain associated with using of prp, since they all consider cell therapies. It was stated that the application of PRP reducing post-surgical pain in patients treated with PAOO, which supports our results.[29]

The level of satisfaction and the easiness of the procedures were high. The patients were satisfied with the idea of using a minimally invasive technique to speed up the tooth movement. After approximately 2-3 months of the first application of stem cells, most of the patients asked to do the stem cells again, so the orthodontic treatment could be finished earlier. Moreover, most of the patients did not mind repeating the procedure if they need it, and they were willing to recommend it to others.

CONCLUSIONS

Within the limitations of the current study, it can be concluded that:

1. Bone marrow stem cells (BMSCs) accelerated the orthodontic tooth movement, particularly in the first month of application.
2. The pain related to the stem cell procedure significantly decreased at 12 hours except for the pain with eating and mouth opening, which is significantly decreased at 24 hours.
3. The pain associated with canine retraction was lower in the stem cell group.
4. The level of patients' satisfaction regarding the stem cell procedure was high.
5. Loss of anchorage found to be minimum with the use of miniscrews.

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