

## Nonsurgical miniscrew-assisted rapid maxillary expansion results in acceptable stability in young adults

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### ABSTRACT

**Objective:** To evaluate the stability of nonsurgical miniscrew-assisted rapid maxillary expansion (MARME) in young adults with a transverse maxillary deficiency.

**Materials and Methods:** From a total of 69 adult patients who underwent MARME followed by orthodontic treatment with a straight-wire appliance, 20 patients (mean age, 20.9 ± 2.9 years) with follow-up records (mean, 30.2 ± 13.2 months) after debonding were selected. Posteroanterior cephalometric records and dental casts were obtained at the initial examination (T0), immediately after MARME removal (T1), immediately after debonding (T2), and at posttreatment follow-up (T3).

**Results:** Suture separation was observed in 86.96% of subjects (60/69). An increase in the maxillary width (J-J; 1.92 mm) accounted for 43.34% of the total expansion with regard to the intermolar width (IMW) increase (4.43 mm;  $P < .001$ ) at T2. The amounts of J-J and IMW posttreatment changes were -0.07 mm ( $P > .05$ ) and -0.42 mm ( $P = .01$ ), respectively, during retention. The postexpansion change in middle alveolus width increased with age ( $P < .05$ ). The postexpansion change of interpremolar width (IPMW) was positively correlated with the amount of IPMW expansion ( $P < .05$ ) but not with IMW. The changes of the clinical crown heights in the maxillary canines, first premolars, and first molars were not significant at each time point.

**Conclusions:** Nonsurgical MARME can be a clinically acceptable and stable treatment modality for young adults with a transverse maxillary deficiency. (*Angle Orthod.* 2016;86:713–720.)

**KEY WORDS:** MARME; Transverse maxillary deficiency; Adults; Stability

### INTRODUCTION

Rapid maxillary expansion (RME) is commonly used to correct transverse maxillary deficiencies that are

accompanied by unilateral or bilateral posterior cross-bite or as a conservative nonextraction modality to increase the arch perimeter and relieve crowding in adolescents and children.<sup>1</sup> However, orthopedic maxillary expansion using nonsurgical conventional RME in adult patients has been considered either impossible or rarely successful because the midpalatal suture and adjacent articulations begin to fuse by late adolescence and become more rigid with age.<sup>2,3</sup> Potential limitations and side effects of conventional RME in adults have been reported, such as expansion failure or limited skeletal expansion, instability of results, pain, tissue swelling, buccal crown tipping, gingival recession, root resorption, and ulceration.<sup>4</sup>

Surgically assisted RME (SARME) has been frequently used to overcome the above-mentioned limitations through surgical release of the closed sutures that resist expansion forces in adults.<sup>5,6</sup> However, patients tend to be reluctant to undergo multiple surgical procedures, and the demand for nonsurgical treatment has been increasing. Furthermore, surgery is costly and requires hospitalization with attendant morbidity, and it is challenging in patients with maxillary constriction

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Accepted: January 2016. Submitted: October 2015.

Published Online: March 3, 2016

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combined with severe anteroposterior discrepancies, because this condition inevitably requires phase 2 surgery.<sup>7</sup>

Recently, successful maxillary skeletal expansion with a tooth-bone-borne RME device based on miniscrews (miniscrew-assisted RME [MARME]) was introduced<sup>7</sup> and is based on previous findings that the true bony obliteration of the midpalatal suture in radiographs does not correlate with chronological age.<sup>8–10</sup> Lin et al.<sup>11</sup> reported that bone-anchored RME produced greater orthopedic effects and fewer dentoalveolar side effects compared with conventional RME in late adolescents. Taken together, it appeared crucial to incorporate bone anchorage to secure the expansion of the maxillary basal bone.

To date, most studies on maxillary expansion have focused on the initial expansion effects in adolescents. To determine the validity of bone anchorage, the clinical efficacy and stability in adults following expansion need to be evaluated. To our knowledge, few studies have investigated the success rate, posttreatment stability, and factors contributing to dental and skeletal post-expansion changes in adults who underwent maxillary expansion.

The aim of this study was to evaluate the long-term stability of MARME in young adults with a transverse maxillary deficiency. We also investigated the success rate of MARME in the study population and determined whether treatment changes were correlated with postexpansion changes during retention.

## MATERIALS AND METHODS

### Study Design and Subjects

This retrospective cohort study included 69 young adults with a transverse maxillary deficiency who underwent MARME between 2004 and 2010 at the Department of Orthodontics, Yonsei Dental Hospital, Seoul, Korea. The study protocol conformed to the Declaration of Helsinki and was approved by the Institutional Review Board of Yonsei Dental Hospital (IRB No. 2-2015-0028).

The inclusion criteria for this study were as follows: older than 18 years, maxillary constriction with unilateral or bilateral posterior crossbite, a maxillomandibular transverse discrepancy 5 mm greater than the normal value,<sup>12</sup> good oral hygiene, healthy periodontal tissues, no prior history of orthodontic treatment and/or orthognathic surgery, no severe dentofacial anomalies such as a cleft lip or palate, requirement for nonextraction treatment, and the availability of a complete series of identifiable posteroanterior (PA) cephalograms and dental casts, including the follow-up records (Figure 1).

Failure of maxillary expansion using MARME was defined when the midpalatal suture opening and

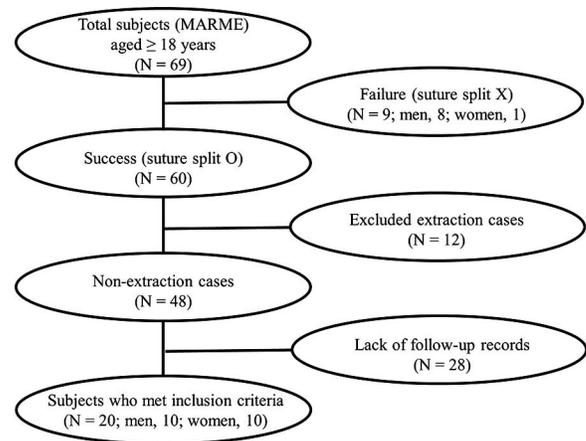


Figure 1. Study flow chart.

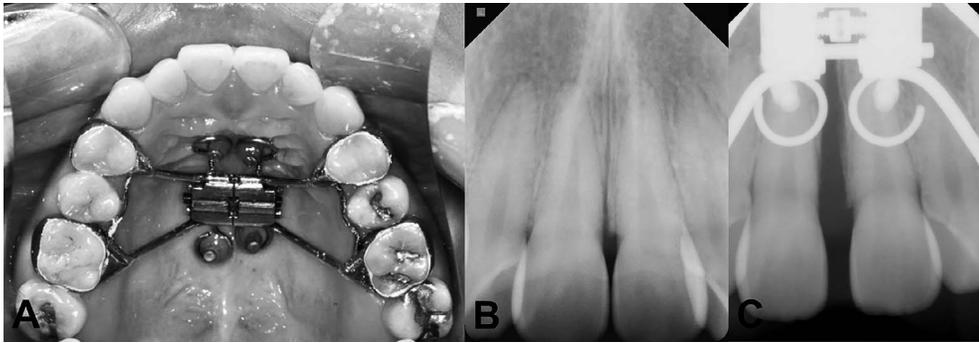
a diastema were not observed on periodic periapical radiographs up to 4 weeks after the initiation of maxillary expansion (Figure 2). Among the 69 patients, suture split was not observed in 9 patients; expansion was then discontinued, and the treatment plan was revised in these subjects.

Eventually, 20 patients (10 men and 10 women) who fulfilled the inclusion criteria were enrolled in the study (Table 1). The mean age at the start of expansion was  $20.9 \pm 2.9$  years (range, 18–28 years). The average period from the end of expansion to debonding was  $17.4 \pm 6.4$  months. The mean posttreatment duration was  $30.2 \pm 13.2$  months.

### Appliances and Orthodontic Treatment

All orthodontic treatments were performed by an orthodontist at the Department of Orthodontics, Yonsei Dental Hospital. As previously described, the MARME device is composed of four rigid stainless steel wire connectors with helical hooks soldered on the base of Hyrax screws (Figure 2).<sup>7</sup> Following MARME cementation, four miniscrews (diameter, 1.8 mm; length, 7.0 mm; self-drilled type, ORLUS, Ortholution, Seoul, Korea) were inserted perpendicular to the center of the helical hooks (diameter, 4.0 mm) under local infiltration anesthesia. The heads of the miniscrews were then attached to the hooks with light-cured resin (Transbond, 3M Unitek, St Paul, Minn) to minimize irritation of the tongue and increase the postinsertion stability of the miniscrews.

The MARME device was activated by one-quarter of a turn (0.2 mm) every other day (slow expansion) to minimize tissue damage, pain, and discomfort. The maxillary expansion was discontinued when the maxillary cusp of either maxillary first molar came in contact with the corresponding buccal cusp tips of the mandibular first molars. After active expansion, the MARME device was maintained for 3 months to allow



**Figure 2.** Fixation of the miniscrew-assisted rapid maxillary expansion (MARME) device and periapical views before and after expansion. (A) A MARME appliance. (B) Before expansion. (C) After 2 weeks of expansion, a diastema caused by splitting of the midpalatal suture can be observed.

bone formation in the separated maxillary suture. Subsequently, the patients underwent orthodontic treatment with a straight-wire appliance. After fixed orthodontic treatment, removable circumferential retainers were worn at night by all subjects during retention.

### Measurement Time Points

Dental casts and PA cephalograms (Cranex 3+ ceph, Soredex, Helsinki, Finland) were obtained before treatment (T0), immediately after MARME removal (T1), immediately after debonding (T2), and posttreatment (T3). To minimize positional errors caused by rotations through the transverse hinge axis, the PA cephalograms were obtained in the natural head position, with the vertical distance from the middle point of the ear rod of the X-ray machine to the exocanthus of the patient being identical at all time points, as previously described.<sup>13</sup>

### Cast and Cephalometric Analyses

On the PA cephalograms, nasal cavity width (N-N), maxillary width (J-J), and middle alveolus width (Ma-Ma) were digitized by using V-ceph 5.5 (Osstem, Seoul, Korea) by one observer who was blinded to the clinical

status of the patients (Table 2; Figure 3). All linear measurements were corrected for magnification using the scale in each cephalometric film. On the study casts, the width of the maxillary dental arch and the average clinical crown heights were measured. The change in crown height was used to measure the buccal attachment loss at different time points (T0, T2, and T3).

### Reliability

Reproducibility was determined by comparing measurements obtained from original examinations with those obtained from repeated examinations. All measurements were repeated by the same observer after 2 weeks. The method error was calculated by using the intraclass correlation coefficient, which was  $>0.95$  for all cephalometric and cast variables measured in this study.

### Statistical Analysis

All statistical analyses were performed with IBM SPSS software, version 21.0 (IBM Korea Inc, Seoul, Korea) for Windows. Based on the preliminary study, a minimum sample size of 10 was required (G\*Power 3, Dusseldorf, Germany) using a significance level of a  $P$  value less than .05, a power of 90%, and an effect size of 0.21 to detect differences in skeletal and dental changes at each time point using a repeated-measures analysis of variance (RMANOVA).

The Shapiro–Wilk test was used to verify the normality of the data distributions. Descriptive statistics, including means and standard deviations, were used to describe each variable analyzed in the study.

RMANOVA was used to evaluate treatment and posttreatment changes over time (T0, T1, T2, and T3). Since there were six  $t$  tests for skeletal and dental changes, the level of significance was corrected by using the Bonferroni correction ( $\alpha = .05/6$ ) to prevent type 1 error.

**Table 1.** Characteristics of Subjects<sup>a</sup>

	Total (N = 20)
Sex	
Men	10
Women	10
Age at treatment initiation, year	20.9 ± 2.9, (range, 18–28)
Time from end of expansion to debonding (T2–T1, months)	17.4 ± 6.4
Total treatment duration (T2–T0, months)	21.6 ± 6.4
Post-treatment duration (T3–T2, months)	30.2 ± 13.2

<sup>a</sup> Values are expressed as means ± standard deviations. T0 indicates at the initial examination; T1, immediately after MARME removal; T2, immediately after debonding; T3, at posttreatment.

**Table 2.** Definitions of the Parameters Measured in This Study

Parameter	Description
Nasal cavity width (N-N)	Linear distance (mm) between the left and right points at the lowest part of the maximum concavity of the piriform rim
Maxillary width (J-J)	Linear distance (mm) between the left and right jugula, with jugula defined as the point on the jugal process at the intersection between the outline of the maxillary tuberosity and the zygomatic process
Middle alveolus width (Ma-Ma)	Linear distance (mm) between the left and right points at the center of the maximum concavity of the maxillary alveolar bone
Inter canine width (ICW)	Linear distance (mm) between the cusp tips of the left and right maxillary canines
Interpremolar width (IPMW)	Linear distance (mm) between the mesial fossae of the left and right maxillary first premolars
Intermolar width (IMW)	Linear distance (mm) between the central fossae of the left and right maxillary first molars
Clinical crown height of the maxillary canine (CH3)	Linear distance (mm) of the maxillary canine from the cusp tip to the most apical point of the gingival margin
Clinical crown height of the maxillary first premolar (CH4)	Linear distance (mm) of the maxillary first premolar from the buccal cusp tip to the most apical point of the gingival margin
Clinical crown height of the maxillary first molar (CH6)	Linear distance (mm) of the maxillary first molar from the buccal groove to the most apical point of the gingival margin

Correlations among treatment (T1–T0) and post-expansion changes (T3–T1) and other variables were evaluated by using Pearson correlation coefficient. With regard to the strengths of the correlations,  $r > .40$  indicated a moderate-to-strong correlation, and  $r < .40$  indicated a weak correlation.

## RESULTS

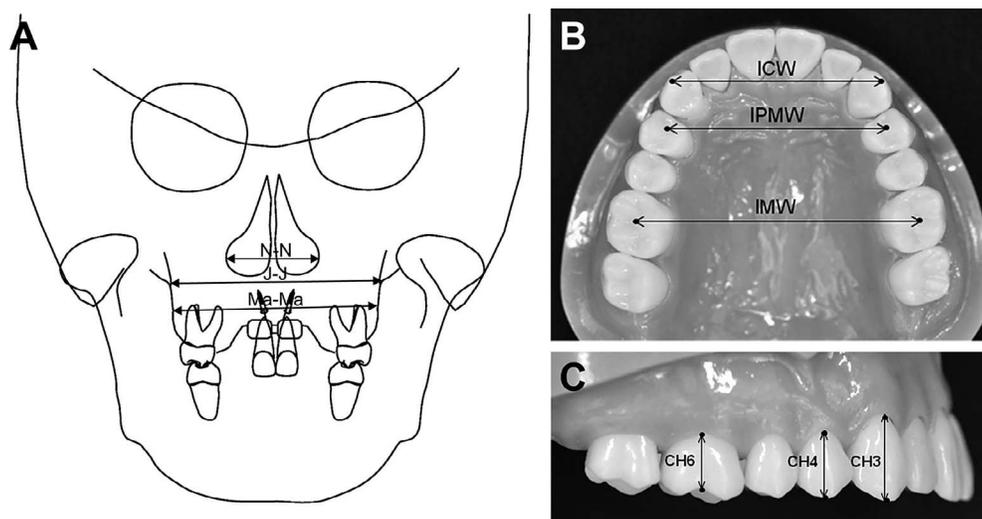
Among the 69 patients, nine (eight men and one woman; mean age,  $21.6 \pm 2.9$  years; range, 19–26 years) exhibited failure of maxillary expansion; therefore, the success rate of MARME was 86.96% in this study (Figure 1).

Immediately after MARME removal (T1), all skeletal and dental variables were larger at T1 than at T0

( $P < .001$ ; Table 3; Figure 4). The midpalatal suture opened in a triangular shape, with the smallest increase observed in N-N (1.07 mm) and the largest increase observed in intermolar width (IMW; 8.32 mm; Table 4). Expansion of IMW was 3.94 times greater than that of J-J (2.11 mm).

Immediately after debonding (T2), the change in all skeletal variables was negligible, averaging  $-0.24$  to  $-0.19$  mm (Table 4). However, greater postexpansion change was noted across the first molars ( $-3.89$  mm;  $P < .001$ ) at T2. An increase in J-J (1.92 mm) accounted for 43.34% of the total expansion with regard to IMW increase (4.43 mm;  $P < .001$ ; Figure 5) at T2.

After treatment (T3), none of the patients showed relapse of the posterior crossbite or edge-to-edge bite. Interpremolar width (IPMW) and IMW were smaller at



**Figure 3.** Skeletal and dental measurements. (A) N-N, nasal cavity width; J-J, maxillary width; Ma-Ma, middle alveolus width. (B) ICW, intercanine width; IPMW, interpremolar width; IMW, intermolar width; CH3, clinical crown height of the canine; CH4, clinical crown height of the first premolar; CH6, clinical crown height of the first molar.

**Table 3.** Mean and Standard Deviation of Skeletal and Dental Variables at Each Time Point<sup>a</sup>

Variable	T0	T1	T2	T3	P Value <sup>b</sup>
<b>Skeletal</b>					
N-N, mm	32.79 ± 2.01 <sup>1</sup>	33.86 ± 2.32 <sup>2</sup>	33.65 ± 2.34 <sup>2</sup>	33.58 ± 2.39 <sup>2</sup>	<.001
J-J, mm	72.89 ± 4.11 <sup>1</sup>	75.00 ± 4.20 <sup>2</sup>	74.82 ± 4.07 <sup>2</sup>	74.75 ± 4.08 <sup>2</sup>	<.001
Ma-Ma, mm	66.69 ± 4.89 <sup>1</sup>	68.94 ± 5.38 <sup>2</sup>	68.69 ± 5.29 <sup>2</sup>	68.64 ± 5.28 <sup>2</sup>	<.001
<b>Dental</b>					
ICW, mm	33.97 ± 1.60 <sup>1</sup>	36.83 ± 1.59 <sup>3</sup>	36.35 ± 1.57 <sup>2</sup>	36.26 ± 1.57 <sup>2</sup>	<.001
IPMW, mm	35.05 ± 1.14 <sup>1</sup>	41.14 ± 1.17 <sup>3</sup>	39.21 ± 1.19 <sup>2</sup>	38.82 ± 1.04 <sup>2</sup>	<.001
IMW, mm	46.94 ± 3.35 <sup>1</sup>	55.26 ± 3.21 <sup>4</sup>	51.36 ± 2.48 <sup>3</sup>	50.95 ± 2.65 <sup>2</sup>	<.001

<sup>a</sup> N-N indicates nasal cavity width; J-J, maxillary width; Ma-Ma, middle alveolus width; ICW, intercanine width; IPMW, interpremolar width; IMW, intermolar width; T0, at the initial examination; T1, immediately after MARME removal; T2, immediately after debonding; T3, at posttreatment. Increasing mean values are expressed in ascending numerical order.

<sup>b</sup> By repeated-measures analysis of variance with Bonferroni correction.

T3 than at T2, but the amount of decrease in the arch width was not clinically significant (approximately 0.4 mm; Table 4; Figure 5).

The postexpansion change in Ma-Ma increased with increasing age ( $r = -.597$ ;  $P < .05$ ; Table 5). As the amount of IPMW expansion increased, the amount of IPMW postexpansion change also increased ( $r = -.587$ ;  $P < .05$ ).

The measurements for the left and right clinical crown heights of each tooth were not significantly different and were pooled. The changes in clinical crown heights of canines (CH3), first premolars (CH4), and first molars (CH6) were not significantly different at each time point. The amount of gingival recession was not significant, averaging 0.57 mm to 0.86 mm at T3 (Figure 6).

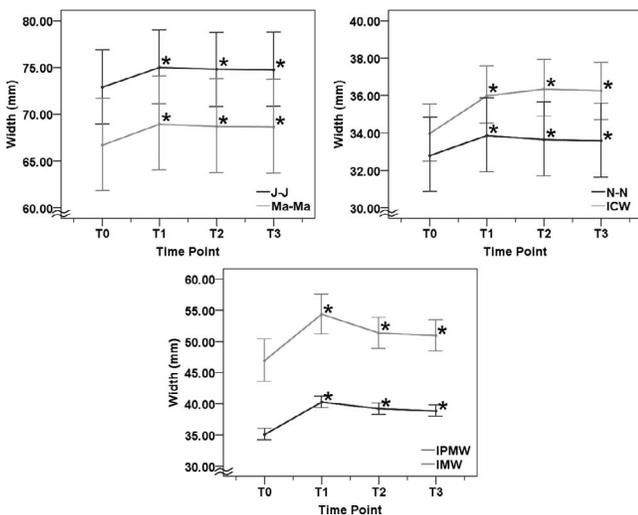
**DISCUSSION**

In using MARME, some clinical factors need to be considered. The first thing may be the success of miniscrews in this study. Among the 69 patients, 5.0% of the miniscrews dislodged during expansion and 13.0% showed clinically acceptable mobility (Periotest value [Siemens AG, Bensheim, Germany] <10),<sup>14</sup> while the rest remained stable until the retention period. If suture split was observed, even if one miniscrew at one side failed, the maxillary expansion was continued using the remaining miniscrews. The second factor is irritation of the maxillary mucosa by MARME. We can prevent mucosal swelling by accurate placement of the miniscrews and hooks, elaboration of appliance fabrication, and scrupulous oral hygiene maintenance, including copious saline irrigation followed by gingival massage.

Our study group comprised young adults with a mean chronological age of  $20.9 \pm 2.9$  years at the start of MARME treatment; the maturation stage was CVMI stage 6. Midline diastema and radiologic suture opening were observed in 86.96% of the patients (60/69; Figure 1). In contrast, nine patients exhibited failure of suture separation. Variations in suture obliteration and the resistance from craniofacial structures could be the reason for expansion failure in adults.<sup>7</sup>

Both IPMW and IMW increased significantly at T1 and subsequently decreased, following alignment and comprehensive orthodontic treatment at T2 (Table 4). Significant increases in N-N (0.86 mm), J-J (1.92 mm), and Ma-Ma (2.00 mm) accounted for 19.41%, 43.34%, and 45.15%, respectively, of the total expansion with regard to IMW (4.43 mm) at T2 (Figure 5). The measurements accounted for a triangular expansion, allowing greater buccal displacement of alveolar crestal area.<sup>15</sup> These results suggest that even a small amount of split of the suture (the upper part of the triangle) may be crucial to minimize the possible bony dehiscence related to expansion.

The clinical superiority of SARME over nonsurgical expansion RME has been controversial, possibly



**Figure 4.** Changes over time after MARME in the skeletal and dental measurements. N-N, nasal cavity width; J-J, maxillary width; Ma-Ma, middle alveolus width; ICW, intercanine width; IPMW, interpremolar width; IMW, intermolar width; T0, at the initial examination; T1, immediately after MARME removal; T2, immediately after debonding; T3, at posttreatment. An asterisk means that there was a significant difference between each time point and T0. Error bar, standard deviation.

**Table 4.** Effect of Time on Treatment and Posttreatment Changes After MARME Removal<sup>a</sup>

Variable	T1-T0			T2-T0			T3-T0		
	Difference	95% CI Min/Max	P Value <sup>b</sup>	Difference	95% CI Min/Max	P Value <sup>b</sup>	Difference	95% CI Min/Max	P Value <sup>a</sup>
<b>Skeletal</b>									
N-N, mm	1.07	0.63/1.51	<.001	0.86	0.42/1.29	.003	0.79	0.31/1.27	.016
J-J, mm	2.11	1.54/2.68	<.001	1.92	1.33/2.52	<.001	1.85	1.26/2.45	<.001
Ma-Ma, mm	2.24	1.59/2.90	<.001	2.00	1.37/2.63	<.001	1.95	1.34/2.57	<.001
<b>Dental</b>									
ICW, mm	2.86	2.07/3.64	<.001	2.38	1.59/3.16	<.001	2.29	1.50/3.08	<.001
IPMW, mm	6.09	5.37/6.81	<.001	4.16	3.44/4.88	<.001	3.77	3.14/4.40	<.001
IMW, mm	8.32	7.27/9.37	<.001	4.43	3.38/5.48	<.001	4.01	2.96/5.06	<.001

<sup>a</sup> N-N, nasal cavity width; J-J, maxillary width; Ma-Ma, middle alveolus width; ICW, intercanine width; IPMW, interpremolar width; IMW, intermolar width; T0, at the initial examination; T1, immediately after MARME removal; T2, immediately after debonding; T3, at posttreatment; CI, confidence interval; NS, not statistically significant.

<sup>b</sup> By repeated-measures analysis of variance with Bonferroni correction.

because of the lack of controlled study, especially in adults. Obviously, SARME can secure the basal bone expansion in most attempted cases. However, the amount of basal bone expansion and its stability in this study can be comparable to those of surgical expansion.<sup>16</sup> Further controlled studies are required among different treatment modalities.

There was a significant correlation between the amount of expansion and postexpansion change in the maxillary first premolar region (Table 5). The rigid structure of RMEs tends to induce parallel expansion of IMPW and IMW.<sup>17,18</sup> As a result, the premolars may be lingually relocated during alignment according to arch form. In addition, with increasing age, the amount of IPMW postexpansion change was large if the dentoalveolar changes were significant. With age, the rigidity of the craniofacial skeleton could limit skeletal effects of MARME.<sup>2,3</sup>

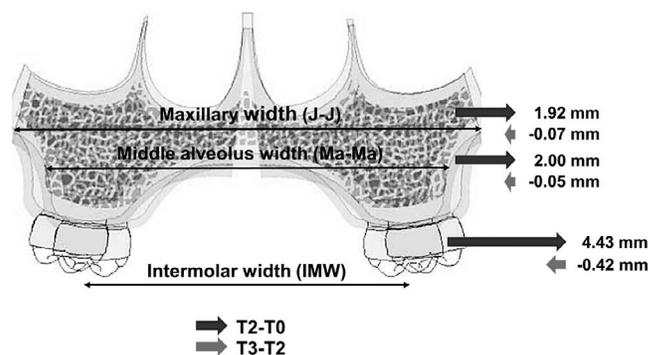
Handelman reported that the maxillary arch width could be maintained after debonding following conventional RME.<sup>19</sup> Nevertheless, previous studies have frequently warned of the risk of gingival recession and/or bony dehiscence caused by dentoalveolar expansion.<sup>3,12,20</sup> In contrast, clinical crown heights were not significantly different in the treatment and posttreatment periods in this study (Figure 6). Gingival recession of < 0.21 mm to 0.52 mm was not clinically significant during orthodontic treatment with MARME, which was in accordance with the findings of Lin et al.<sup>11</sup> Use of the miniscrew could distribute the stress throughout the palate, decreasing the concentration of the stress around the anchor teeth.<sup>17</sup>

To overcome the retrospective nature of this study, all attempted cases were collected and followed regardless of the treatment outcome. In addition, measurement of the clinical crown height is an indirect quantification of buccal attachment loss, which does

not directly reflect hard tissue attachment.<sup>19</sup> Although the PA cephalograms were obtained with calibration and standardization, projection errors may be unavoidable.<sup>21</sup> However, scanning voxel size and soft tissue condition can also affect the accuracy of the measurement from cone-beam computed tomography images.<sup>22</sup> To demonstrate the clinical efficacy of MARME compared with conventional RME or SARME, additional case-controlled studies are required.

## CONCLUSIONS

- Suture separation was observed in 86.96% subjects (60/69) in this study.
- Skeletal changes (about 2 mm) and dental changes (about 4 mm) remained stable during retention.
- Postexpansion change in the middle alveolus width was correlated with age. The postexpansion change in IPMW, but not IMW, was positively correlated with the amount of IPMW expansion.



**Figure 5.** Schematic diagram after MARME. T0, at the initial examination; T2, immediately after debonding; T3, at posttreatment.

**Table 4.** Extended

Difference	T2-T1		Difference	T3-T2	
	95% CI Min/Max	P Value <sup>b</sup>		95% CI Min/Max	P Value <sup>b</sup>
-0.21	-0.35/-0.08	NS	-0.07	-0.20/0.07	NS
-0.19	-0.38/0.00	NS	-0.07	-0.16/0.02	NS
-0.24	-0.43/-0.05	NS	-0.05	-0.19/0.09	NS
-0.48	-0.65/-0.31	.016	-0.09	-0.26/0.09	NS
-1.93	-2.56/-1.30	<.001	-0.39	-0.67/-0.11	NS
-3.89	-4.94/-2.84	<.001	-0.42	-0.67/-0.17	.01

**Table 5.** Correlations Among Treatment and Postexpansion Changes and Other Variables<sup>a</sup>

	Variable				
	J-J (T3-T1)	Ma-Ma (T3-T1)	ICW (T3-T1)	IPMW (T3-T1)	IMW (T3-T1)
Age	.250	-.597*	.197	.066	.240
Sex	.520	.174	-.082	.248	-.206
J-J (T1-T0)	-.491	-.524	.355	.438	.500
Ma-Ma (T1-T0)	-.127	-.169	.073	.027	.000
ICW (T1-T0)	-.473	-.141	.115	-.201	.159
IPMW (T1-T0)	-.227	-.305	.192	-.587*	-.049
IMW (T1-T0)	-.155	-.087	.099	-.118	-.082

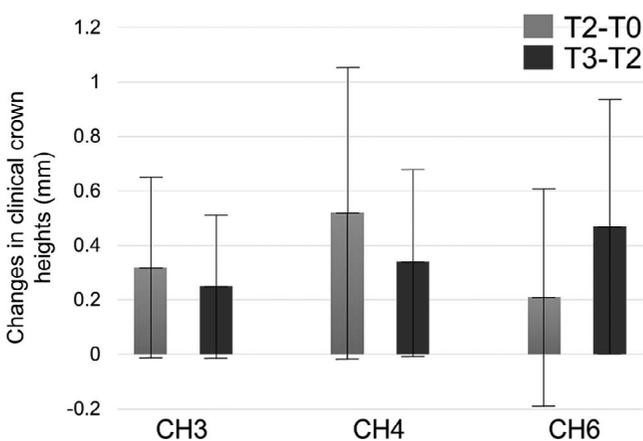
<sup>a</sup> J-J, maxillary width; Ma-Ma, middle alveolus width; ICW, intercanine width; IPMW, interpremolar width; IMW, intermolar width; T0, at the initial examination; T1, immediately after MARME removal; T3, at posttreatment. Sex (men, 0; women, 1).

\*  $P < .05$ .

- The clinical crown heights of the maxillary canines, first premolars, and first molars were not significantly different during retention.
- The amounts of skeletal and dental postexpansion changes were considered clinically acceptable, since none of the subjects presented obvious

dental posterior crossbite or edge-to-edge bite, respectively.

- These findings suggest that nonsurgical MARME can be a clinically acceptable and stable treatment modality for maxillary constriction in young adults.



**Figure 6.** Changes over time after MARME in the clinical crown heights of the canine (CH3), first premolar (CH4), and first molar (CH6). T0, at the initial examination; T2, immediately after debonding; T3, at posttreatment. The changes in clinical crown heights of canines (CH3), first premolars (CH4), and first molars (CH6) were not significantly different at each time point. Error bar, standard deviation.

**ACKNOWLEDGMENTS**

This research was supported by Basic Science Research Program Through the National Research Foundation of Korea(NRF) funded by the Ministry of Education, Science and Technology (2009-0075637).

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