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Randomized Controlled Trial

Nasal ventilation and rapid maxillary expansion (RME): a randomized trial

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Summary

Objective: To assess three rapid maxillary expansion (RME) appliances in nasal ventilation.
Trial design: Three-arm parallel randomized clinical trial.
Methods: Sixty-six growing subjects (10–16 years old) needing RME as part of their orthodontic treatment were randomly allocated (1:1:1 ratio) to three groups of 22 patients receiving Hyrax (H), Hybrid-Hyrax (HH), or Keles keyless expander (K). The primary outcome of nasal ventilation (pressure and velocity) and secondary outcomes (skeletal, dental, soft tissue, and nasal obstruction changes) were blindly assessed on the initial (T0) and final (T1, 6 months at appliance removal) cone-beam computed tomography (CBCT) data by applying computational fluid dynamics (CFD) method. Differences across groups were assessed with crude and adjusted for baseline values and confounders (gender, age, skeletal maturation, expansion amount, mucosal/adenoid hypertrophy, nasal septum deviation) regression models with alpha = 5%.
Results: Fifty-four patients were analysed (19H, 21HH, 14K). RME reduced both nasal pressure (H: –45.8%, HH: –75.5%, K: –63.2%) and velocity (H: –30%, HH: –58.5%, K: –35%) accompanied with nasal obstruction resolution (H: 26%, HH: 62%, K: 50%). Regressions accounting for baseline severity indicated HH expander performing better in terms of post-expansion maximum velocity ($P = 0.03$) and nasal obstruction resolution ($P = 0.04$), which was robust to confounders. Mucosal/adenoid hypertrophy and nasal septum deviation changes were variable, minimal, and similar across groups. The HH resulted in significantly greater increase in the nasal cross-sectional area (62.3%), anterior (14.6%), and posterior (10.5%) nasal widths. Nasal obstruction resolution was more probable among younger ($P = 0.04$), skeletally immature ($P = 0.03$), and male patients ($P = 0.02$) without pre-treatment mucosal hypertrophy ($P = 0.04$), while HH was associated with marginal greater probability for obstruction resolution.
Conclusions: RME resulted in improvement of nasal skeletal parameters and simulated ventilation with the former being in favour of the HH and the latter not showing significant differences among the three appliances.
Limitation: Attrition in the K group due to blocked activation rods possibly leading to limited sample to identify any existing group differences.

Harms: Replacement of blocked Keles expanders for finalizing treatment.
Protocol: The protocol was not published before the trial commencement.
Registration: Australian and New Zealand Clinical Trial Registry; ACTRN12617001136392.

Introduction

Rapid maxillary expansion (RME) is a well-established method to address maxillary skeletal and dental constriction while also being advocated as an effective means to alleviate nasal airway obstruction by improving airflow ventilation parameters (1–3). RME, with or without additional surgical assistance, could potentially lead to transition from mouth to nasal breathing, promote favourable pharyngeal adaptations and subsequently reduce negative pressure, improve head and tongue posture, and serve as adjunctive procedure in obstructive sleep apnoea (OSA) patients with concomitant transversally constricted maxilla and posterior dental crossbites (4–7).

Various types of RME appliances exist with a different design. Conventional tooth-anchored expanders increase intermolar and nasal width, nasal volume, and minimal cross-sectional area (minCSA) in similar ways (8–10). Hybrid expanders anchored on both teeth and temporary anchorage devices were introduced to enhance the skeletal effects of RME and reduce the load to anchor teeth by delivering the expansion forces closer to the centre of resistance of the nasomaxillary complex via palatal mini-implants (11, 12). Short-term rhinomanometric comparisons, before and immediately after expansion, of tooth-anchored versus hybrid expanders, showed higher nasal airflow values and greater reduction of nasal airflow resistance for hybrid designs (13). RME induces stable increases in nasal cavity volume (14); however, either purely bone-anchored or hybrid expanders seem to outperform conventional tooth-anchored devices in sutural opening, minimization of dental side-effects, and improved nasal airway resistance (15).

Anteroposterior cephalograms (9), cone-beam computed tomography (CBCT) (2, 8), and acoustic rhinometry (AR) (1, 10, 16) have been traditionally used for nasal airway assessment. Radiographic methods evaluate the size (width diameter, CSA, volume) and form without providing extensive information relevant to ventilation functional parameters with CBCT having been found as accurate as AR in measuring anterior nasal volume, nasal minimal CSA, pharyngeal volume, and pharyngeal minimal CSA (17). Computational fluid dynamics (CFD) have been used as a method to estimate functional parameters of nasal airflow meaning the pressure developed on the walls of the airway and the velocity of air during its flow within the anatomic areas of interest (3, 7). A three-dimensional (3D) model of the airway is built from CBCT data and CFD simulate airflow to a breathing state evaluating not only ventilation condition of the upper airway and its compartments but also adenoids, soft palate, and palatine tonsils.

The aim of this trial was to assess changes in nasal ventilation parameters induced by RME with conventional tooth-borne (Hyrax), tooth-bone-borne (Hybrid-Hyrax), and the Keles keyless expander using CBCT data and CFD.

Materials and methods

Trial design and any changes after trial commencement

This was a single-centre, three-arm parallel randomized clinical trial (RCT) with a 1:1:1 allocation ratio. The trial was registered at Australian and New Zealand Clinical Trial Registry (ACTRN12617001136392). Ethics approval was obtained from the Sydney Local Health District RPAH Zone (X17-0075).

Participants, eligibility criteria, and settings

Sixty-six growing healthy patients (10–16 years of age) were recruited from the orthodontic waiting list of Sydney Dental Hospital from January to July 2017. Eligibility criteria: unilateral or bilateral posterior crossbite; maxillary transverse deficiency (distance from the palatal cusp of the first permanent maxillary molars being more than 5 mm less than the distance of the central grooves of the mandibular first permanent molars measured clinically); maxillary first permanent molars and premolars present; appropriate oral hygiene; no previous orthodontic treatment; no syndromes or other craniofacial defects. Written informed consent was obtained from the patients' parents/guardians.

Interventions

Participants were randomly assigned to a Hyrax, Hybrid-Hyrax, or Keles keyless expander. Conventional orthodontic diagnostic records (study models, extra-oral and intra-oral photos) and initial CBCT data were collected at baseline (T0). Bands were fitted on maxillary permanent molars and premolars for the Hyrax and Keles groups. Hybrid-Hyrax group received bands only on the first maxillary permanent molars and 2 Benefit mini-implants (9 × 2 mm) (PSM Medical Solutions, Tuttlingen, Germany) bilateral to the mid-palatal suture, at the level of the third palatal rugae. Appliances in the Hyrax and Hybrid-Hyrax groups were constructed by soldering a conventional activation screw (Hyrax, Dentaurum, Ispringen, Germany) while the Keles group had the keyless expander screw (Keles, Istanbul, Turkey). Glass ionomer cement (Unitek™ Multi-Cure Glass Ionomer Orthodontic Band Cement, 3M Oral Care, Maplewood, MN, USA) was used for cementation. Activation protocol was 2 turns/day (total 0.5 mm) with weekly follow-up appointments until posterior crossbite overcorrection (palatal cusps of the maxillary first molars being in contact with the buccal cusps of the mandibular first molars) to account for post-expansion relapse. Expanders were left in place as retention devices, without additional orthodontic treatment, for 6 months while after their removal a second CBCT (T1) was taken. Patients were placed in the tomograph (NewTom 5G, Cone Beam 3D Imaging, Verona, Italy) in supine position with the Frankfort horizontal plane perpendicular to the floor and instructed to remain still after expiration, not to swallow or move, keep teeth in centric occlusion with perioral soft tissues and tongue at rest. Settings of the imaging system were 110 kV, 20 mAs, field-of-view 18 × 16 cm, 0.3 mm voxel size, and 3.6 sec/section.

Outcomes (primary and secondary) and any changes after trial commencement

Primary outcome was the treatment-induced changes in the nasal airway ventilation (pressure and velocity) using CFD from reconstructed CBCT data. Secondary outcomes were skeletal, dental, and soft tissue changes.

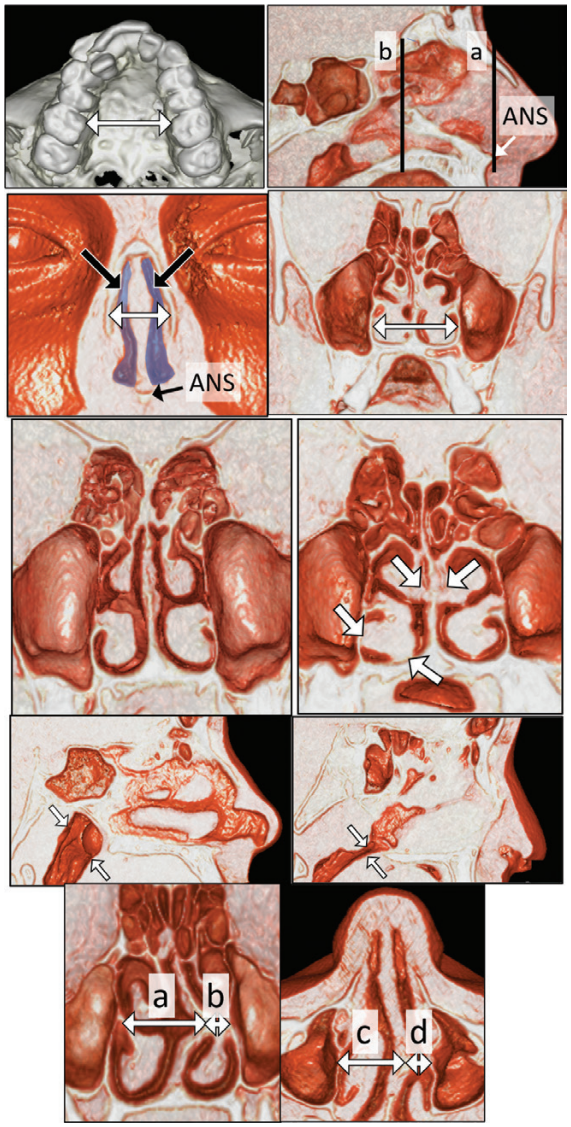

Figure 1. *First row.* Left: Intermaxillary molar width measured as the distance between the most medial points of the constricted part of the maxillary first molars. Right: Anteroposterior levels of anterior nasal width measurement at anterior nasal spine-ANS (a) and posterior nasal width measurement first molars (b). *Second row.* Left: Nasal width as widest part of the nasal aperture (white arrow) and nasal cross-sectional area (CSA) (black arrows, grey area) at ANS plane. Right: Nasal width as widest part of the nasal aperture (white arrow) at frontal maxillary molar plane. *Third row.* Evaluation of nasal airway mucosa hypertrophy. Left: Normal case without nasal mucosa hypertrophy and no collapsed part. Right: case with nasal mucosa hypertrophy. Due to mucosa hypertrophy, nasal airway collapsed (white arrows). *Fourth row.* Measurement of relative adenoid size at midsagittal plane as the distance from the posterior outline of the soft palate to the closest point on the adenoid tissue (white arrows). Left: Case without adenoid hypertrophy (16 mm). Right: Case with adenoid hypertrophy (4 mm, white arrows). *Fifth row.* Measurement of nasal septum deviation (NSD). Case with NSD in frontal (left) and transversal (right) views. The difference between right (a, c) and left (b, d) nasal chamber widths was calculated. Nasal chamber widths were measured as the distance from the nasal septum to the lateral nasal wall in coronal and transverse sections at the level of maximal nasal septum deviation.

Volume-rendering software (INTAGE Volume Editor; Cybernet, Tokyo, Japan) was used to manually create 3D volumes (Figure 1). A medical image analysing system (ImagnosisVE, Imagnosis, Kobe, Japan) was implemented to construct a 3D-coordinate system and 3D images to perform measurements (3, 7). Skeletal, dental, and soft-tissue measurements were nasal CSA at the level of the anterior nasal spine (ANS), anterior and posterior nasal widths at the levels of the ANS and the first maxillary molars, respectively, nasal obstruction, intermolar width (IMW) at first molars as the narrowest distance between them, mucosal and adenoid hypertrophy and nasal septum deviation (NSD). Mucosal hypertrophy was assessed in the frontal plane and the nasal cavity was reviewed for any abnormal presence of mucosal thickening. The enlargement of the adenoids was evaluated by measuring the distance from the posterior outline of the soft palate to the closest point of the adenoid tissue in the midsagittal plane. Adenoids were considered hypertrophic when this distance was 5 mm or less. NSD was considered present when the difference between the right and the nasal chamber widths in the coronal and transverse sections at the level of maximal NSD was more than 4 mm (18, 19) (Figure 2; details of Supplement 1).

The 3D nasal airway was generated from the CBCT data by volume-rendering software (INTAGE Volume Editor; Cybernet Systems, Tokyo, Japan) (18). The nasal airway was segmented primarily on the basis of image intensity with the threshold set midway between the soft tissue and clear airway value. We standardized the threshold of the nasal airway model such that nasal airway resistance obtained from CFD corresponded to rhinomanometry (RM) nasal airway resistance. Subsequently, using mesh-morphing software (DEP MeshWorks/Morpher; IDAJ, Kobe, Japan), the 3D model was converted to a smoothed model without losing the patient-specific pattern of the airway shape. The models were exported to CFD software (Phoenics; CHAM Japan, Tokyo, Japan) in stereolithographic format. CFD of the nasal airway models was analysed under the following conditions: (1) the volume of air was flowing at a velocity of 500 cm^3/s, (2) the wall surface was not slippery, and (3) the simulations were repeated 1000 times to calculate mean values. The simulation estimated airflow pressure, where air flowed from the choanae horizontally and was exhaled through both external nares. The nasal airway resistance model was then conformed to nasal RM and calculated from air mass flow with the difference in pressure between external nares and choanae according to Ohm's law (18). In the present study, cases with nasal obstruction were defined as these that their measured pressure to the standard airflow (500 ml/seconds) resulted in ratio values for nasal airflow resistance greater than 0.3 Pa/ml/seconds.

Outcomes were assessed against confounders such as their baseline values, age, gender, amount of expansion (days kept by patients in calendars), and cervical vertebrae maturation (CVM) stage.

Error measurement

Ten patients (20%) were randomly selected and re-measured after 2 months. This included repeating all procedures meaning re-segmentation, landmarking, and measurements. The Dahlberg error, concordance correlation coefficient (20), and Bland–Altman method (21) were used to test intra-examiner reliability/agreement.

Sample size calculations

Sample size calculation was based on data from a previous study using similar methods to evaluate nasal ventilation changes after RME with the Hyrax appliance (3). The means and standard deviations of pre- (147.70 ± 94.87) and post- (80.55 ± 76.59) RME pressures, with $\alpha = 0.05$ and a power of 80% in a two-sided paired *t*-test indicated 16 patients in order to detect significant changes due to

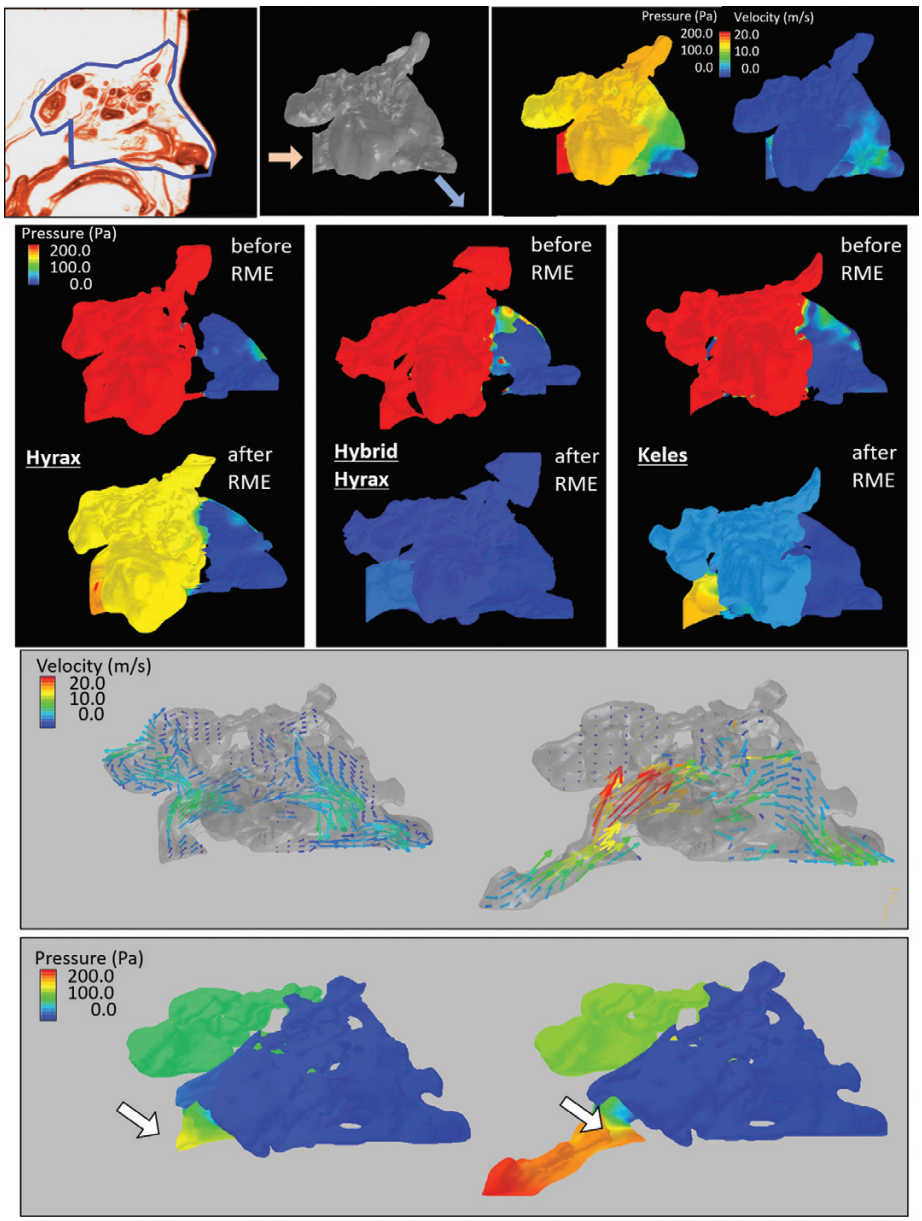

Figure 2. *First row.* Evaluation of nasal airway ventilation via computational fluid dynamics (CFD). Left: Extraction of the nasal airway. Middle (grey): Volume-rendering and numeric simulation (orange arrow, inlet airflow; light blue arrow, outlet airflow). Right: Evaluation of nasal airway ventilation (left, pressure; right, velocity). Maximum pressure and velocity were measured. *Second and third rows.* The difference of improvement effects of nasal airway ventilation condition by RME (second row; before expansion, third row; after expansion). A: Hyrax. B: Hybrid-Hyrax. C: Keles keyless expander. Before RME, all groups showed increased pressure while all groups showed improvements after RME. Hybrid-Hyrax shows greater reduction in pressure and subsequent improvement in obstructions. *Fourth row.* Nasal airway ventilation (airflow velocity) without and with adenoid hypertrophy. Left: Model without adenoids. Airflow was relatively slow in all parts. Right: Model with adenoids. Airflow showed a faster part (red arrow and yellow arrow) and slow part. *Fifth row.* Nasal airway ventilation condition (pressure) without and with adenoid hypertrophy. Left: Model without adenoids. Pressure was relatively low at choana (white arrow). Right: Model with adenoids. Pressure was large at choana (white arrow).

RME. Twenty-two patients were assigned to each group to account for dropouts or any issues pertinent to CBCT quality.

Randomization (random number generation, allocation concealment, implementation)

Randomization sequence was performed using the 'RANDBETWEEN' command in Excel 2016 software (Microsoft, Washington), to create three groups of 22 patients each. Allocation concealment with separate sealed and opaque envelopes was kept by a staff member at the Sydney Dental Hospital, independent to the treating clinicians.

Blinding

Blinding to the intervention was not possible for treating clinicians and patients. CBCT datasets were de-identified and coded. Assessors performing CFD measurements and statistical analyses were blinded. Codes were kept by staff not involved in all above processes and were broken after completing the statistical analyses.

Statistical analysis

After normality check, descriptive statistics were calculated and crude differences across groups were assessed with Fisher's exact test

or linear regression (after data transformations, when needed), followed by *post hoc* comparisons (details of Supplement 2). Adjusted regressions were run to control for potential confounders, which were selected with a 10% change-in-estimate approach. *Post hoc* prediction of nasal obstruction resolution (among patients with baseline obstruction) was done with multivariable regularized logistic regression with rigorous penalization. All analyses were run in StataSE 13.0 (StataCorp, College Station, TX) with a two-sided alpha of 5% and an open dataset available through Zenodo (22).

Results

Participant flow, numbers analysed, and baseline data

Sixty-six eligible for RME patients were recruited between January and July 2017 and randomized in a 1:1:1 ratio to Hyrax, Hybrid-Hyrax, or Keles expander (Figure 3). Considerable attrition (n = 8) in the Keles group was noted due to appliance blockage, which did not allow further expansion, and mandated expander replacement. Moreover, 2 CBCTs in the Hyrax and 1 CBCT in the Hybrid-Hyrax were excluded due to poor quality. Baseline characteristics of the 54 ultimately analysed patients (19 Hyrax, 21 Hybrid-Hyrax, 14 Keles expander) are given in Supplementary Table 1.

Measurement error

Dahlberg error was minimal for all variables, while the concordance correlation coefficient and the Bland–Altman method indicated excellent intra-examiner reliability and agreement (Supplementary Table 2).

Primary and secondary outcomes

Table 1 shows the changes in the 3 expanders for nasal ventilation. Pressure drop from baseline was greatest with Hybrid-Hyrax (−75.5%), followed by Keles (−62.3%), and Hyrax expander (−45.8%). Similar trend was noted for velocity, which dropped by −58.5%, −35.0%, and −30.0% in the corresponding groups; both across-groups differences were not statistically significant (P = 0.17 and P = 0.08, respectively).

Skeletal, dental, and obstruction parameters are given in Table 1. Total nasal CSA increased by 62.3%, 52.9%, and 35.6% in the Hybrid-Hyrax, Keles, and Hyrax groups, respectively (P = 0.009). *Post hoc* comparisons (Supplementary Table 3) indicated that Hybrid-Hyrax and Keles performed similarly (P = 0.40) and both increased nasal CSA more than Hyrax. Likewise, significant differences (P = 0.005) in anterior nasal width increase at ANS were seen among Hybrid-Hyrax (14.6%), Hyrax (10.7%), and Keles (9.3%), where *post hoc* comparisons showed that the Hybrid-Hyrax induced changes significantly greater to both tooth-borne expanders, which performed similarly (P = 0.55) (Supplementary Table 3). This was also the case for posterior nasal width change at the level of first molars (P < 0.001), where Hybrid-Hyrax induced greater increase of 10.5% than both Hyrax (8.2%) and Keles (6.8%) (Table 1 and Supplementary Table 3). Nasal obstruction was seen in 81% of included patients and an obstruction resolution was noted in 62%, 50%, and 26% of the Hybrid-Hyrax, Keles, and Hyrax groups,

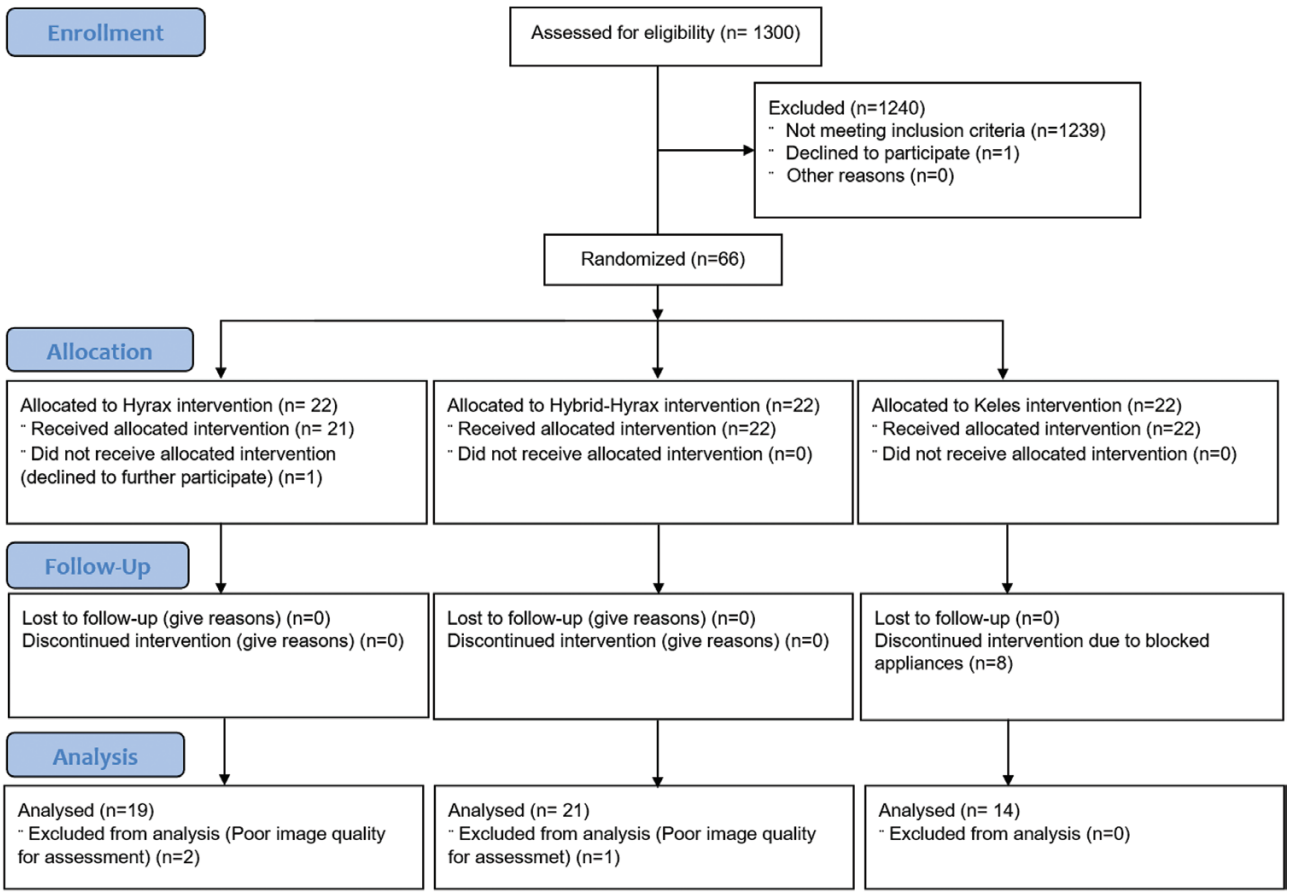

Figure 3. CONSORT flow diagram.

Table 1. Effect of treatment on nasal airway, nasal skeletal, and dental characteristics.

Variable	Data	Hyrax (n = 19)	Hybrid-Hyrax (n = 21)	Keles (n = 14)	P
Pressure pre-RME (Pa)	Median (IQR)	227.0 (139.0, 502.9)	417.0 (384.7, 642.0)	284.0 (158.0, 429.0)	
Pressure post-RME (Pa)	Median (IQR)	136.0 (70.0, 325.0)	99.0 (65.0, 160.0)	90.8 (68.4, 229.8)	0.17*
Pressure % change	Median	−45.8%	−75.5%	−62.3%	
Velocity pre-RME (m/s)	Median (IQR)	25.0 (16.0, 35.6)	32.5 (24.1, 36.6)	22.0 (16.0, 27.0)	
Velocity post-RME (m/s)	Median (IQR)	17.0 (9.1, 27.5)	10.8 (8.0, 15.0)	11.5 (8.6, 22.3)	0.08**
Velocity % change	Median	−30.0%	−58.5%	−35.0%	
CSA right pre-RME (mm^2)	Mean (SD)	74.6 (23.4)	62.7 (22.4)	73.7 (23.2)	
CSA left pre-RME (mm^2)	Mean (SD)	79.3 (26.1)	69.0 (19.4)	74.5 (24.2)	
CSA total pre-RME (mm^2)	Mean (SD)	153.9 (37.0)	131.7 (33.0)	146.8 (31.4)	
CSA right post-RME (mm^2)	Mean (SD)	92.9 (23.3)	93.7 (25.6)	101.6 (25.7)	
CSA left post-RME (mm^2)	Mean (SD)	96.5 (26.9)	100.3 (23.9)	98.0 (16.8)	
CSA total post-RME (mm^2)	Mean (SD)	189.5 (29.5)	194.0 (38.6)	200.0 (32.5)	0.009***
CSA total % change	Mean	+35.6%	+62.3%	+52.9%	
Nasal width (ANS) pre-RME (mm)	Mean (SD)	22.3 (1.8)	23.5 (1.4)	22.8 (1.5)	
Nasal width (ANS) post-RME (mm)	Mean (SD)	24.7 (2.3)	26.9 (1.7)	24.9 (1.6)	0.005***
Nasal width (ANS) % change	Mean	+10.7%	+14.6%	+9.3%	
Nasal width (M1) pre-RME (mm)	Mean (SD)	30.8 (3.3)	31.3 (2.5)	31.1 (1.9)	
Nasal width (M1) post-RME (mm)	Mean (SD)	33.2 (3.1)	34.7 (2.1)	33.2 (2.4)	<0.001***
Nasal width (M1) % change	Mean	+8.2%	+10.5%	+6.8%	
Nasal width ratio pre	Mean (SD)	0.73 (0.07)	0.75 (0.05)	0.74 (0.05)	
Nasal width ratio post	Mean (SD)	0.74 (0.07)	0.78 (0.05)	0.75 (0.04)	0.27***
Nasal width ratio % change	Mean	+2.4%	+3.3%	+2.3%	
Nasal obstruction pre-RME (Pa/500 ml/s)	n (%)	14 (74%)	19 (90%)	11 (79%)	
Nasal obstruction post-RME (Pa/500 ml/s)	n (%)	9 (47%)	6 (29%)	4 (29%)	
Nasal obstruction resolution	n (%)	5 (26%)	13 (62%)	7 (50%)	0.08****
IMW pre-RME (mm)	Mean (SD)	31.2 (3.6)	30.9 (2.8)	31.3 (1.7)	
IMW post-RME (mm)	Mean (SD)	38.6 (3.4)	38.1 (2.5)	37.9 (1.6)	0.25***
IMW % change	Mean	+24.0%	+23.7%	+21.3%	

RME: rapid maxillary expansion; CSA, cross-sectional area; IMW, intermolar width; IQR, interquartile range; M1; first permanent molar; ANS, anterior nasal spine; SD, standard deviation.

Nasal obstruction is calculated by dividing pressure (Pa) by nasal airflow (ml/s) set at 500 ml/s.

*From regression on transformed (inverse square root) post-treatment value with transformed (log) pre-treatment values as covariate.

**From regression on transformed (inverse) post-treatment value with transformed (log) pre-treatment values as covariate.

***From linear regression on post-treatment value with pre-treatment value as covariate.

****From Fisher's exact test.

respectively, with no statistically significant differences (P = 0.08). Similarly, no statistically significant differences were seen across groups regarding IMW, mucosal or adenoid hypertrophy, and nasal-septum deviation changes (Table 1, Supplementary Table 4).

Adjusted-for-confounders (Supplementary Table 5) models for the primary outcomes and nasal obstruction resolution of all patients gave relatively similar results with the crude models (Table 2), with small variations in effect sizes. Both for maximum velocity and obstruction resolution the Hybrid-Hyrax outperformed the Hyrax expander. This effect remained even after adjusting for possible confounders (age, gender, amount of expansion, mucosal hypertrophy, and CVM stage) (Table 2, Figure 2). Multivariable logistic regressions on nasal obstruction resolution only among patients with pre-existing obstruction at baseline resulted in two models (Supplementary Table 6), with the second model using optimal cut-offs for baseline nasal width and maximum pressure fitting better to the data (sensitivity 92.0%, specificity 84.2%, and correct classification for 88.6% of the cases). Based on this model, the odds for resolution of a pre-existing nasal obstruction were significantly higher in the Hybrid-Hyrax compared to the Hyrax group. Additionally, the odds of obstruction resolution were significantly higher for male patients, patients without baseline mucosa hypertrophy, patients with baseline nasal width at ANS ≥24.0 mm, and patients with baseline maximum pressure of ≤490 Pa (Supplementary Table 6).

Harms

In the Keles expander group, activation rod blockage necessitated replacement of the failed devices by conventional Hyrax expanders the same day for assurance of best patient care. Patients of the Keles group, who continued and were assessed in the study, experienced excessive tipping of the anchor teeth, which did not allow for overcorrection of the posterior crossbite leading to less amount of expansion in this group.

Discussion

The present trial assessed the effect of three RME designs on nasal ventilation and the skeletal/dental structures. RME not only expands the two maxillary skeletal halves and the dentition but also increases nasal volume in growing patients (14). The effects of RME on nasal cavity have been assessed using CBCT (23), AR (2, 10), and posteroanterior cephalograms (8, 9). Hyrax and Hass RME anchored to permanent or deciduous teeth increases nasal floor and wall widths similarly in younger (8) and older growing patients (2). Sökücü et al. (10) compared nasal dimensional changes by AR

Table 2. Crude (univariable) and adjusted (multivariable) regression on the nasal airway pressure and velocity and resolution of nasal obstruction.

		Maximum pressure (Pa)		Maximum velocity (m/s)		Nasal obstruction (Pa/500 ml/s)	
Analysis adjusting for	Category	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*	Relative risk (95% CI)	*P*
- (Unadjusted)	Hyrax	Reference		Reference		Reference	
	Hybrid-Hyrax	0.02 (0, 0.05)	0.07	0.03 (0, 0.06)	0.03	2.4 (1.0, 5.4)	0.04
	Keles	0.02 (−0.01, 0.04	0.21	0.02 (−0.01, 0.05)	0.23	1.9 (0.8, 4.8)	0.17
Age (years)	Hyrax	Reference		Reference		Reference	
	Hybrid-Hyrax	0.02 (0, 0.05)	0.06	0.04 (0.01, 0.06)	0.008	2.4 (1.0, 5.4)	0.04
	Keles	0.02 (−0.01, 0.05)	0.19	0.02 (−0.01, 0.05)	0.12	2.0 (0.8, 4.9)	0.15
Male	Hyrax	Reference		Reference		Reference	
	Hybrid-Hyrax	0.02 (0, 0.05)	0.07	NT		2.5 (1.2, 5.4)	0.02
	Keles	0.02 (−0.01, 0.05)	0.21	NT		2.2 (0.9, 5.2)	0.08
Expansion (mm)	Hyrax	Reference		Reference		Reference	
	Hybrid-Hyrax	0.02 (0, 0.05)	0.09	0.03 (0, 0.06)	0.03	2.2 (1.0, 5.1)	0.06
	Keles	0.02 (−0.01, 0.05)	0.12	0.02 (−0.01, 0.05)	0.17	2.0 (0.8, 5.2)	0.13
Mucosal hypertrophy	Hyrax	Reference		Reference		Reference	
	Hybrid-Hyrax	0.02 (0, 0.0.5)	0.11	0.03 (0, 0.05)	0.02	2.3 (1.0, 5.3)	0.04
	Keles	0.01 (−0.01, 0.04)	0.38	0.01 (−0.02, 0.04)	0.44	1.8 (0.7, 5.3)	0.23
Adenoid hypertrophy	Hyrax	Reference		Reference		Reference	
	Hybrid-Hyrax	0.02 (0, 0.05)	0.12	NT		NT	
	Keles	0.01 (−0.01, 0.04)	0.28	NT		NT	
CVM (stages 1–6)	Hyrax	NT		NT		Reference	
	Hybrid-Hyrax	NT		NT		2.5 (1.1, 5.7)	0.03
	Keles	NT		NT		2.1 (0.8, 5.1)	0.13

All models are based on the post-treatment value with the pre-treatment as covariate (all transformed to normality).
CI, confidence interval; CVM, cervical vertebrae maturation; NT, not tested.
Nasal obstruction is calculated by dividing pressure (Pa) by nasal airflow (ml/s) set at 500 ml/s.

following RME with acrylic-bonded full tooth-tissue-borne appliances with either Hyrax or fan-type screws and found that immediately post-RME nasal volume and min-CSA increases did not differ across groups; however, the results obtained by the Hyrax were more stable 6-month post-RME. In the present study, the Hybrid-Hyrax increased nasal widths (anterior and posterior) and CSA significantly more compared to tooth-anchored expanders. Anatomic dimensional changes though cannot be directly extrapolated to changes in nasal airway ventilation conditions. In the present study, CFD analysis showed significant pressure and velocity reductions with changes being incrementally greater to the two-dimensional anatomic improvements. More specifically, 7–15% increase in nasal width resulted to 45–75% reduction in pressure and 30–58% reduction in velocity. Crude analyses showed a trend to greater effects by the Hybrid-Hyrax design without significant differences across groups.

A debate exists regarding possible extended RME effects in terms of improved breathing functional parameters. Previous studies have investigated nasal resistance alterations from Haas-RME at baseline, immediately and 90-day post-expansion using AR, rhinomanometry, and nasofibroscopy for diagnosing concurrent pathologies (turbinates and adenoids hypertrophy and septal deviations). One study (1) using acoustic RM found that even though min-CSA was not substantially improved after Haas-RME, mean inspiration and expiration resistance gradually reduced and reached statistical significance after 90 days of follow-up. Similar findings of post-expansion improvement in nasal flow and resistance were reported on 5- to 10-year-old children with nasal obstructions (24). On the other side, another study (13) reported that considerable post-expansion improvement in increased nasal airflow and reduced nasal resistance were seen only with Hybrid-Hyrax, but not regular Hyrax RME. This is in agreement with our findings on better post-treatment values in the Hybrid-Hyrax for reducing maximum velocity, which translates into improved airflow, and nasal obstruction resolution taking baseline values as covariate. Even after adjusting for possible confounders, the effect remained stable and in favour of the Hybrid-Hyrax, indicating that differences could most probably be attributed to the device's design transferring expansion stresses to maxillary sutures rather than teeth (25). A recent meta-analysis (26) found statistically significant decreases in nasal resistance (0.12 Pa s/cm^3) and increases in airflow (29.9 cm^3/s) after RME in children, but these gains were not wholly retained when limiting results to controlled studies, and the included studies were in high risk of bias. Furthermore, these changes might not be necessarily maintained 30 months post-RME, (27). Inflammatory, anatomic, and physiologic factors contribute to the aetiology of nasal obstructions (28). From the perspective of oto-rhino-laryngologists, addressing pathologic conditions is of primary importance (26), which aligns to the position paper developed by orthodontic experts on sleep apnoea (29). These findings corroborate our results because within the total sample 80% presented with nasal obstructions baseline and 35% post-RME, showing that not all cases resolved. According to the literature, this could be attributed to pre-existing factors, which were beyond RME's capacity to resolve, irrespective to expander type. This was also reflected to our findings of RME not exerting any critical effects in neither mucosal and/or adenoid hypertrophy nor NSD.

Contrary to average AR changes measured post-expansion that remain stable for at least 9–12 months, RME patients report subjectively improved nasal breathing in only about 60% of the times (15, 2). These findings might indicate that not all cases react similarly to RME and patient-specific (complicated nasal airway form, nasal mucosa hypertrophy, adenoids, and NSD) or treatment-specific

parameters (expander design, expansion amount, age, skeletal maturation, activation protocol, retention period, evaluation method) might account as contributing factors to the unpredictability of each patient's response to RME (30).

In the present study, CFD were used to investigate the interrelations of RME effects in nasal morphology and nasal functional dynamics. Several methods have been developed to either evaluate the subjective perception or objectively measure breathing capacity. The European Position Paper on Diagnostic Tools in Rhinology exhaustively updated the methods used for nasal obstruction diagnosis including subjective patient-reported outcome measure questionnaires (NOSE scale); clinical subjective tests (clinical examination, nasendoscopy, and imaging); and objective tests such as peak nasal inspiratory flow, RM, and AR (31). However, the lack of strong correlations among subjective and objective diagnostic methods mandates the implementation of collective approaches and differential diagnosis for comprehensive, evidence-based care addressing the actual aetiology in patients with sinonasal conditions (31, 32). AR is one of the commonly used methods to objectively assess nasal ventilation in paediatric populations being though highly technique-sensitive to patient cognitive maturation for co-operation. Nevertheless, great concordance exists between AR results, clinical examination, and patient's subjective symptoms to those obtained from CFD, indicating CFD reliability to perform functional analysis for assessing paediatric nasal airflow (33) and determine precise locations of nasal obstruction (28). Clinicians practicing in public health care systems have to encounter a significant problem with regard to long waiting times for providing orthodontic treatment and any other type of dental and/or medical specialist services. Given that technology is more involved in the everyday medical and subsequently orthodontic clinical practice and the fact that specialist ENT (ear-nose-throat) assessment can have timely and geographic limitations for some populations, CFD could be implemented as a triage test (34) for initial evaluation in the first line of airway diagnosis. More specifically, in a clinical setting like the one described above and in patients subjectively reporting symptoms of nasal breathing difficulties accompanied by an orthodontic problem that requires either RME and/or any another type of dentofacial orthopaedic treatment, CFD could be implemented to identify possible upper airway constrictions while waiting for specialist ENT assessment. This software-assisted evaluation method is non-invasive, does not harm patients, utilizes initial CBCT data, when and if available, and can provide some valuable initial information for patients with subjective symptoms on whether an upper airway obstruction problem might be actually present when its definitive diagnosis with existing ENT tests is not feasible in a timely manner. In order to optimize the use of CBCT, the Field of View (FOV) should be justifiable, patient-specific, and indication-oriented (35). This was done in the present study, as a very modest 18 × 16 cm FOV was implemented. The Image Gently in Dentistry campaign recommends selecting radiographs for each patient's needs and using CBCT only when lower-dose imaging techniques cannot answer the clinical question that prompts the imaging (36). The present study is part of a bigger randomized trial that aimed to assess the upper airways, skeletal, and dental effects after RME (23), outcomes that cannot be adequately assessed with other imaging modalities. CBCT provides three-dimensional assessment for alveolar boundary conditions, craniofacial anatomy, and maxillary transverse dimensions (37) while it makes feasible the concomitant and accurate assessment of the upper airways (35, 38, 39); however, further studies are required to justify the combined CBCT and CFD use as a replacement, triage, or add-on test (34) to the existing diagnostic pathway of upper airway pathology.

Lack of concordance between nasal min-CSA and nasal resistance has been attributed to experimental errors of AR operator experience or sound leakage rather than lack of actual relationship between anatomy and function. Using CFD to test the applicability of Bernoulli obstruction theory (orifice theory) in the relevance of anatomic and functional parameters confirmed their inverse relationship showing also that a localized anatomic constriction does not cause invariable nasal obstruction rather the presence of a severe constriction that exceeds a certain critical size threshold (min-CSA <0.37 cm^2) outweighs the resistance of other nasal regions and raises it above normal values (40). Anterior nasal width ≤22 mm is considered narrow in adults, needing surgical enlargement (41); however, adult cases with nasal obstruction and 18.4–18.6 mm piriform aperture width, which is significantly lower than population-based averages, did not improve even after surgery (42). This is in accordance with our predictive model for the resolution of nasal obstruction considering baseline anatomic and ventilation conditions thresholds since baseline nasal width ≥24 mm and pressure <490 Pa were prerequisites for effective RME. Treatment with the Hybrid-Hyrax proved a significant predictor for nasal obstruction resolution, which could be attributed to its superiority in increasing nasal dimensions by delivering expansion forces closer to maxillary centre of resistance (12).

The overcorrection expansion protocol was implemented in the present study because there is insufficient robust evidence supporting the superiority of Hybrid-Hyrax skeletal expansion effects against tooth-borne expanders. A purely bone-bone expander (4 palatal implants) resulted in greater suture opening compared to the tooth-borne Hyrax (43); however, their bone-borne expander was supported by 2 more implants and had no tooth support compared to the Hybrid-Hyrax used in the present study. Another study that used appliances similar to ours (Hyrax versus Hybrid-Hyrax) showed similar skeletal changes (maxillary, palatal, interpterygoid, nasal width) induced in both groups (44). Finally, the latest meta-analysis on the effects of different RME expanders concluded that based on the limited evidence from randomized trials, purely bone-borne or hybrid expanders might be advantageous to sutural opening, reduced tooth tipping, and lower airway resistance compared to tooth-borne expanders; however, definitive conclusions cannot be drawn due to the limited number of studies and issues pertinent to conduction and reporting (15). Given the above evidence, the very limited data on the mid- and long-term relapse of skeletally anchored expanders over conventionally anchored ones and for protocol standardization reasons, we planned and performed overcorrection. This was not possible though in the Keles group as the excessive tipping of the anchor teeth precluded such an approach for patient safety reasons.

Limitations

Limitations of the present trial are the significant attrition in one of the groups (Keles expander), the lack of ENT examination prior to RME, and the relatively short follow-up. Another limitation could be considered that the molar angulation protocol (45) was not used for the initial diagnosis; however, all cases had at least one buccal segment in full crossbite as this is a criterion against which patients are clinically evaluated for being eligible to enter the orthodontic treatment waitlist in the public system. Even though the use of the molar angulation protocol could have helped in differentiating severe from non-severe cases, one could hardly advocate that a patient with full posterior crossbite of at least one side can be corrected with arch-wire expansion and/or posterior tooth uprighting only and it

can be advocated by any practicing clinician that some type of skeletal expansion is required.

All existing nasal airway function tests come with shortcomings. The devices used must follow physical, mathematical, and technical requirements for accuracy with CFD considered a 'state-of-the-art' approach, given standardization of the software, hardware, and imaging protocols (46). These prerequisites were met in the present study as the researchers performing CFD analyses have developed the above expertise; however, CFD is still only a computer prediction which estimates (under many assumptions) how air will flow through the upper airway.

Additionally, lack of longitudinal follow-up cannot ascertain the stability of the effects as the moderate evidence of improved nasal breathing after RME is available from studies with short follow-up (47). There might have also been possible coincidence of the study duration with the upper airway growth during adolescent growth spurt (48), which could have contributed to improved functional parameters. Nevertheless, the impact of growth was similar for all groups and the short study duration imparts minimal incremental growth contribution to the overall results. Another factor that cannot be ruled out is the potential presence of allergic rhinitis or upper respiratory infections that might have resulted in inflammatory edoema, which subsequently affected soft-tissue and functional measurements as there is a strong relationship between upper airway function (nasal airflow and obstruction) and nasal eosinophilic infiltration (49, 50).

Generalizability

The sample and the clinical setting reflect conditions similar to the everyday clinical practice with the findings being applicable to any random adolescent population requiring RME as part of malocclusion correction, which increases the generalisability of the present findings to all patients with maxillary constriction and irrespective to accompanying malocclusions.

Conclusions

Comparative assessment showed that the Hybrid-Hyrax induced significantly greater effects in increasing nasal width and CSA. Similar trend was noted in reducing pressure and maximum airflow velocity than Hyrax and Keles expanders; however, comparisons did not reach statistical significance. Post-RME nasal obstruction resolution was more probable with Hybrid-Hyrax expanders and in younger, skeletally immature, male patients without pre-RME mucosal hypertrophy.

Supplementary material

Supplementary material is available at the *European Journal of Orthodontics* online.

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Conflicts of interest

The authors do not have any conflict of interest.

Data availability

The data underlying this article are available in Zenodo at http://doi.org/10.5281/zenodo.4026863.

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