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Association between Rapid Maxillary Expansion and Nocturnal Enuresis in Children: A Pilot Study for a Randomized Controlled Clinical Trial

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Abstract: Objectives: This pilot study was conducted to test the protocol of a randomized controlled trial evaluating whether rapid maxillary expansion (RME) can relieve nocturnal enuresis (NE) and improve breathing in children, after ruling out a placebo effect, and investigating whether the effects of RME and NE are related to the morphology of the upper airway. **Methods:** Seventy 6–15-year-old patients with NE were assessed for eligibility (e.g., constricted maxilla). Enrolled subjects were randomized to immediate treatment with RME (Group 1) or to have the same treatment (RME) delayed for at least six weeks (Group 2). Outcomes comprised the number of wet nights per week, the nocturnal urine production, and the scores of a pediatric sleep questionnaire at baseline, after active treatment (Group 1) or delayed treatment (Group 2), and after 3 months' retention. Cone beam computed tomographies were taken at baseline and after retention. **Results:** Six patients were randomized: three in each group. In four of six patients, the number of wet nights per week decreased. Moreover, in responders, nocturnal urine production was reduced following RME. **Conclusions:** This pilot study suggested that RME might reduce the severity of NE and showed that the protocol of this randomized controlled clinical trial was appropriate.

Keywords: rapid maxillary expansion; nocturnal enuresis; sleep-disordered breathing

1. Introduction

Nocturnal enuresis (NE) is the involuntary loss of urine during sleep. The condition affects 7% to 10% of all 7-year-olds and 0.5% to 2% of young adults [1–3]. NE is a multifactorial disease, characterized by the production of an excessive amount of urine at night, termed nocturnal polyuria (NP), and it is the cause of bedwetting in a large number of children [4,5]. NP can be either the result of the inadequate secretion of nocturnal arginine vasopressin (AVP) or secondary to osmotic diuresis, natriuresis, hypercalciuria, or other renal factors [5–7].

The treatment options for NE are commonly directed against the pathogenesis of the condition: the first-line treatment recommended by the International Children's Continence Society comprises desmopressin, a synthetic analogue of an antidiuretic hormone, or the enuresis conditional alarm [4]. In the last few years, increasing evidence suggests sleep-disordered breathing (SDB) as one of the underlying etiologies of NE [8–11]. Treatment of SDB by adenotonsillectomy, respiratory support, or orthodontic treatment seems to lead to the amelioration or cure of bedwetting [12,13]. Signs or

symptoms of SDB in a young patient suffering bedwetting suggest the need for a referral for sleep studies, sometimes in combination with orthodontic treatment [14].

SDB is common in children in need of orthodontic treatment because of skeletal and dental transversal deficiencies [15]. The orthodontic treatment aiming at resolving these deficiencies often sees, as a secondary effect, the enlargement of the upper airway (UA), and the resolution of NE is occasionally seen at treatment completion [12].

One of the available treatment modalities to correct the transversal discrepancy is rapid maxillary expansion (RME). This procedure increases the maxillary arch width by opening the mid-palatal suture, thus achieving skeletal expansion [16,17]. As such, RME has been associated with an improvement in breathing [18]. In the literature, some evidence is available regarding the effect of RME on NE [12,19–21].

Therefore, a randomized controlled clinical trial (RCT) was designed to evaluate whether RME could reduce the frequency of NE and improve quality of life in children after ruling out a placebo effect to investigate whether the effects of RME on NE are related to the morphology of the nasal and pharyngeal airway. The hypothesis was that RME treatment would lead to a reduction in nocturnal urine production as a result of improved breathing obtained by enlarging the nasal and pharyngeal airway. The purpose of this pilot study was to investigate the appropriateness of this RCT protocol.

2. Materials and Methods

2.1. Trial Design

The RCT was designed as a 2-arm parallel-group interventional study with a 1:1 allocation ratio. The patients and their parents were informed about the study both orally and with an information leaflet. The parent(s) or the legal guardian(s) of the patients (all of minor age) were asked to sign an informed consent. This study was approved by the Ethical Committee of Research of the Human Being of Central Jutland, Denmark (reference number: 1-10-72-228-18). The data were analyzed with the permission of the Danish Data Protection Agency (Datatilsynet number 2015-57-0002 and Aarhus University number 2016-051-000001-1120).

Inclusion criteria were: (1) age range 6–15 years; (2) nocturnal enuresis with at least 3 wet nights per week; (3) constricted maxillary arch, with or without posterior crossbite (labial tipping of the maxillary molars was the criteria for maxillary constriction in the absence of crossbite). Exclusion criteria were: (1) daytime lower urinary tract symptoms; (2) Attention deficit hyperactivity disorder, autism or other neuropsychiatric disorders; (3) constipation defined using the Rome IV criteria; (4) current or recurrent urinary tract infections; (5) ongoing treatment for ne; (6) previous orthodontic treatment; (7) poor oral hygiene; (8) insufficient number of teeth for bonding an RME device; (9) craniofacial syndromes, cleft lip, or palate, or major nasal obstruction; (10) other disease or conditions expected to hinder the ability of the patients to participate in the study or expected to influence the measured parameters.

2.2. Participants, Eligibility Criteria, and Settings

To recruit participants, two approaches were followed: First, patients were screened at two incontinence clinics in Region Midt (Central Denmark Region): Center for Child Incontinence at the Department of Pediatrics Aarhus University Hospital, Aarhus, Denmark; and Community Nurse Incontinence Clinic Aarhus, Denmark. Second, possible subjects were recruited through an announcement in a local newspaper (Århus Onsdag, Aarhus, Denmark).

An experienced orthodontist (M.C.) screened all NE subjects for transversal maxillary deficiency to identify eligible participants. The eligible participants were referred to the orthodontic clinic at Section of Orthodontics, Department of Dentistry and Oral Health, Aarhus University.

2.3. Sample Size

The sample size calculation for the RCT was based on an alpha significance level of 0.05 and a beta of 0.20 to achieve a power of 80%. According to a systematic review, the effectiveness of RME

to cure NE is 48% (95% CI 0.26–0.73) [21]. A spontaneous resolution rate of approximately 15% per year is the expected proportion of cure rate for the control group [22]. The calculation indicated that a sample of 30 patients in each group would be required (www.clincalc.com). We estimated a dropout rate of 15%; thus, for this RCT, at least 35 patients in each group should be included. These preliminary results would test the RCT protocol on the first six enrolled patients.

2.4. Randomization

When patients fulfilled all the inclusion and exclusion criteria, and after the informed consents were obtained, the patients were enrolled and randomized to receive immediate treatment with RME (Group 1) or to have the same treatment (RME) delayed for at least 6 weeks (Group 2). Randomization was achieved by following random permuted blocks of six randomly generated numbers. The allocation sequence was concealed using numbered and sealed opaque envelopes. An independent administrator who did not participate in the trial prepared these envelopes. The pilot study was planned to include the patients from the first randomization block.

2.5. Blinding

This was a single-blind study, in which the outcome assessors were blinded.

The participants were informed about the main purpose of the project (the effectiveness of RME to cure NE), and that they would be randomized into two groups, differing with regards to the expansion protocols (i.e., the timing of activation of the expansion screw), without knowing the differences in the activation of the device.

A unique identifier was created for each participant to code the recorded data appropriately. This was kept in a secure, password-protected location separate from the collected data. A blinded examiner (X.N.) assessed all recorded data.

2.6. Interventions

RME was offered to all subjects: participants were treated with a hyrax-type palatal expander (12-mm self-locking screw) using a CAD/CAM procedure without physical impressions or printed models (Figure 1) [23]. The digital design of the hyrax was prepared and then printed via a laser melting procedure. The bonding in the patients' mouths was achieved by preparing the molars' surfaces with Scotchbond universal adhesive (3M Unitek, Monrovia, CA, USA) and, subsequently, with Transbond XT (3M Unitek, Monrovia, CA, USA).

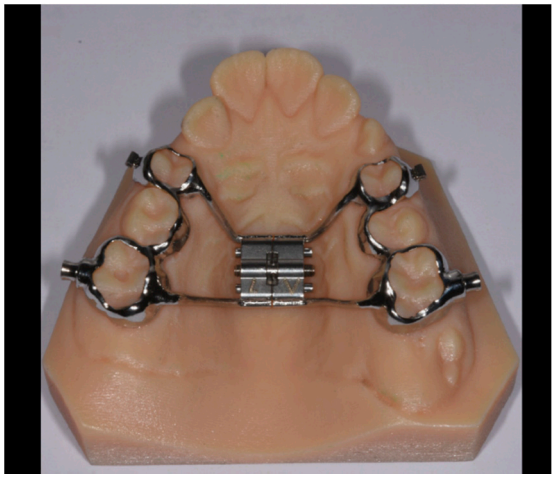

Figure 1. Rapid maxillary expansion (RME) appliance. For illustration purposes only, for this Hyrax dental model was printed as well.

In Group 1, the protocol followed the standard procedure for RME. Starting at T0, the appliance was activated twice a day, each morning and evening, by a quarter turn (0.45 mm/day) by one of the participant's parents until 2 mm of overcorrection of the transverse dimension was achieved (T1), as a small relapse was expected. After the expansion period, the appliance was left in the mouth without any activation for at least 3 months (T2) for retention of the acquired expansion. The participants were not treated with any other appliance during the retention period.

In Group 2, the participants received a delayed treatment. The appliance was bonded at T0 as in Group 1, but the expansion was delayed for 6 weeks (T1). After six weeks, the same expansion and retention protocol as for Group 1 was followed (Figure 2).

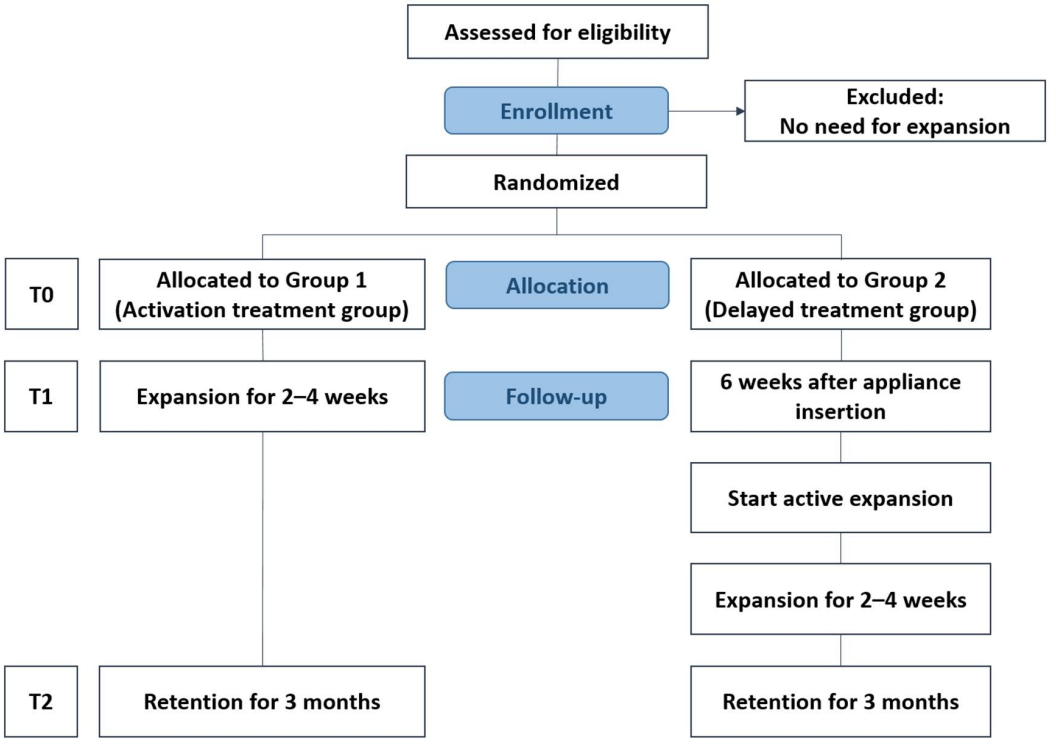

Figure 2. Flow chart for protocol.

The parents filled out the Pediatric Sleep Questionnaire (PSQ) [24], and performed 1 week of NE-related home recordings (i.e., number of wet night per week; the participants used diapers for 7 days to be able to measure urine production. Total night-time urine production = the difference in diaper weight ((dry diaper + urine) − wet diapers) + the first morning void) at each time point (T0, T1, and T2). Subjects had cone beam computed tomography (CBCT) scans at T0 and at T2.

2.7. CBCT

A low-radiation dose dental CBCT scanner (NewTom 5G, QR, Verona, Italy) was used to acquire the 3D morphology of the facial skeleton and the nasal and upper airway (110 kVp, 5 mA, 0.3 mm isotropic voxel dimension, 18 s of scanning time with 3.6 s of exposure time, a field of vision (FOV) of 18 × 16 cm). Scanning protocols for acquisition ensured that the subjects were in centric occlusion with their lips and tongue in a resting position; during scanning, the subjects were also instructed to lie still to prevent motion artefacts. Raw data obtained from the CBCT scanner were exported in the DICOM format and imported into a specific software (Mimics 21, Materialise, Leuven, Belgium).

The segmentation was performed following the same method as described elsewhere [25]. Landmark definitions for the dental, skeletal, and airway parameters, as well as plane definitions, are presented in Table 1. Four linear measurements were assessed to evaluate the transverse skeletal

changes after expansion (Table 2 and Figure 3). Two reference planes were defined: Frankfort Horizontal, used as the horizontal plane, and Sagittal SN plane, used as the sagittal plane. The total pharyngeal airway (PA) was divided into three parts according to the location of PNS-So, PNS-Ba, and occlusal and E planes, and their volumes were assessed (Table 2 and Figure 4). Based on the midline of the total PA, the cross-sectional area (CS) and hydraulic diameter (D_H) were assessed, both perpendicular to the center line. All measurements were conducted by one operator (X.N.).

Table 1. Landmarks and Reference Planes selected for the airway analysis.

Points	Description
ANS	The most anterior point on the nasal spine
Ba	The most posteroinferior point on the clivus
E	Most superior point of the epiglottis
LD-L	The most inferior point of the left lacrimal duct
LD-R	The most inferior point of the right lacrimal duct
LF-L	Centroid of the Lacrimal foramen left
LF-R	Centroid of the Lacrimal foramen right
MoL	The distal-palatal tip of the first left molar in the upper jaw
MoR	The distal-palatal tip of the first right molar in the upper jaw
N	The intersection of the internasal and frontonasal sutures in the midsagittal plane
Ntip	The tip of the nasal bone
OrL	Orbital left, the most inferior anterior point on left orbit's margin
OrR	Orbital right, the most inferior anterior point on right orbit's margin
PNS	The most posterior point on the nasal spine
Pl	Centroid of the greater palatine foramen left
Pr	Centroid of the greater palatine foramen right
PoL	Porion Left: the most upper point on the left bony external auditory meatus
PoR	Porion Left: the most upper point on Right bony external auditory meatus
S	The midpoint of the sella turcica
So	The midpoint of the sella-basion line
ii	The point midway between the incisal edges of the maxillary central incisors
References Planes	**Description**
Frankfurt plane	A plane passing through the inferior borders of the bony orbits, encompassed by OrR and OrL, and the upper margin of the auditory meatus encompassed by PoL
Sagittal SN plane	Plane perpendicular to Frankfurt plane passing through S and N points
NTip-ANS plane	Plane through NTip and ANS points, perpendicular to Sagittal SN plane
PNS-So plane	Plane through PNS and So points, perpendicular to Sagittal SN plane
PNS-Ba plane	Plane through PNS and Ba points, perpendicular to Sagittal SN plane
Occlusion plane	Plane through MoL, MoR, and ii points
E plane	Plane through E point, parallel to Frankfurt plane

Table 2. NC and PA volumes and cross-sections.

	Description
NC measurment	
NCV	Bounded anteriorly by NTip-ANS plane and posterior by PNS-So plane
PA measurments	
TPAV	Bounded superiorly by PNS-So plane and inferiorly by E1-E2 plane
Miminal CS	The minimal cross-sectional area in Total PA
Minimal D_H	The minimal hydraulic diameter in Total PA
Width	**Description**
Inter lacrimal duct distanct (LD)	Distance between Ld-L and Ld-R
Inter lacrimal foramen distance (LF)	Distance between Lf-L and Lf-R
Inter-molar distance	Distance between MoL and MoR
Palatal width	Distance between Pl and Pr

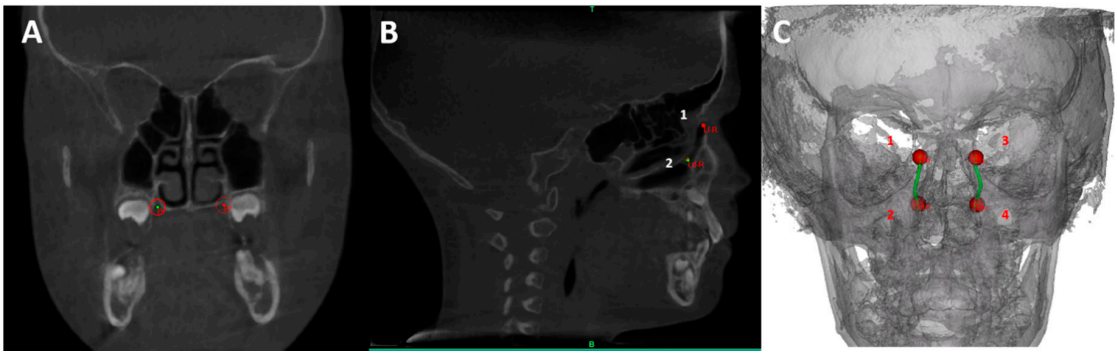

Figure 3. Landmarks and measurements. (**A**) Coronal CBCT image showing the left and right greater palatine foramen. (**B**) Sagittal CBCT image showing: 1. centroid of the lacrimal foramen right (LF-R) and 2. the most inferior point of the right lacrimal duct (LD-R). (**C**) 3D image showing the left and right lacrimal canal, 3. centroid of the lacrimal foramen left (LF-L), and 4. the most inferior point of the left lacrimal duct (LD-L).

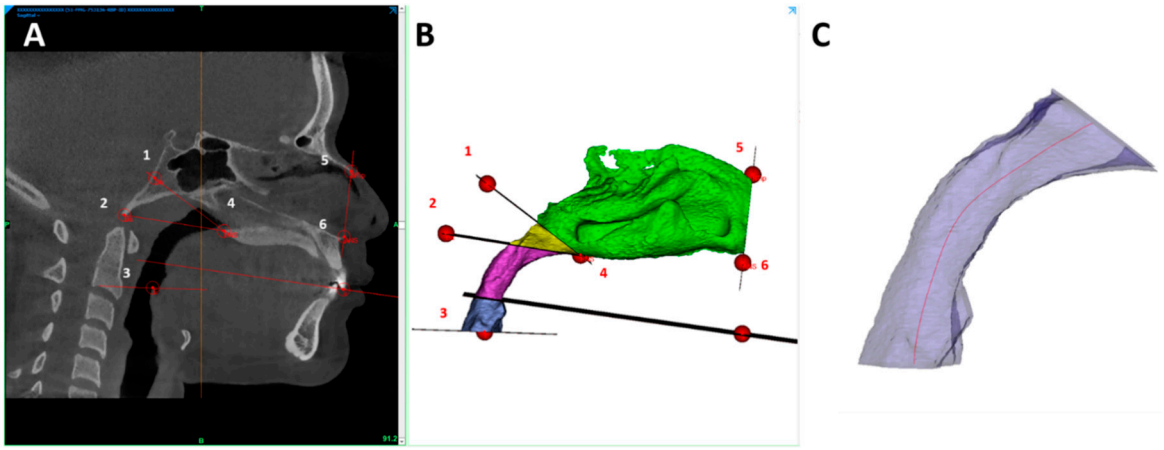

Figure 4. (**A**) Sagittal CBCT image showing 1. the midpoint of the sella-basion line (So), 2. the most posteroinferior point on the clivus (Ba), 3. the most superior point of the epiglottis (E), 4. the most posterior point of the nasal spine (PNS), 5. the tip of the nasal bone (NTip), and 6. the most anterior point of the nasal spine (ANS). (**B**) 3D reconstruction of the nasal cavity (green), nasopharynx (yellow), velopharynx (pink), and oropharynx (purple), delimited by five anteroposterior planes. (**C**) The centerline for the total airway.

2.8. Outcomes (Primary and Secondary)

To elucidate the effect of RME on bedwetting, we used the number of wet nights per week as the primary outcome, and the nocturnal urine production as the secondary outcome. The effect of the intervention on airway size as measured by CBCT was also assessed as an outcome parameter and predictor for the effect on NE. The results of the PSQ were calculated and children were grouped as high risk or low risk according to the 0.33 cut off value of the PSQ, with the score of the high-risk group having more than 0.33 of the PSQ [24]. The pretreatment nocturnal urine production was evaluated as a predictor for the response to the intervention.

3. Results

Of the 70 subjects who were screened for inclusion, 53 did not meet the inclusion criteria and 11 were not willing to participate (Figure 5). A total of six patients were enrolled in this pilot study (from 1 October 2018 to 30 June 2020): Group 1, three boys; Group 2, three patients (two boys and one girl).

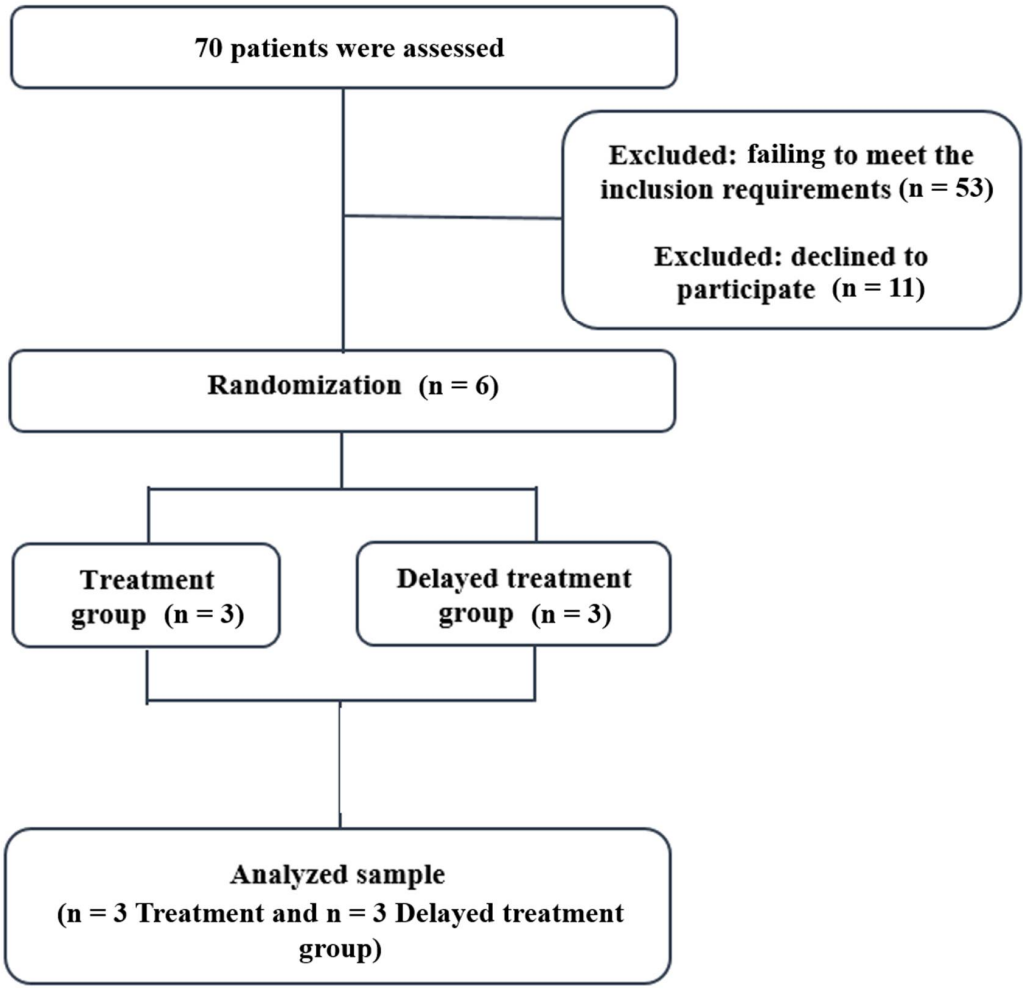

Figure 5. CONSORT diagram of patient selection and randomization allocation. CONSORT, Consolidated Standards of Reporting Trials.

Baseline characteristics are summarized in Table 3. In Group 1, all subjects were wet every night before treatment start; after RME treatment, one patient decreased from seven to one enuresis episode per week. In Group 2, the frequency of bedwetting decreased in one patient before activating the appliance, and one patient had a reduced number of wet nights per week from seven to four after expansion (Table 4). Regarding urine production volume, four of the six patients showed a decrease after the active treatment started (Figure 6).

Table 3. Baseline characteristics.

Patient	Age, y	Gender [a]	Groups [b]	Frequency of Bedwetting per Night, No	Previous Treatment for Bedwetting	PSQ Score
1	7.34	M	1	7	Medicine	0.24
2	12.66	M	1	7	Alarm	0.10
3	8.56	M	1	7	Medicine	0.62
4	9.08	M	2	7	Medicine	0.57
5	12.28	M	2	7	No treatment	0.36
6	13.28	F	2	3	Medicine and Alarm	0.25

Note: [a] M indicates male; F, female. [b] 1 indicates Group 1 (Activation treatment group); 2, Group 2 (Delayed treatment group).

Table 4. Frequency of bedwetting, Pediatric Sleep Questionnaire (PSQ) score, and CBCT measurements for three time points.

Patient	Group	Frequency of Bedwetting per Week			PSQ Score			CBCT Measurements: Differences T2–T0							
		T0	T1	T2	T0	T1	T2	NCV	TPAV	Minimal CS	Minimal D_H	Inter-Molar Distance	Palatal Width	Inter-LD Distance	Inter-LF Distance
1	1	7	7	7	0.24	0.17	0.45	−54	−911	−15.92	0.04	0.5	0.22	−0.12	0.19
2	1	7	3	1	0.1	0.41	0.36	2939	3766	22.85	0.32	1.15	0.35	0.65	0.12
3	1	7	7	7	0.62	0.59	0.64	312	7496	104.45	2.73	1.27	0.46	0.57	0.59
4	2	7	7	7	0.57	0.5	0.38	519	−107	0.32	−0.09	4.63	1.16	0.38	−0.21
5	2	7	7	4	0.36	0.45	0.45	456	−151	−3.12	0.10	0.48	0.00	0.11	0.94
6	2	3	1	1	0.25	0.21	0.1	2513	3670	52.46	1.77	3.35	0.62	0.2	0.44

Note: T, treatment group; D, delayed treatment group; T0, before treatment; T1, after active treatment (Group 1) or after 6-week delay period (Group 2); T2, after retention.

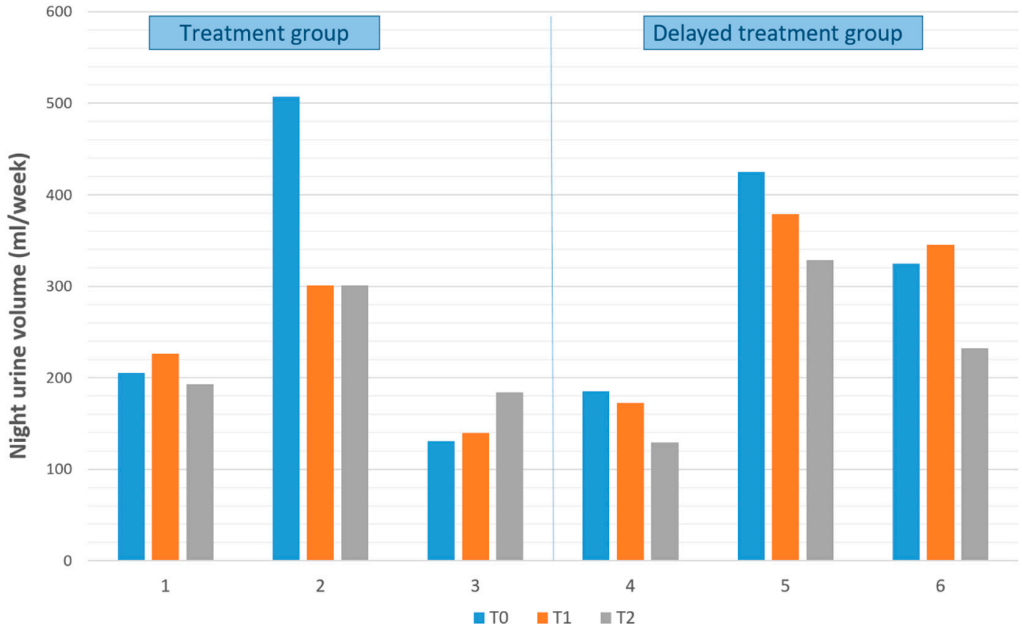

Figure 6. The average of night voided volume per week for the patients at the three time points.

A total of 23 out of the 70 evaluated NE patients answered the PSQ: 57% (13/23) of the patients were identified as at high risk of SDB. Of the six children included in the RCT, three were identified as being at high risk for SDB before treatment.

The transverse maxillary expansion was performed in 10 to 15 days, and the amount of expansion was in the range of 3.5 to 4.5 mm. The inter-molar distance increased by 4.15 mm, while the palatal width increased by 1.16 mm (Table 3).

4. Discussion

NE is a common condition among children with breathing problems and the relationship between sleep-disordered breathing and enuresis has been discussed for many years [26]. Several studies reported enuresis in children suffering sleep apneas or heavy snoring becoming dry when their airway obstruction was treated [27,28]. One epidemiological study indicated that more children with NE were at high risk of SDB (13.6%) compared to the mean prevalence in the orthodontic population (10.3%), with this difference being statistically significant [29]. In the present study, of the 23 NE patients who filled in the PSQ, 13 patients had a PSQ score characterizing them as at high risk of SDB (56.5%). This supports the hypothesis that children with bedwetting have a significant higher chance to present SDB problems, which thus should be looked for.

If SDB is the background for enuresis for some children, these children are expected to be refractory to first line treatment with desmopressin and an enuresis alarm. In the current study, only one child had not been previously treated; two patients were refractory to the enuresis alarm, two failed a desmopressin (Minirin) treatment, and one was refractory to both alarm and desmopressin.

To the best of our knowledge, there are ten studies dealing with the effect of RME on NE: nine of ten studies treated children characterized by normal transverse dimensions with expansion therapy, with the only aim being the cessation of NE [12,14,19,20,30–34]. A 100% relapse of the dental overexpansion was assumed. On the contrary, in the present study, to be included, all the patients had to be diagnosed with a constricted palate, as it was considered inappropriate, potentially iatrogenic, and ethically questionable to over-expand patients without a constricted maxillary.

All the patients of the present study were treated with a hyrax-type palatal expander using a CAD/CAM procedure. This fully digital approach was chosen as it was shown to be precise, quicker to put in place, and does not require the use of separators [23]. The amount of maxillary expansion was in the range of 3.5 to 4.5 mm, which was more limited compared with previous studies [19,35].

Timms reported that the amount of expansion varied from 6 to 10 mm [35]; two studies reported a 5–8 mm expansion [30,33]. Ji et al. checked the intermolar distance and the change was 5.7 mm after RME [34], which is larger than the result of the present study.

As relief of breathing problems could help the children with NE, the hypothesis was raised that RME could be related with resolution of bedwetting in some patients. In 1990, Timms first published a paper to test this hypothesis. All the ten patients in his study became dry at night following treatment [35]. Al-Taai et al. reported significant improvement with respect to NE after RME and became completed dry after 3 years (19 patients, aged 6–15 years) [14]. In the present study, four out of six patients had a decreased amount of nocturnal urine production. The number of included participants was too low for statistical analysis as this was a pilot study; however, it seems that, in responders, nocturnal urine production was reduced following RME, and the reduction in frequency of bedwetting seemed associated with this reduction in nocturnal urine volume.

The effect of RME on NE was based on the possible relationship between breathing patterns and NE. Therefore, before and after RME treatment, CBCTs were taken to assess the morphological changes in the nasal cavity (NC) and pharyngeal airway (PA). The CBCT results showed that two patients displayed a large volume increase in NC and PA. According to these results, we hypothesized that the greater the expansion, the greater the effect on NE.

One speculation for the association of the nasal airway obstruction and NE could be that SDB may decrease arousal response, resulting in an impaired arousal response to a full bladder [12]. Several studies mentioned that the improvement of NE is linked to an improvement in breathing capacity and better oxygen saturation of blood, which may make it easier for NE patients to wake up [14,20,27]. Studies have also suggested that SDB leads to excess urine production at night by activating sodium regulating hormones and altering in urodynamics [28,36].

As the possibility of a placebo effect exists, we designed this study for a randomized placebo-controlled trial where the participants in the control group had treatment delayed by 6 weeks. No difference was found between the two groups when comparing the change of frequency of NE from T0 to T1.

The results from this pilot study are only preliminary, but they suggest an improvement for four patients, with two of them having a greater amount of expansion. The association between nocturnal urine volume and amount of expansion is worth mentioning. A larger sample will possibly strengthen this association when the RCT is completed. Of the four improved patients, two of them showed an increase in upper airway volume after RME. This finding seems to be consistent with that of Bazargani et al., who reported a significant correlation between an increase in nasal volume and a reduction in NE frequency [12]. This pilot study validated the appropriateness of the design to perform the planned RCT. Moreover, this pilot study might stimulate additional research into this field.

5. Conclusions

These preliminary results suggest that RME reduces the frequency of NE and that there might be an association between the amount of expansion and the reduction in night urine volume. This pilot study proved that the protocol of the RCT is appropriate.

Author Contributions: X.N. recruited the participants, provided treatment of patients, measured, analyzed, interpreted the data, and drafted the manuscript. M.A.C. designed the protocol, provided treatment of patients, and revised the manuscript for important intellectual content. K.K. designed the protocol, interpreted the data, and revised the manuscript. P.M.C. designed the protocol, trained the examiners for measurements, helped in interpreting the data, revised the manuscript for important intellectual content, and approved the version to be published. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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