The effect of nasal tramazoline with dexamethazone in obstructive sleep apnoea patients
A randomised placebo-controlled crossover trial

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ABSTRACT

Although there is a strong correlation between oral/oro-nasal breathing and apnoea-hypopnoea index (AHI) in patients with obstructive sleep apnoea (OSA) and normal nasal resistance at wakefulness, it remains unknown whether the pharmacological prevention of potential nasal obstruction during sleep could decrease oral/oro-nasal breathing and increase nasal breathing and subsequently decrease AHI. This study evaluated the effect of a combination of a nasal decongestant with corticosteroid on breathing route pattern and AHI.

Twenty-one patients with OSA (mean AHI 31.1 events·h⁻¹) and normal nasal resistance at wakefulness were enrolled in a randomized crossover trial of one-week treatment with nasal tramazoline and dexamethazone compared with one-week treatment with nasal placebo. At the start and end of each treatment period, patients underwent nasal resistance measurement and overnight polysomnography with attendant measurement of breathing route pattern.

Nasal tramazoline with dexamethazone was associated with decrease in oral/oro-nasal breathing epochs and concomitant increase in nasal breathing epochs, and mean decrease of AHI by 21%. The change in nasal breathing epochs was inversely related to the change in AHI (Rs=0.78; p<0.001).

In conclusion, nasal tramazoline with dexamethazone in OSA patients with normal nasal resistance at wakefulness can restore the preponderance of nasal breathing epochs and modestly improve AHI.

Keywords: apnoea-hypopnoea index; nasal breathing epochs; nasal tramazoline with dexamethazone; obstructive sleep apnoea.
INTRODUCTION

Humans preferentially breathe via the nasal route, the purpose being to filter, warm and humidify the inspired air [1]. During sleep healthy subjects free of nasal disease are estimated to inhale via the mouth only ~4% of the total ventilation [2], but, when nasal obstruction occurs, the proportion of oral breathing increases and snoring with obstructive apnoeas appear [3, 4]. Thus, increased nasal resistance is considered an independent risk factor for obstructive sleep apnea (OSA) [5].

Despite the relationship between nasal obstruction and OSA, the therapeutic effect of improving nasal airway patency on OSA severity remains a point of conjecture [6]. In fact, in OSA patients with rhinitis administration of intranasal corticosteroids has been shown to improve sleepiness and reduce the apnoea-hypopnoea index (AHI) [7], whereas the use of topical decongestants, external nasal dilators and nasal surgery has provided inconsistent results [8].

The present authors have demonstrated a strong correlation between AHI and oral/oro-nasal breathing epochs in patients with OSA and normal nasal resistance at wakefulness [9]. Additionally, KOHLER et al [10] have shown that nasal resistance presents substantial variability and may increase during sleep. Therefore, it is plausible to hypothesize that OSA patients presenting with normal nasal resistance at wakefulness could demonstrate increased nocturnal nasal resistance during sleep which might predispose to oral/oro-nasal breathing and elicit apnoea/hypopnoeas. Thus, pharmacological prevention of nocturnal nasal obstruction in such OSA patients might decrease oral/oro-nasal breathing and eventually be beneficial for OSA by decreasing apnoea/hypopnoeas. Additionally, the evaluation of this pharmacological intervention during sleep could be an important step in understanding the upper airway physiology in OSA patients.

Therefore, the present study aims to investigate whether ensuring nasal airway patency during sleep by pharmacological prevention of nasal obstruction could alter breathing route pattern and lead to a decrease in the number of apnoea/hypopnoeas in OSA patients with normal nasal resistance at wakefulness. A combination of a fast-acting nasal decongestant with a nasal corticosteroid, which can attenuate nasal inflammation associated with OSA [11, 12], will be used. The hypothesis that we want to test is that the application of this combination decreases oral/oro-nasal breathing and subsequently AHI.
METHODS

Study subjects

Consecutive patients who referred from April 2010 to January 2012 to the Center of Sleep Disorders of “Evangelismos” General Hospital of Athens for suspected sleep disordered breathing were recruited. The enrolment criteria were: i) AHI greater than 10 events·h$^{-1}$ at baseline, ii) normal nasal resistance measured in supine position with active anterior rhinomanometry (≤3.0 cmH$_2$O·L$^{-1}$·s), iii) no recent surgery involving the upper airway, iv) central apnoeas less than three per hour or five percent of total apnoeas, v) no use of medications known to influence nasal resistance (antihistamine, decongestants, etc), vi) no upper or lower respiratory tract disease, including a history of nasal allergy, and vii) no smoking. Exclusion criterion was considered the treatment of OSA with continuous positive airway pressure (CPAP) during the course of the study. Prior to enrolment to the study, each participant provided signed informed consent. The study was approved by the hospital ethics committee.

Protocol

A randomized, double-blind, placebo-controlled, crossover design was used (Figure 1). Using a table of random numbers, subjects were randomized into two groups. The patients of the first group initially underwent one-week therapy with nasal tramazoline and dexamethazone (application 2 times per day) followed by two-week washout period and one-week of therapy with an identically looking nasal placebo (sodium chloride, 0.9% solution; application 2 times per day). The patients of the second group initially underwent one-week therapy with nasal placebo followed by two-week washout period and one-week therapy with nasal tramazoline and dexamethazone. A two-week washout period between the one-week regimens was employed because the time needed for the effect of medication to vanish is approximately one week [13, 14]. The patients underwent four assessments, at the start and end of each treatment period. Every assessment consisted of an overnight polysomnography with concomitant measurement of breathing route pattern (oral, nasal, oro-nasal breathing epochs) as previously described [9], along with nasal resistance measurement. The ClinicalTrials.gov identifier is NCT01601509.

Rhinomanometry

For each subject, nasal resistance to airflow was measured at the night of the polysomnography during wakefulness without decongestion, first in the upright
seated position and then in supine position after lying down for 10 minutes. by active 
Active anterior rhinomanometry (PDD-301/r, Piston, Budapest, Hungary) using a 
standard protocol [9]. was performed and international recommendations were 
followed [15]. In brief, patients wore a closely fitting face mask which didn’t distort 
the nostrils or the nasal valve and breathed through one only nostril (first the left and 
afterwards the right) with the mouth closed. The pressure probe was placed at the 
opening of the contralateral occluded nostril not being tested. Total resistance was 
then automatically calculated from the 2 unilateral measurements. Nasal resistance 
was given at a pressure difference of 150 Pascal across the nasal passage. Anterior 
rhinomanometry requires minimal cooperation, and has increased reproducibility rate 
and minimal failure rate [15].

Polysomnographic methods

A full-night diagnostic polysomnography (EMBLA S7000, Medcare Flaga, 
Iceland) was performed in each subject. To determine the stages of sleep an 
electroencephalogram (with four channels, C4-A1, C3-A2, O2-A1, O1-A2), electro-
oculogram and electromyogram of the submentalis muscle were obtained. Arterial 
blood oxyhemoglobin was recorded with the use of a finger pulse oximeter. 
Thoracoabdominal excursions were measured qualitatively by respiratory effort 
sensors [XactTrace belts featuring Respiratory Inductive Plethysmography (RIP), 
Medcare Flaga, Iceland] placed over the rib cage and abdomen. Snoring was detected 
with a vibration snore sensor and body posture with a body position sensor. Airflow 
was monitored using an oral thermistor (oral flow sensor, Medcare Flaga, Iceland) 
placed in front of the mouth and a nasal cannula/pressure transducer (21in/53cm, 
Medcare Flaga, Iceland) inserted in the opening of the nostrils and linked to 
independent channels, as previously described [9]. All variables were recorded with a 
digital acquisition system (Somnologica 3.3, Medcare Flaga, Iceland).

Pharmacological therapy

A combination of a nasal decongestant (tramazoline hydrochloride 120 
microgram) with a nasal corticosteroid (dexamethazone-21 isonicotinate 20 
microgram per dose) was used (Dexa-Rhinaspray N; Boehringer Ingelheim). 
Tramazoline (imidazoline derivative) is a nasal decongestant, which attains its 
maximal effect between 30 and 210 min after application [11], while nasal 
dexamethazone can attenuate nasal inflammation associated with OSA [12].

Data analysis
The code of the medication was maintained during randomization and was broken only after the completion of data analysis. Sleep stage was scored manually in 30-s epochs [16]. Obstructive respiratory events were scored using standard criteria [16, 17]. Thus, apnoea was defined as the absence of airflow for more than 10 s in the presence of continued respiratory efforts [16]. Hypopnoea was defined as the reduction in chest wall movement to an amplitude that was smaller than approximately 70% of the baseline level, lasting more than 10 s, and leading to a decrease in hemoglobin saturation of at least 4% [17]. The number of episodes of apnoeas and hypopnoeas per hour of sleep is referred to as the AHI, whereas the number of episodes of apnoeas, hypopnoeas and respiratory effort-related arousals per hour of sleep is referred to as the respiratory distress index [16].

Route of breathing was evaluated by using the oral and nasal sensor signals to classify each 30-s epoch as nasal, oral or oro-nasal based on the predominant breathing route, and was expressed in % total sleep epochs (TSE), as previously described [9]. Cross-contamination between the oral and nasal channel was meticulously excluded by regular testing during polysomnographic calibration. Thus, we asked subjects to breathe normally and exclusively through the nose for 30 s and subsequently through the mouth for another 30 s in both supine and lateral postures so that we could verify that each sensor was activated exclusively. We continuously checked sensors during the recording to avoid dislodgement. All measurements were analyzed by a single investigator to ensure consistency and all polysomnographies were scored by a single experienced sleep technologist and subsequently reviewed by the same investigator, who was blinded to the patient’s group identity.

**End-points**

The primary outcome was AHI. Secondary outcomes included nasal resistance values, breathing route pattern, and Epworth Sleepiness Scale (ESS) score as a measure of subjective sleepiness [18].

**Statistical analysis**

The minimum sample size was calculated on the basis of 80% power and a two-sided 0.05 significance level (G*Power 3.0.10). Sample size capable of detecting a change of 5 events·h⁻¹ for AHI after pharmacological intervention was estimated using the standard deviations obtained from our previous study [8]. The critical sample size was estimated to be 19 patients. Values are presented as mean±SD or median (interquartile range) after testing for normal distribution (Kolmogorov–
Smirnov test). Depending on the distribution of variables, either parametric (paired t-test) or nonparametric (Wilcoxon signed rank, Spearman’s rank) tests were used. Data were analyzed according to the method of JONES and KENNARD [19]. Comparison of data at the entry to each study period, i.e., at the start of the study and at the end of the washout period, was performed by using paired t-test. The treatment effect for each variable was estimated using the difference between the value at the end of treatment minus the value at the beginning of treatment. Treatment effect differences between nasal tramazoline with dexamethazone and nasal placebo were compared using Wilcoxon signed rank test. Relationships between variables were determined by the Spearman’s rank correlation coefficient \( R_s \). A two-tailed p-value of \(<0.05\) was considered statistically significant.

RESULTS

In total, 21 patients (13 males) were enrolled and completed the study uneventfully. The baseline demographics and patients characteristics are detailed in table 1. Eleven patients were randomly assigned to the first group and ten patients to the second group (fig.1).

Study entry and post wash-out

Patient characteristics at the entry to each period of the study are shown in table 2. No carryover effect on the measured parameters was observed. As can be seen, there was no significant difference in AHI, respiratory distress index, nasal resistance, and breathing route pattern between the entry to the first period of the study (fig.1, first assessment) and the end of the washout period (fig.1, third assessment), i.e. entry to the second period of the study. Only total and REM sleep time increased in the third assessment compared to the first assessment.

Treatment effect differences

Treatment effect differences are summarized in table 3. AHI, AHI in supine position, respiratory distress index, nasal resistance, oral breathing epochs, oro-nasal breathing epochs and non-REM sleep time decreased, whereas nasal breathing epochs, minimum oxygen saturation, and REM sleep time increased with nasal tramazoline and dexamethazone compared with nasal placebo. ESS score change was not different between the nasal tramazoline and dexamethazone and nasal placebo groups.
The change of AHI after one-week therapy with nasal tramazoline with dexamethazone was inversely related to the change of nasal breathing epochs ($R_s=0.78; p<0.001; \text{fig. 2A}$). Conversely, the change of AHI after one-week therapy with nasal placebo did not correlate with the change of nasal breathing epochs ($R_s=0.38; p=0.055; \text{fig.2B}$). Additionally, the change of nasal resistance after one-week therapy with nasal tramazoline with dexamethazone did not correlate with either the change of AHI ($R_s=0.126; p=0.234$) or the change of nasal breathing epochs ($R_s=0.228; p=0.095$).

**Effect of treatment with nasal tramazoline and dexamethazone on AHI**

Individual and mean values of AHI at the start and end of the treatment period with nasal tramazoline and dexamethazone are shown in figure 3. There was a mean decrease of AHI by 21%. Among 21 patients, 3 (14%) had post-treatment AHI<10 events·h$^{-1}$.

**DISCUSSION**

The main findings of this randomized, placebo-controlled, double-blind, crossover trial on the effects of one-week application of nasal tramazoline with dexamethazone in OSA patients with normal nasal resistance at wakefulness were that this therapy: i) is associated with a decrease in oro-nasal breathing epochs, and a concomitant increase in nasal breathing epochs; ii) is associated with a mean decrease of AHI by 21%; and iii) the change in nasal breathing epochs is inversely related to the change in AHI, so that the increase in nasal breathing epochs explains 63.6% of the variance of the decrease in AHI.

The findings of this study corroborate the pathophysiologic pathway between nasal breathing and OSA. Indeed, given that nasal resistance measured at the beginning of the night is lower than subsequent measurements by 26±20%, it was assumed that nocturnal increased nasal resistance might play a role in the appearance of apnoeas in OSA patients with normal nasal resistance at wakefulness [10]. The current study adds to the literature by recruiting OSA patients with normal nasal resistance at wakefulness and demonstrating that the pharmacological prevention of the potential nocturnal increase of nasal resistance changes the breathing route pattern of OSA patients and decreases AHI, suggesting a strong correlation between
restoration of nasal breathing and improvement of AHI. Indeed, all previous studies, examining the role of nasal airway in sleep disordered breathing, have recruited OSA patients with nasal pathology or increased nasal resistance at baseline [6-8].

The factors that could explain the aforementioned correlation have been thoroughly studied in several trials, and are associated either with mouth opening/breathing or absence of nasal breathing. Thus, MEURICE et al [20] demonstrated that mouth opening increases upper airway collapsibility due to a combination of upper airway narrowing and a decrease in the efficiency of upper airway dilator muscle contraction. Further evidence in the same direction was added by MORIKAWA et al [21] who observed that opening the jaw decreased the mean distance between the tongue and posterior pharyngeal wall from 17.5 to 11 mm. Similarly, KUNA and REMMERS [22] suggested that mouth opening is associated with an inferior movement of the mandible compromising pharyngeal diameter. Combining the above observations with cephalometric studies [23], which demonstrate that apnoeics have a more posteriorly displaced mandible than normal subjects, it is not surprising that in OSA patients mouth opening leads easier to upper airway collapse. Additionally, there is data suggesting that irritation of nasal airflow-sensitive receptors during nasal breathing is important in maintaining upper airway patency by increasing oro-pharyngeal muscle activity. In fact, WHITE et al blocked these receptors using 4% lidocaine local anesthesia and provoked a four fold increase in the sleep disordered breathing events [24], and BASNER et al measured increased genioglossal and alae nasi electromyographic activity in awake humans breathing through the nose [25].

There are few randomized studies which all, as opposed to our study, recruited OSA patients with increased nasal resistance at baseline and investigated the effect of nasal medication on nocturnal breathing disturbances. In fact, KERR et al [26] studied the effect of oxymetazalone in combination with a vestibular stent, and found no change in AHI or in sleep efficiency, and an only minor reduction in arousal index despite a considerable reduction in nasal resistance. Furthermore, MCLEAN et al [27] applied oxymetazoline twice during the night in combination with an external nasal-valve dilator strip. This intervention was associated with a modest decrease in AHI and an improved sleep efficiency and architecture. KIELY et al [7] investigated the effect of nasal corticosteroid in OSA patients with rhinitis and found a modest reduction of nasal resistance, which was positively correlated with a decrease in AHI.
Lastly, CLARENBACH et al [13] applied once a nasal decongestant and measured nasal conductance continuously during sleep. The authors found reduced AHI during maximal nasal decongestion and thus suggested a pathophysiologic link between nasal resistance and sleep disordered breathing. The findings of most of the aforementioned trials are in accordance with the results of the current study, which also showed a modest decrease in AHI and an improvement in sleep architecture, as indicated by the increase in REM sleep time (table 3).

Besides the importance of the findings of the current study in elucidating upper airway physiology in OSA patients with normal nasal resistance at baseline, in terms of clinical relevance, AHI decreased by 21% and only 3 among 21 patients, notably those with the lowest AHI at baseline, had post-treatment AHI <10 events·h⁻¹. Therefore, our data suggest that the use of the combination of a nasal decongestant with a corticosteroid is not an effective treatment for OSA patients and could only be regarded as potential therapy for the less severe cases (i.e. AHI <15 events·h⁻¹) or as complementary to other treatment modalities. Moreover, the possibility of side-effects from the long-term use of the combination of nasal decongestant with nasal steroid should be borne in mind [28]. Indeed, each course of treatment should not exceed 14 days, because prolonged use has been associated with rebound congestion of the nasal mucosa and systemic effects of corticosteroids [28]. Consequently, it is evident that the benefits obtained by the combination of medication used in the current trial could only be achieved safely if used in a short-term basis, and thus the clinical relevance of our findings in the long-term remains unknown.

Some issues and possible weaknesses of the current study must be acknowledged and deserve consideration. Firstly, the study was adequately powered to detect an improvement in AHI of 5 events·h⁻¹, because any less improvement is unlikely to be clinically relevant. Secondly, the instrumentation of nasal cannula/pressure transducer and oral thermistor to detect airflow presents some drawbacks that have been thoroughly discussed previously [9]. Although these devices are non-obtrusive and easily tolerated, their signal-flow relationship is non-linear resulting in underestimation of nasal ventilation and overestimation of oral ventilation, especially at low flows [9]. Therefore, it would be possible that oral only breathing may still have a nasal component, and any detection of oral only breathing might actually be scarce. Thirdly, although sensor dislodgement from the nose or mouth was meticulously checked by the technician on duty, it is possible that slight
deviations in thermistor position may not have been completely avoided, and this may have then resulted in nasal airflow contamination of the oral signal. Fourthly, in the current study nasal resistance was not measured continuously, and thus it was not possible to directly, minute by minute, evaluate the association between nocturnal nasal resistance with the change in nasal breathing epochs and AHI. Fifthly, the increase in REM and total sleep time at the third assessment (table 2) could be attributed to the so called “first night effect” [29]. Lastly but not least, ESS is not designed to assess changes in the propensity to fall asleep within one week. However, experience with the rapid changes in subjective sleepiness that occur when OSA patients are treated with continuous positive airway pressure suggests that ESS might be adequate measure of sleepiness’ fluctuations even in a short-term basis [30].

In conclusion, the findings of the present study suggest that one-week application of nasal tramazoline with dexamethazone in OSA patients with normal nasal resistance at wakefulness decreases AHI by increasing nasal breathing epochs. However, the decrease in AHI is modest, thus the therapeutic role of preserving nasal airway patency on OSA severity remains rather limited.
REFERENCES


FIGURE LEGENDS

Figure 1. Study protocol. The study was undertaken according to a randomized, placebo-controlled, crossover design. After the first assessment, patients underwent a one-week treatment with either nasal tramazoline with dexamethazone or nasal placebo, followed by a washout period of two weeks and a one-week treatment with the other regimen. At the start and end of each treatment period, patients underwent an assessment, which consisted of an overnight polysomnography with concomitant measurement of breathing route pattern along with nasal resistance measurement.

Figure 2. Relationship between the change in nasal breathing epochs and the change in apnoea-hypopnoea index (events·h⁻¹) A) after one-week therapy with nasal tramazoline with dexamethazone (Rₛ=0.78; p<0.001), and B) after one-week therapy with nasal placebo (Rₛ=0.38; p=0.055). TSE: total sleep epochs.

Figure 3. Individual (circles) and mean (horizontal lines) values of apnoea-hypopnoea index (events·h⁻¹) at the start and end of treatment period with nasal tramazoline and dexamethazone.
Table 1. Anthropometric data and baseline sleep parameters and nasal resistance values.

<table>
<thead>
<tr>
<th>Study participants n</th>
<th>21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age  yrs</td>
<td>38.0±7.7</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>13 (62)</td>
</tr>
<tr>
<td>Body mass index  kg·m⁻²</td>
<td>30.7±2.9</td>
</tr>
<tr>
<td>Apnoea-hypopnoea index events·h⁻¹</td>
<td>31.1±14.8</td>
</tr>
<tr>
<td>Respiratory distress index  events·h⁻¹</td>
<td>33.6±17.5</td>
</tr>
<tr>
<td>Nasal Resistance supine cmH₂O·L⁻¹·s</td>
<td>2.2±0.3</td>
</tr>
<tr>
<td>Lowest oxygen saturation  %</td>
<td>84.7±4.2</td>
</tr>
<tr>
<td>Mean duration of apnoea-hypopnoea  s</td>
<td>18.8±5.8</td>
</tr>
<tr>
<td>Longest duration of apnoea-hypopnoea  s</td>
<td>27.5±7.9</td>
</tr>
<tr>
<td>Total sleep time min</td>
<td>304.5±68.3</td>
</tr>
<tr>
<td>Sleep efficiency  %</td>
<td>88.4±13.3</td>
</tr>
<tr>
<td>Non-REM  min</td>
<td>248.9±57.8</td>
</tr>
<tr>
<td>REM  min</td>
<td>55.6±21.8</td>
</tr>
<tr>
<td>Sleep time in supine posture min</td>
<td>155.5±104.0</td>
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<tr>
<td>Epworth Sleepiness Scale score</td>
<td>9.9±3.6</td>
</tr>
</tbody>
</table>

Data are presented as n, n (%) or mean±SD.
Table 2. Patient characteristics at the entry to each study period

<table>
<thead>
<tr>
<th></th>
<th>Start of study#</th>
<th>End of washout period\¶</th>
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<tbody>
<tr>
<td>Apnoea-hypopnoea index events·h(^{-1})</td>
<td>31.1±14.8</td>
<td>28.8±11.9</td>
</tr>
<tr>
<td>Respiratory distress index events·h(^{-1})</td>
<td>33.6±17.5</td>
<td>31.2±19.2</td>
</tr>
<tr>
<td>Nasal Resistance supine cmH(_2)O·L(^{-1})·s(^{-1})</td>
<td>2.2±0.3</td>
<td>2.1±0.4</td>
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<tr>
<td>Nasal breathing epochs %</td>
<td>64.3±6.8</td>
<td>67.0±6.2</td>
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<tr>
<td>Oral breathing epochs %</td>
<td>2.4±1.4</td>
<td>2.1±1.5</td>
</tr>
<tr>
<td>Oronasal breathing epochs %</td>
<td>33.3±4.6</td>
<td>30.9±4.9</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale score</td>
<td>9.9±3.6</td>
<td>8.8±2.0*</td>
</tr>
<tr>
<td>Total sleep time min</td>
<td>304.5±68.3</td>
<td>345.8±43.7*</td>
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<tr>
<td>Non-REM sleep time min</td>
<td>248.9±57.8</td>
<td>242.6±49.9</td>
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<tr>
<td>REM sleep time min</td>
<td>55.6±21.8</td>
<td>103.2±42.5*</td>
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<tr>
<td>REM sleep time/total sleep time %</td>
<td>18.3±3.8</td>
<td>29.8±4.3*</td>
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<tr>
<td>Sleep efficiency %</td>
<td>88.4±13.3</td>
<td>92.5±10.1</td>
</tr>
</tbody>
</table>

Data are presented as mean±S.D. \#: first assessment in figure 1; \¶: third assessment in figure 1. \*: p<0.05 versus start of study (paired t-test).
Table 3. Treatment effect differences

<table>
<thead>
<tr>
<th></th>
<th>Nasal tramazoline with dexamethazone</th>
<th>Nasal placebo</th>
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<tr>
<td>Apnoea-hypopnoea index events·h⁻¹</td>
<td>-6.1(-10.7–-2.2)</td>
<td>-1.2 (-5.3–5.0)*</td>
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<tr>
<td>Respiratory distress index events·h⁻¹</td>
<td>-8.2 (-12.8–-4.1)</td>
<td>0.1(-3.1–8.4)*</td>
</tr>
<tr>
<td>Nasal Resistance supine cmH₂O·L⁻¹·s</td>
<td>-0.6(-0.8–-0.3)</td>
<td>-0.1 (-0.2–-0.1)*</td>
</tr>
<tr>
<td>Nasal breathing epochs % TSE</td>
<td>13.0(9.5-16.6)</td>
<td>-0.4 (-3.4–2.4)*</td>
</tr>
<tr>
<td>Oral breathing epochs % TSE</td>
<td>-0.8(-1.9—0.4)</td>
<td>0.0 (-0.6–0.2)*</td>
</tr>
<tr>
<td>Oronasal breathing epochs % TSE</td>
<td>-10.0(-13.2—7.6)</td>
<td>0.3 (-1.6–3.4)*</td>
</tr>
<tr>
<td>Minimum oxygen saturation %</td>
<td>0.6(-0.2–0.9)</td>
<td>0.1(-0.5–1.1)*</td>
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<tr>
<td>Average oxygen saturation %</td>
<td>0.9(-0.1–1.9)</td>
<td>0.3(-0.5–1.4)</td>
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<tr>
<td>Epworth Sleepiness Scale score</td>
<td>-1.0(-4.0–0.0)</td>
<td>-1.0(-2.0—0.5)</td>
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<tr>
<td>Total sleep time min</td>
<td>4.6(-7.2–15.9)</td>
<td>2.2(-8.2–19.9)</td>
</tr>
<tr>
<td>Non-REM sleep time min</td>
<td>-16.6(-36.2–7.9)</td>
<td>-3.8(-12.5–11.9)*</td>
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<tr>
<td>REM sleep time min</td>
<td>23.6(5.2–35.9)</td>
<td>5.6(1.2–15.6)*</td>
</tr>
<tr>
<td>Sleep efficiency %</td>
<td>2.9(0.8–10.2)</td>
<td>2.4(0.2–8.6)</td>
</tr>
<tr>
<td>Sleep time in supine position %</td>
<td>1.0 (-1.2–4.2)</td>
<td>2.1 (-0.6–5.6)</td>
</tr>
<tr>
<td>Apnoea-hypopnoea index in supine position events·h⁻¹</td>
<td>-3.1 (-8.9–7.6)</td>
<td>0.8 (-3.2–8.9)*</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range). TSE: total sleep epochs. *: p<0.01 versus nasal tramazoline with dexamethazone (Wilcoxon signed rank test).
*Figure 1.* Study protocol. The study was undertaken according to a randomized, placebo-controlled, crossover design. After the first assessment, patients underwent a one-week treatment with either nasal tramazoline with dexamethazone or nasal placebo, followed by a washout period of two weeks and a one-week treatment with the other regimen. At the start and end of each treatment period, patients underwent an assessment, which consisted of an overnight polysomnography with concomitant measurement of breathing route pattern along with nasal resistance measurement.
Figure 2. Relationship between the change in nasal breathing epochs and the change in apnoea-hypopnoea index (events·h⁻¹) A) after one-week therapy with nasal
tramazoline with dexamethazone ($R_s=0.78; p<0.001$), and B) after one-week therapy with nasal placebo ($R_s=0.38; p=0.055$). TSE: total sleep epochs.

**Figure 3.** Individual (circles) and mean (horizontal lines) values of apnoea-hypopnoea index (events·h$^{-1}$) at the start and end of treatment period with nasal tramazoline and dexamethazone.