BACKGROUND

Obstructive sleep apnoea (OSA) is characterised by recurrent episodes of partial or complete upper airway collapse during sleep and is highly prevalent in the general population.1,2 Daytime consequences of OSA are a range of symptoms, including excessive sleepiness, neurocognitive impairment and mood disturbance, which significantly impair the quality of life.3 In addition, there is an increased incidence of cardiovascular mortality, stroke and heart attack.4-6 Thus, OSA is a major public health problem, imposing a financial burden on healthcare systems.7,8

There are a variety of treatment options currently available for OSA ranging from lifestyle modifications, such as weight loss, to invasive soft tissue and/or orthognathic surgery. Continuous positive
Airway pressure (CPAP) is the most efficient treatment for OSA and has been demonstrated to improve many health outcomes, including sleepiness and quality of life, and to reduce the incidence of cardiovascular events. Despite these changes, adherence is often poor with many patients either rejecting treatment or only partially tolerating it, which may result in untreated OSA. Mandibular advancement devices (MAD) are widely used for the treatment of OSA. Although the overall effects of these devices on sleep-disordered breathing may be inferior to CPAP, their acceptance is generally higher. MAD have some limitations of contraindication for patients with severe periodontal disease, temporomandibular joint dysfunction or edentulous. As it is difficult to cover all OSA patients by CPAP and OA, development of new treatments for OSA is desired.

The concept of nasopharyngeal tube insertion to maintain airflow through the upper airway during sleep was reported in the 1980s and was recently reviewed. This systematic review demonstrated that nasopharyngeal airway stent devices (nasal trumpet) were successful in decreasing airway obstruction in the short term, such as for emergency care professionals, but had limited effectiveness and low tolerability. The nasal airway stent (Nastent), which was a tube-shaped medical device, was developed from a softer and thinner material than previous devices and termed as a nasopharyngeal airway stent device instead of nasal trumpet. Nastent is specifically designed as a nasopharyngeal stent that maintains the patency of the nasal airway to the nasopharynx and retropalatal oropharynx during sleep. Nastent treatment is a new concept different from CPAP and MAD treatment and has the potential for use in OSA patients who cannot tolerate CPAP or have contraindications for MAD due to a poor dental condition. We performed a prospective study to evaluate the efficacy of Nastent treatment and examine the predictors for Nastent treatment outcomes.

2 | METHODS

2.1 | Subjects

Consecutively, the subjects were recruited from Osaka University Dental Hospital, Japan, between December 2016 and February 2017. To meet the inclusion criteria, each subject required a previous diagnosis of OSA by overnight polysomnography defined as an AHI >5.0 in a sleep laboratory using standard parameters. Subjects were excluded if they had previous nasal surgery or exhibited neuromuscular disease and/or cardiovascular disease. Written informed consent was obtained from all participants before this study, which was approved by the Osaka University Ethics Committee (Osaka University Dental Hospital, No. H28-E25). This study was registered with the Japanese Clinical Trial Registry “UMIN-CTR” on 4 November 2016 (UMIN000024617).

2.2 | Nasal airway stent

The nasal airway stent (Nastent) used in this trial is a preformed silicon device that maintains the patency of the nasal airway to the nasopharynx and retropalatal oropharynx by mechanically preventing upper airway obstruction (Seven Dreamers Laboratories, Inc., Tokyo, Japan). A point of difference from previous nasopharyngeal airway stents was a softer and thinner material to improve a wear feeling. The device consists of a tube-shaped shaft (4.4-mm in internal diameter) encapsulated by a water-soluble gel as a lubricant and a proximal nose clip to fix the device in the appropriate position for optimal treatment efficacy (Figure 1A). Although the material of Nastent was softness, it accomplished to maintain not to collapse by a pressure of more than 20 cm H$_2$O in an airflow of 0.1 to 0.51 L/s, approximately the maximum speed of inspiration under normal breathing conditions. Nastent devices in a variety of lengths (120 to 145 mm) were...
manufactured to enable appropriate treatment efficacy for all subjects. The distal end of the Nastent is inserted via the nostril into the nasal cavity until it reaches the retropalatal oropharynx (Figure 1B).

2.3 | Sleep study
The sleep study was performed with the Watch-PAT (Itamar Medical Caesarea, Israel), an FDA-approved portable diagnostic device, consisting of peripheral arterial tonometry (PAT) probe, a wrist-mounted device and oxygen saturation monitor, with snoring monitor to assess the state of OSA at baseline and follow-up. The Watch-PAT was chosen for this study because it does not require a nasal pressure or airflow sensor, which may disturb Nastent fitting. The Watch-PAT has been well validated against standard in-laboratory polysomnography. The device records PAT, heart rate, oxygen saturation and actigraphy, which are then analysed by the device software. The PAT detects episodes of upper airway obstruction indirectly through identification of altered sympathetic tone, whereas actigraphy data are used to distinguish sleep versus wakefulness and estimate sleep time.

2.4 | Cephalogram
In this study, lateral cephalometric radiographs CX150WT (Asahi, Kyoto, Japan) were obtained to analyse the craniofacial morphology at baseline. The film was taken when the subject sat upright with Frankfort plane parallel to the ground, naturally closed lips, and the bite in intercuspal occlusion with relaxation of the tongue and perioral muscles as previously described. To analyse the cephalograms, all distances and angles were manually measured by image analysis software (ImageJ; http://imagej.nih.gov/ij/). To minimise identification error, all measurements were performed blindly such that the investigator was unable to identify names of patients. Cephalometric analysis was carried out as previously described (Figure 2).

2.5 | Study protocol and treatment outcome
For baseline assessment, standardised cephalometric radiographs were obtained. Each subject completed the Epworth Sleepiness Scale (ESS) questionnaires and portable sleep study with Watch-PAT to evaluate the baseline level of OSA at home. Upon intervention, the first author (K.O.) selected the appropriate Nastent length to place the tip of the Nastent between the uvula and the epiglottis for each subject, and then instructed and trained all subjects on how to insert the Nastent into the nasal cavity by themselves. After a one-month acclimatisation period, the follow-up assessment was performed. Subjective compliance was evaluated by measuring hours per night and the number of days per week from the questionnaires. Each subject completed the ESS questionnaires and a second portable sleep study with Watch-PAT to evaluate the efficacy of the Nastent device at home.

Primary outcomes were respiratory event index (REI), oxygen desaturation index (ODI), lowest SpO₂ and cumulative time percentage with SpO₂ < 90% (CT90), as the indices of respiratory disorders. Secondary outcome was ESS, as the index of daily sleepiness. Treatment responders were defined as subjects who had a reduction in REI of >50% compared with the baseline REI.

2.6 | Statistical analysis
All data were analysed by SPSS 15.0 statistical software (SPSS Inc., Chicago, IL, USA). Descriptive statistics for clinical characteristics were presented as mean ± SD. Continuous variables were evaluated
with a paired $t$ test to compare between baseline and follow-up, and with an unpaired $t$ test to compare between responders and non-responders follow-up. A receiver operator characteristic (ROC) curve was used to analyse the predictors and the best cut-off value for the treatment responders. A $P$-value of <0.05 indicated significance.

## 3 | RESULTS

Forty-six patients who meet the inclusion criteria were recruited in this study. Sixteen subjects refused enrolment. The reasons of non-participant were time constraint ($n = 7$), unwilling to insertion of Nastent ($n = 7$) and desire to other treatments ($n = 2$). Thirty subjects consented to participate in this study and signed the consent form. One subject dropped out from the study because of uncomfortable treatment. In total, 29 subjects completed this study. Table 1 shows the subject characteristics. The percentage of males was 62.1%, with a mean age of 61.6 ± 10.2 years and body mass index (BMI) of 24.3 ± 3.3 kg/m². The baseline AHI was 25.2 ± 16.5/h.

Table 2 presents the efficacy of Nastent treatment. There were significant decreases in REI, ODI, CT90 and ESS, and a significant increase in the lowest SpO₂ by Nastent treatment. Subjects were divided into responders and non-responders based on a reduction in REI of >50% compared with the baseline REI. The number of responders was 11 subjects and of non-responders was 18 subjects. In the responders group, there were greater improvements in REI, ODI, lowest SpO₂, CT90 and ESS compared with all subjects. Side effects of the Nastent device were uncomfortable nasal insertion and discomfort while wearing the Nastent device and during swallowing. Three subjects reported that a little blood was attached to the outside of the Nastent tube, but there was no bleeding from the nose. Although one subject dropped out due to discomfort from the Nastent device, side effects in all other patients did not affect their adherence during this study. Therefore, these side effects were considered to be minor.

Table 3 shows the subject characteristics and cephalogram parameters in responders and non-responders. There was no significant difference between responders and non-responders in age, BMI or baseline AHI. On cephalograms, there was no significant difference between responders and non-responders in SNA, SNB or ANB as the indices of skeletal structure. There was also no significant difference in PNS-P as the index of the length of the soft palate, in PNS-Eb as the index of the vertical length of the upper airway or in MP-H as the index of the position of the hyoid. Furthermore, there was no significant difference in middle airway width (MAW). Only inferior airway width (IAW) was significantly greater in responders than in non-responders. We further analysed the ratio of IAW and MAW (IAW/MAW) as the index of the narrowest site of the airway. IAW/MAW was significantly higher in responders than in non-responders.

We further focused on the IAW/MAW as a parameter to predict Nastent treatment response. Figure 3 shows the ROC curves for the IAW/MAW for the responders to Nastent treatment. The estimated area under the curve (AUC) was 0.87. The best cut-off value for the IAW/MAW was 1.10. The best combination of sensitivity/specifity and positive predictive value (PPV)/negative predictive value (NPV) was 90.9%/88.9% and 83.3%/94.1%, respectively, whereas positive likelihood ratio (LR+)/negative likelihood ratio (LR−) was 8.18/0.10 when IAW/MAW was set at 1.10.

## 4 | DISCUSSION

This study demonstrates the efficacy of the Nastent device in patients with mild to severe OSA and predicts Nastent treatment response using cephalograms. This predictive method is clinically straightforward and has good sensitivity and specificity. This study is the first to evaluate the efficacy of the Nastent device and the clinical utility of cephalograms for the prediction of Nastent treatment outcomes in patients with mild to severe OSA.
In a pilot study, AHI after Nastent treatment improved from 19.5 ± 6.6 to 10.4 ± 5.0 in six OSA patients. All patients tolerated the Nastent device with good compliance and had improvements in AHI and oxygen saturation. This pilot study had a limitation that there were only six patients with mild or moderate OSA, and severe OSA was not included. In the current study, 29 subjects with mild to severe OSA were included.

Positioning of the nasal airway stent is important for effective therapy. It was recommended that the distal tip of the nasal trumpet protrudes beyond the pharyngeal surface of the soft palate, but not past the epiglottis. Stoneham et al reported that the ideal position for the distal tip of the nasopharyngeal airway was within 10 mm of the tip of the epiglottis; for most men, this would be a length of 150 mm and 130 mm for most women. In our study, the first author (K.O.) selected the appropriate Nastent length to place the tip of the Nastent between the uvula and the epiglottis in each subject, and the mean length of the Nastent was 140.8 ± 5.5 mm in men and 128.6 ± 6.7 mm in women. These were shorter than in previous studies, and there may be a difference in the craniofacial morphology between Caucasians and Asians.

In terms of the efficacy of Nastent, there were significant changes in REI, ODI, lowest SpO2, CT90 and ESS. Although there was significant improvement in all subjects, the number of responders with a reduction in REI of >50% compared with the baseline REI was 11 subjects. This result was not clinically sufficient. The stenting effects of the nasal airway stent help to prevent obstruction at the level of the nasopharynx and oropharynx. It has been noted that the soft palate has a wing-like shape, which causes the palate to lift upward into the nasopharynx when there is negative intranasal pressure, predisposing the patient to airway collapse. Additionally, the outer nose itself is susceptible to structural changes.

**TABLE 3** Patient characteristics of responders and non-responders

<table>
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<th>All</th>
<th>Responders</th>
<th>Non-responders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean ± SD</td>
<td>mean ± SD</td>
<td>mean ± SD</td>
</tr>
<tr>
<td>Age (y)</td>
<td>61.6 ± 10.2</td>
<td>61.2 ± 8.7</td>
<td>61.9 ± 11.3</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>24.3 ± 3.3</td>
<td>25.5 ± 3.6</td>
<td>23.5 ± 3.0</td>
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<td>AHI (/h)</td>
<td>25.2 ± 16.5</td>
<td>23.9 ± 15.2</td>
<td>26.1 ± 17.6</td>
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<tr>
<td>Usage (d/wk)</td>
<td>6.2 ± 1.5</td>
<td>5.6 ± 2.2</td>
<td>6.6 ± 0.8</td>
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<tr>
<td>Usage (h/d)</td>
<td>6.5 ± 1.1</td>
<td>6.0 ± 1.2</td>
<td>6.9 ± 1.1</td>
</tr>
</tbody>
</table>

**Cephalometry**

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Responders</th>
<th>Non-responders</th>
</tr>
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<tbody>
<tr>
<td>SNA (°)</td>
<td>83.0 ± 3.6</td>
<td>82.4 ± 3.3</td>
<td>83.4 ± 3.8</td>
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<tr>
<td>SNB (°)</td>
<td>78.7 ± 3.0</td>
<td>78.4 ± 3.0</td>
<td>78.9 ± 3.0</td>
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<td>ANB (°)</td>
<td>4.3 ± 2.3</td>
<td>4.0 ± 2.0</td>
<td>4.5 ± 2.5</td>
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<tr>
<td>PNS-P (mm)</td>
<td>41.3 ± 6.7</td>
<td>43.0 ± 6.5</td>
<td>40.3 ± 6.7</td>
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<tr>
<td>PNS-Eb (mm)</td>
<td>78.2 ± 8.2</td>
<td>79.6 ± 9.2</td>
<td>77.3 ± 7.7</td>
</tr>
<tr>
<td>MP-H (mm)</td>
<td>17.5 ± 5.0</td>
<td>18.9 ± 4.2</td>
<td>16.6 ± 5.3</td>
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<tr>
<td>MAW (mm)</td>
<td>11.2 ± 3.3</td>
<td>10.0 ± 3.3</td>
<td>11.9 ± 3.1</td>
</tr>
<tr>
<td>IAW (mm)</td>
<td>11.7 ± 3.4</td>
<td>13.5 ± 3.5</td>
<td>10.6 ± 2.9</td>
</tr>
<tr>
<td>IAW/MAW</td>
<td>1.1 ± 0.4</td>
<td>1.4 ± 0.3</td>
<td>0.9 ± 0.4</td>
</tr>
</tbody>
</table>

Data are shown as mean ± SD. *P < 0.05, **P < 0.01. BMI, body mass index; AHI, apnoea hypopnea index; ODI, oxygen desaturation index; ESS, Epworth sleepiness scale; MAW, middle airway width; IAW, inferior airway width.

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**FIGURE 3** Receiver operating characteristic curves for the ratio of IAW and MAW (IAW/MAW). The best cut-off value for the IAW/MAW was 1.10. The best combination of sensitivity/ specificity and PPV/NPV was 90.9%/88.9% and 83.3%/94.1%, respectively, whereas LR+/LR− was 8.18/0.10 when IAW/MAW was set at 1.10 [Colour figure can be viewed at wileyonlinelibrary.com]
to Bernoulli’s principle, as the negative intranasal pressure may induce collapse of the internal and external nasal valves in some patients. The Nastent is also designed to maintain airflow through the nasopharynx and retropalatal oropharynx by mechanically preventing upper airway obstruction by the movement and vibration of the soft palate during sleep, but it does not ameliorate hypopharyngeal airway obstruction theoretically. It was reported that the upper airway collapse patterns during sleep were at the level of the palate, the tongue base and the epiglottis. There were frequently observed combinations of collapse levels. Collapse at the epiglottis level was observed in 44.1%. In this study, non-responders may have had a collapse pattern at the epiglottis level where the Nastent tube did not reach.

We focused on the obstruction site in the airway as the predictor for Nastent treatment response. We further analysed the ratio of IAW and MAW (IAW/MAW) as the index of the narrowest site of the airway. The IAW/MAW was significantly higher in responders than in non-responders and provided ROC curves for the responders to Nastent treatment with high predictive accuracy. This suggests that the Nastent treatment may be more effective in patients with a narrower velopharynx than hypopharynx.

This study has a number of potential limitations. The first limitation was the small sample size and the potential for selection bias because all subjects were selected from a specialised university dental hospital clinic with a research interest. However, we consider this to be of minimal influence because this study had data from both responders (n = 11) and non-responders (n = 18). Another potential limitation is the limited sleep study. In the current study, the WatchPAT, a limited sleep study without electroencephalogram, was used to assess the level of OSA. Therefore, it was impossible to assess the influence on sleep architecture by Nastent treatment. This was necessary because of the expense associated with the sleep studies. We believe portable sleep study is appropriate for treatment follow-up once the diagnosis of OSA has been established. In terms of AHI validity and reliability, high validity and reliability were reported compared with polysomnography. Therefore, we consider the efficacy for sleep-disordered breathing to be of minimal influence. Lastly, only the short-term efficacy and side effects were observed in this study. Ideally, a long-term study design is desired, especially regarding treatment adherence.

In conclusion, this study validated the efficacy of Nastent treatment in patients with mild to severe OSA. Our study demonstrated improvement in OSA with the Nastent device and predicted treatment response with good sensitivity and specificity using cephalograms. This suggests that Nastent treatment may be more effective in patients with a narrower velopharynx than hypopharynx.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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