The effect of neck extension on success rate of blind intubation through Ambu® AuraGain™ laryngeal mask: a randomized clinical trial

Effet de l'extension du cou sur le taux de succès d'intubation à l'aveugle à travers le masque laryngé Auragain™ d'Ambu®: étude clinique randomisée

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Abstract

Purpose Although the use of fiberoptic guidance is recommended for tracheal intubation through supraglottic airway devices, it can also be performed in a blind manner. Based on the previous finding that a fiberoptic view of the vocal cords was better in the extended neck position than in the neutral position, we hypothesized that neck extension can better facilitate blind intubation through the Ambu® AuraGain™ laryngeal mask than the neutral position.

Methods Patients undergoing general anesthesia were randomly assigned to the extension group or the neutral group. After induction of anesthesia, the AuraGain™ was placed in the oropharynx, followed by blind intubation through the AuraGain™ in the assigned neck position within a maximum of two attempts. The primary outcome was successful blind intubation through the AuraGain™ in the first attempt.

Results Of 168 adult patients screened, 124 patients were enrolled and 121 patients were included in the final analysis (extension group, $n = 59$; neutral group, $n = 62$).

The incidence of successful blind intubation on the first attempt was significantly higher in the extension group than in the neutral group (68% vs. 47%, respectively; relative risk [RR], 1.45; 95% confidence interval [CI], 1.05 to 1.99; $P = 0.02$). The overall incidence of successful blind intubation was also significantly higher in the extension group than in the neutral group (71% vs 50%, respectively; RR, 1.42; 95% CI, 1.06 to 1.92; $P = 0.02$). The time required for successful blind intubation and the incidence of hoarseness, cough, or sore throat at 24 hr after extubation did not differ between groups.

Conclusion Neck extension can be used to facilitate blind intubation through the Ambu® AuraGain™ laryngeal mask. Considering the relatively high failure rate, blind intubation via the AuraGain™ should be used as an alternative, not as a first-line choice.

Trial registration www.ClinicalTrials.gov (NCT03408431); registered 24 January 2018.

Résumé

Objectif Même si l'utilisation de l'endoscopie est recommandée pour l'intubation trachéale à travers des dispositifs pour voies respiratoires supraglottiques, elle peut être réalisée à l'aveugle. Considérant qu'il a été démontré que la vue endoscopique des cordes vocales était meilleure lorsque le cou est en extension que lorsqu'il est en position neutre, nous avons émis l'hypothèse que l'intubation en aveugle à travers le masque laryngé Auragain™ d'Ambu® pouvait être plus facile avec le cou en extension qu'avec le cou en position neutre.

Méthodes Des patients subissant une anesthésie générale ont été randomisés dans un groupe « en extension » ou

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dans un groupe « position neutre ». Après induction de l'anesthésie, l'AuragainTM a été positionné dans l'oropharynx, avant une intubation à l'aveugle à travers l'AuragainTM dans la position assignée avec un maximum de deux tentatives. Le critère d'évaluation principal était la réussite de l'intubation à l'aveugle à travers l'AuragainTM à la première tentative.

Résultats Sur les 168 patients adultes sélectionnés, 124 ont été recrutés et 121 patients ont été inclus dans l'analyse finale (groupe en extension, $n = 59$; groupe en position neutre, $n = 62$). L'incidence des intubations à l'aveugle réussies à la première tentative a été significativement plus élevée dans le groupe en extension que dans le groupe en position neutre (respectivement, 68 % contre 47 %; risque relatif [RR], 1,45; intervalle de confiance [IC] à 95 % : 1,05 à 1,99; $P = 0,02$). L'incidence globale des intubations à l'aveugle réussies a aussi été significativement plus élevée dans le groupe en extension que dans le groupe en position neutre (respectivement, 71 % contre 50 %; RR, 1,42; IC à 95 %, 1,06 à 1,92; $P = 0,02$). Le temps nécessaire à la réussite de l'intubation à l'aveugle et les incidences de voix rauque, de toux et de mal de gorge 24 heures après l'extubation étaient comparables entre les deux groupes.

Conclusion Le positionnement du cou en extension peut faciliter une intubation à l'aveugle à travers le masque laryngé AuragainTM d'Ambu®. Considérant le taux d'échec relativement élevé, la technique d'intubation à l'aveugle au moyen de l'AuragainTM doit être utilisée comme une alternative et non en première intention.

Enregistrement de l'essai clinique www.ClinicalTrials.gov (NCT03408431); enregistré le 24 janvier 2018.

Traditionally, tracheal intubation was considered to be the most important part of airway management, but in recent years, supraglottic airway devices (SADs) have provided a crucial alternative to airway management in the field of anesthesia and emergency medicine. Several guidelines for difficult airway management have included the use of SADs, especially for “can't intubate, can't oxygenate” patients.^{1,2}

Since the introduction of the intubating laryngeal mask airway (LMA® FastrachTM Airway; Teleflex Medical, Athlone, Ireland),³ a number of second generation SADs have been developed; these devices can also be used as a conduit for tracheal intubation. In previous studies, the success rate of intubation through SADs was reported as 79–96% under fiberoptic guidance,^{4,5} and 15–77% in a blinded manner.^{6–9} Considering the low success rate and wide variability, according to the type of SAD used and the

experience of the operator, blind intubation through SADs is not currently implemented in routine practice.

Recently, a high success rate of blind intubation through the air-Q®sp Self-Pressurizing Masked Laryngeal Airway (Mercury Medical®, FL, USA), a second generation SAD, was reported.¹⁰ Although only fiberoptic-guided tracheal intubation through a SAD was recommended in the guidelines for difficult airway management,¹ it requires special equipment and may be limited by bleeding or secretions. Therefore, blind intubation through SADs still has clinical implications for anesthesiologists who need to manage patients with difficult airways.

In our previous study, we found that a fiberoptic view of the vocal cords through the Ambu® AuraGainTM laryngeal mask (Ambu A/S, Ballerup, Denmark) was improved when using the extended neck position compared with the neutral position.¹¹ We therefore hypothesized that neck extension can better facilitate blind intubation through the AuraGainTM compared with the neutral position. The purpose of this study was to evaluate the effect of neck extension on the success rate of blind intubation by comparing the incidence of successful blind intubation through the AuraGainTM in the extended neck position and in the neutral head and neck position.

Methods

Ethical approval for this study (No. 1709-123-890) was granted by the institutional review board of the Seoul National University Hospital on 10 January 2018. After obtaining written informed consent from patients, we screened adult patients (aged ≥ 19 yr) scheduled for procedures under general anesthesia with tracheal intubation for eligibility. The exclusion criteria were as follows: emergency operation, oropharyngeal disease, cervical spine disorder, insufficient *npo* time, esophageal disease, pregnancy, weak dentation, mouth opening < 2 cm, and other contraindications for insertion of SAD. This randomized-controlled trial was registered at ClinicalTrials.gov (NCT03408431) on 24 January 2018, and was conducted in accordance with the Declaration of Helsinki.

Patients were divided into two groups, an extension group (the extended neck position) or a neutral group (the neutral head and neck position), based on a computer-generated randomization list. We performed blocked randomization with a randomly selected block size of 2 or 4 in a reproducible sequence. The randomization list was kept by the preparing nurse who was not involved in the study, and group allocation was released only before induction of anesthesia. Due to the nature of this study, the operator who performed blind intubation was not blinded

to group allocation, but patients and outcome assessors were blinded to group allocation and the purpose of this study.

Patients were admitted to the operating room without any premedication. Before induction of anesthesia, the following data were collected: Mallampati score, interincisor distance, thyromental distance, range of motion for neck extension, and presence of edentulism. Anesthesia was induced with 2 mg.kg⁻¹ propofol and target-controlled infusion of remifentanyl using Orchestra® Module DPS (Fresenius Kabi AG, Bad Homburg, Germany). After confirmation of loss of consciousness based on a Bispectral Index™ (Medtronic, Minneapolis, MN, USA) value less than 60 and unresponsiveness to their name, 0.6 mg.kg⁻¹ rocuronium was administered for neuromuscular blockade. Following manual ventilation with 3–4% sevoflurane in oxygen, a deflated and lubricated AuraGain™ was gently inserted into the oropharynx in the sniffing position. Considering that size 5 may not be suitable for Asian populations,^{12,13} we chose size 3 for female patients and size 4 for male patients, not based on body weight as per the manufacturer's recommendation. We determined the appropriate position of the AuraGain™ based on the ventilation score, defined as the total score of the following three assessments: 1) no leakage at airway pressure of 15 cmH₂O, 2) bilateral chest expansion, and 3) a square waveform on capnography.¹⁴

After securing the AuraGain™, the patients' head and neck were placed in the neutral or the extended neck position according to group assignment. The neck was extended using a 5 cm pillow under the shoulder in the extension group, while the head and neck were neutrally positioned using a 5 cm pillow under the occiput in the neutral group. The maximal angle allowed for neck extension was 60° to avoid excessive extension and was measured using a protractor. A conventional tracheal tube (Shiley™ TaperGuard Oral/Nasal Tracheal Tube; Medtronic, Minneapolis, MN, USA) with an internal diameter of 6 or 7 mm was chosen for female and male patients, respectively. A lubricated tracheal tube was inserted through the AuraGain™ in a blind manner. Mild adjustments, such as jaw thrust, cricoid pressure, or twisting the tube were allowed if resistance was encountered. Successful blind intubation was determined by detection of end-tidal CO₂ and bilateral chest expansion. Time required for the AuraGain™ insertion was recorded and was defined as the time from the passage of the AuraGain™ through the mouth to the detection of end-tidal CO₂. If blind intubation failed at the first attempt, the tracheal tube was withdrawn and manual ventilation with the AuraGain™ was applied for 20 sec to avoid deoxygenation. In the second attempt, the tracheal tube was rotated 180° to the reverse-tube orientation, which aims the tube straight along the curvature of the AuraGain™. If blind intubation failed in both attempts, the AuraGain™ was removed and tracheal

intubation was performed using direct laryngoscopy. If blind intubation succeeded, the AuraGain™ remained in the oropharynx and was tightly secured to the tracheal tube to prevent accidental extubation. All attempts were conducted by a single investigator (S.Y.) with experience of more than 20 cases of blind intubation through the AuraGain™. Outcomes were assessed by an independent observer.

The primary outcome of this study was the incidence of successful blind intubation through the AuraGain™ on the first attempt. Secondary outcomes included the incidence of overall successful blind intubation, time required for successful blind intubation, and the incidence of hoarseness, cough, and sore throat at 24 hr after extubation. The time required for successful blind intubation was defined as the duration between insertion of a tracheal tube into the AuraGain™ and detection of end-tidal CO₂. Hoarseness was assessed by an independent observer, using a four-point scoring system: none, noticed by the patient only, apparent to an observer, or aphonia.¹⁰ Cough and sore throat were evaluated as none, mild (less than a common cold), moderate (similar to a common cold), or severe (more than a common cold).¹⁵

Statistical analysis

Sample size calculation was based on a previous study that reported a success rate of 68.7% for blind intubation at the first attempt.¹⁰ Assuming that neck extension may increase the success rate of blind intubation to 90%, 56 patients per group would be necessary to provide a power of 0.8 with a two-sided α of 0.05. We chose a sample size of 124 patients overall to allow a dropout rate of 10%.

Continuous variables are presented as mean (standard deviation) or median [interquartile range] after assessing normality by means of the Shapiro-Wilk test. Categorical variables are presented as number (percentage). We used Chi-square tests or Fisher's exact tests (when the contingency table had more than 20% of cells with an expected frequency of less than 5) to compare categorical variables, and Student's *t* test or Wilcoxon rank-sum test to compare continuous variables. A confidence interval (CI) for the difference in medians was calculated using the bootstrap method.

To identify the factors associated with successful blind intubation, we used logistic regression analysis using demographic and anthropometric variables, including age, sex, body mass index, Mallampati score, interincisor distance, thyromental distance, presence of edentulism, and neck extension. All variables were forced to be included in the final model. The results from the logistic regression analyses were presented as odds ratio, 95% CI, and *P*-values. This analysis was defined post-hoc; therefore, the results should be interpreted as exploratory.

R software version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses, and $P < 0.05$ was considered statistically significant.

Results

Of 167 patients screened for eligibility, 124 patients were enrolled in the study between 25 January and 30 April 2018 (Figure 1). Three patients were excluded from analysis due to protocol violation (wrong tracheal tube size, $n = 1$), inappropriate placement of the AuraGain™ ($n = 1$), and abrupt cancellation of the surgery after group assignment ($n = 1$). Finally, 121 patients were analyzed with 59 patients in the extension group and 62 patients in the neutral group. Patient characteristics were comparable between groups (Table 1).

The AuraGain™ was successfully placed in all patients without any difference in the insertion time (Table 2). Six patients with a ventilation score of 2 had air leaks at an airway pressure of 15 cmH₂O, but ventilation was adequate in all patients.

The incidence of successful blind intubation after one attempt was 40/59 (68%) in the extension group and 29/62 (47%) in the neutral group (relative risk [RR], 1.45; 95% CI, 1.05 to 1.99; $P = 0.02$; Table 3). The incidence of overall successful blind intubation was significantly higher in the extension group than in the neutral group (42/59 [71%] vs. 31/62 [50%], respectively; RR, 1.42; 95% CI, 1.06 to 1.92; $P = 0.02$; Table 3). Successful blind intubation time was comparable between groups (Table 3).

The results from the exploratory logistic regression analysis are presented in Table 4. Among the variables, only neck extension was significantly associated with successful blind intubation through the AuraGain™ (odds ratio, 2.84; 95% CI, 1.22 to 6.99, $P = 0.02$; Table 4).

The incidence of adverse events related to blind intubation were similar in both groups (Table 5). Three patients in the neutral group were discharged less than 24 hr after extubation and excluded from the analyses of adverse events. There were no serious complications associated with AuraGain™ insertion and blind intubation, such as airway injury, dental fracture, aspiration, or bronchoscopy.

Discussion

In this study, we aimed to demonstrate that neck extension is an effective method to improve the success rate of blind intubation via SAD, rather than showing that blind intubation is an alternative to fibreoptic-guided intubation

through SAD. The primary hypothesis of this study was that neck extension facilitates successful blind intubation through the AuraGain™ laryngeal mask. This idea was derived from our previous study that showed improved fibreoptic views of the vocal cords when using the extended neck position.¹¹ In this study, we confirmed that neck extension was an effective maneuver for blind intubation through the AuraGain™. The incidence of successful blind intubation was higher in the extended neck position, and intubation time and complication rates were similar, compared with the neutral head and neck position. A possible explanation for this finding is that neck extension aligns the axis of the glottis and the trachea with the ventilation outlet of the AuraGain™.

Although tracheal intubation via a SAD was recommended to be performed under fibreoptic guidance, there may be certain situations where blind intubation is necessary, such as when a fibreoptic bronchoscope is unavailable, the view through a fibreoptic bronchoscope is limited due to bleeding or secretions, or the airway needs to be secured with minimal interruption of cardiac compressions during cardiopulmonary resuscitation. Recent studies have shown a high success rate of blind intubation through various SADs.^{6,8,10} Nevertheless, unacceptably low success rates have also been reported in other studies.^{7,16,17} This discrepancy may be due to the type of SAD used, the experience of the operator, or patient characteristics. Indeed, a recent multicenter prospective study showed a difference in success rate of blind intubation between well-experienced centers and those with less experience.¹⁰ In our study, we achieved a success rate of 47% (95% CI, 34 to 60) with the neutral head and neck position, which was similar to the success rate of 41% (95% CI, 29 to 53) obtained in a center that was previously unfamiliar with blind intubation through SAD.¹⁰ We evaluated whether the success rate of blind intubation increased as the study progressed, as our experience of 20 cases of blind intubation through the AuraGain™ may have been considered insufficient, but we observed no improvement in the success rate with case accumulation. Accordingly, the relatively low success rate in the neutral group may be caused by other factors, such as patient characteristics or the device itself, rather than the inexperience of our institution.

It should be noted that there are several techniques that can increase the success rate of blind intubation through a SAD, such as neck extension. A previous study has suggested that lifting the mandible, twisting the tube, or repositioning the SAD may facilitate blind intubation through a SAD, but this is difficult to standardize.¹⁰ In our study, we also permitted minor adjustments to facilitate blind intubation success, but this may not be sufficient to obtain a high success rate similar to that of well-

Fig. 1 The CONSORT flow diagram

Table 1 Patient characteristics

	Extension group (<i>n</i> = 59)	Neutral group (<i>n</i> = 62)
Age (yr)	51 (16)	55 (15)
Female	44 (75%)	36 (58%)
Height (cm)	162.3 (8.7)	163.0 (9.2)
Weight (kg)	63.7 (10.5)	63.7 (11.0)
Body mass index (kg·m ⁻²)	24.2 (3.6)	23.9 (3.0)
Mallampati score		
1	14 (25%)	20 (33%)
2	21 (37%)	18 (30%)
3	13 (23%)	14 (23%)
4	9 (16%)	9 (15%)
Interincisor distance (mm)*	45 [40–47]	42 [40–48]
Thyromental distance (mm)	72 (10)	74 (11)
Edentulism	5 (8%)	4 (6%)

Data are presented as mean (standard deviation), median [interquartile range],* or number of patients (percentage)

Table 2 Comparison of the AuraGain™ laryngeal mask insertion

	Extension group (<i>n</i> = 59)	Neutral group (<i>n</i> = 62)	<i>P</i>
No. of attempts			0.44 †
1	57 (97%)	57 (92%)	
2	2 (3%)	5 (8%)	
Insertion time (sec)	23 [18–27]	21 [18–27]	0.59
Ventilation score*			0.21 †
1	0 (0%)	0 (0%)	
2	1 (2%)	5 (8%)	
3	58 (98%)	57 (92%)	

*Ventilation score was defined as the total score of the following three assessments: 1) no leakage at airway pressure of 15 cmH₂O, 2) bilateral chest expansion, and 3) a square waveform on capnography

† Fisher's exact test

Data are presented as number of patients (percentage) or median [interquartile range]

Table 3 Success rate and time for blind intubation through the AuraGain™ laryngeal mask

		Extension group (<i>n</i> = 59)	Neutral group (<i>n</i> = 62)	Relative risk /Difference in median	95% CI	<i>P</i>
At first attempt	No. of success	40 (68%)	29 (47%)	1.45	1.05 to 1.99	0.02
	Intubation time (sec)	30 [26–51]	35 [25–46]	5	–3 to 10	0.76
Overall	No. of success	42 (71%)	31 (50%)	1.42	1.06 to 1.92	0.02
	Intubation time (sec)	30 [24–44]	33 [25–46]	3	–4 to 9	0.43

CI = confidence interval

Data are presented as number of patients (percentage) or median [interquartile range]

Table 4 Factors associated with successful blind intubation through the AuraGain™ laryngeal mask (exploratory analysis)

	Unadjusted			Adjusted		
	Odds ratio	95% CI	<i>P</i>	Odds ratio	95% CI	<i>P</i>
Neck extension	2.40	1.15 to 5.09	0.02	2.84	1.22 to 6.99	0.02
Age (per every 10 yr)	0.77	0.6 to 0.98	0.04	0.82	0.59 to 1.13	0.23
Female	0.91	0.42 to 1.95	0.81	0.64	0.25 to 1.60	0.35
Body mass index (per 1 kg·m ⁻²)	0.97	0.87 to 1.08	0.57	1.00	0.86 to 1.16	0.98
Mallampati score						
1	Reference			Reference		
2	0.65	0.25 to 1.65	0.37	0.51	0.17 to 1.46	0.22
3	1.24	0.43 to 3.64	0.69	1.53	0.43 to 5.71	0.52
4	0.50	0.15 to 1.57	0.24	0.30	0.07 to 1.16	0.09
Interincisor distance (per 1 mm)	1.00	0.94 to 1.06	0.95	0.96	0.88 to 1.04	0.30
Thyromental distance (per 1 mm)	1.00	0.96 to 1.04	0.99	1.00	0.95 to 1.05	0.95
Edentulism	0.36	0.10 to 0.91	0.06	0.32	0.08 to 0.90	0.06
Ventilation score after AuraGain™ placement						
3	Reference			Reference		
2	1.54	0.29 to 11.42	0.63	1.82	0.29 to 15.22	0.54
1	N/A			N/A		

CI = confidence interval; N/A = not available

Table 5 Incidence of adverse events related to blind intubation at 24 hr after extubation

	Extension group (<i>n</i> = 59)	Neutral group (<i>n</i> = 62)	<i>P</i>
Blood staining on AuraGain™*	6 (10%)	8 (13%)	0.64
Hoarseness			0.58 †
0	36 (61%)	35 (59%)	
1	11 (19%)	15 (25%)	
2	12 (20%)	9 (15%)	
3	0 (0%)	0 (0%)	
Cough			0.42†
0	52 (88%)	49 (83%)	
1	6 (10%)	10 (17%)	
2	1 (2%)	0 (0%)	
3	0 (0%)	0 (0%)	
Sore throat			0.41†
0	28 (48%)	34 (58%)	
1	20 (34%)	19 (32%)	
2	9 (15%)	6 (10%)	
3	2 (3%)	0 (0%)	

*Blood staining on the AuraGain™ laryngeal mask was assessed at the end of surgery

†Fisher's exact test

Data are presented as number of patients (percentage)

experienced institutions, in the neutral position. Nevertheless, with neck extension, the overall success rate was 71% (95% CI, 58 to 82), which was similar to the

success rate of 84% (95% CI, 80 to 88) reported by such centers.¹⁰

The intubating laryngeal mask airway (Fastrach™) is still considered the gold standard for blind intubation via a

SAD. Previous studies on the intubating laryngeal mask airway showed success rates of 70–80% with the first attempt,^{6,9,18} which was not far from our results. Even though we did not compare the success rate of blind intubation through the AuraGainTM and the intubating laryngeal mask airway in this study, the AuraGainTM can be used for blind intubation as an alternative.

The AuraGainTM has a unique anatomical curvature that is designed to resemble the shape of the oropharynx. Consequently, a tracheal tube inserted into the AuraGainTM would point in a different direction than that inserted into other SADs. This may facilitate successful blind intubation through the AuraGainTM, but it can also discourage blind intubation by interfering with adjustments of the tracheal tube from the outside of the mouth. Indeed, of 52 patients who failed to be intubated blindly on the first attempt, blind intubation was successful in only four patients at the second attempt, with the reverse-tube orientation. A reverse curve direction of the tracheal tube was found to be an effective technique for blind intubation through the intubating laryngeal mask airway in previous studies.^{19,20} Our results suggested that the reverse orientation technique seems to have a minimal effect on blind intubation through the AuraGainTM.

In exploratory logistic regression analysis, neck extension was the sole factor associated with successful blind intubation, rather than other variables known to be predictors of difficult tracheal intubation. Previous studies also revealed that several factors related to difficult airways had no impact on the difficulty encountered in alternative techniques, such as intubation through a SAD.^{21,22} As recommended in several difficult airway guidelines, this suggests that SAD can be used not only for securing an airway, but also as a conduit for intubation in patients with a difficult airway.

There are some limitations to this study. First, we did not evaluate a fiberoptic view of the vocal cords to ensure that we used a blind intubation attempt. In a previous study, a ‘visualized blind technique’ was used, but the procedure was somewhat different from clinical practice for actual blind intubation.⁷ We investigated the effect of neck extension in the context of a real-world clinical situation where blind intubation, without fiberoptic guidance, is required. Second, it was not feasible to blind the operator to group assignment. Nevertheless, the observer who assessed the success rate and time for blind intubation was unaware of the purpose of this study, and postoperative symptoms were evaluated by this blinded investigator. Third, because all procedures were performed by a single operator in this study, the success rate of blind intubation via the AuraGainTM with or without neck extension may be different from when a novice performs the procedure. Lastly, the success rate for blind intubation via the

AuraGainTM was lower than expected for sample size calculation. The success rate of blind intubation was not enough, even in the neck extension position, to be accepted as an alternative to fiberoptic guided intubation through SAD. Nevertheless, the result of this study suggests that neck extension can be used to improve the success rate when blind intubation is required.

In conclusion, this study showed that neck extension can facilitate blind intubation through the AuraGainTM. Although blind intubation should not be used as the first-choice technique due to the relatively high failure rate, neck extension can improve the success rate of blind intubation through a SAD, with similar rates of post-intubation complications, compared with the conventional neutral head and neck position.

Conflicts of interest None declared.

Editorial responsibility This submission was handled by Dr. Philip M. Jones, Associate Editor, *Canadian Journal of Anesthesia*.

Author contributions *Seokha Yoo* contributed to the study design, data acquisition, data analysis, and writing the manuscript. *Sun-Kyung Park* and *Min Hur* contributed to this study by recruiting patients and acquiring data. *Won Ho Kim* contributed to this study by analyzing data and revising the manuscript. *Jae-Hyon Bahk* contributed to study conception and revised the manuscript. *Young-Jin Lim* contributed to study design and revised the manuscript. *Jin-Tae Kim* contributed to study conception and design, and revised the manuscript.

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