

ORIGINAL ARTICLE

Antiadhesive effect and safety of oxidized regenerated cellulose after thyroidectomy: a prospective, randomized controlled study

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Purpose: To evaluate the antiadhesive effects and safety of an oxidized regenerated cellulose (Interceed) after thyroidectomy. **Methods:** Seventy-six thyroidectomized patients were prospectively randomized into two groups with regard to the use of Interceed. We evaluated each group for their adhesive symptoms using four subjective and four objective items at the 2nd week, 3rd and 6th month after thyroidectomy. All patients were examined for vocal cord motility by indirect laryngoscope at each period. **Results:** Total adhesion scores at each postoperative follow-up period decreased with time, but were not significantly different in each group. The median score for swallowing discomfort for liquid was significantly lower in the Interceed group than in the control group 2 weeks after surgery. In addition, the severity of skin adhesion to the trachea was reduced in the Interceed group compared with the control group 6 months after surgery. During the study, there were no adverse effects or significant differences in postoperative complications between the groups. **Conclusion:** Interceed appeared to be safe and effective in improving neck discomfort at early postoperative periods and preventing skin adhesion to the trachea 6 months after thyroidectomy.

Key Words: Adhesion, Neck discomfort, Oxidized regenerated cellulose, Thyroidectomy

INTRODUCTION

Patients with papillary thyroid cancer (PTC), in general, have an excellent prognosis [1-4]. These excellent prognoses accentuate the lower complication rate of thyroid surgery and the improved postoperative quality of life. Traditionally, the main outcome measure in oncology pa-

tients has been survival, based on tumor control, but recently it also has been increasingly recognized that surgeons should perform the thyroid operation to get a lower complication rate of thyroid surgery and an improved postoperative quality of life. In addition to major complications of thyroidectomy, such as hypoparathyroidism and recurrent laryngeal nerve injury, postoperative adhe-

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sive symptoms have been a bane for thyroidectomized patients. Postoperative adhesion occurs after a lot of cervical surgical procedures and can result in various complications such as swallowing difficulty or a pulling sensation during neck extension [5-8]. Moreover, the scars of skin adhesion after neck surgery are often externally visible (Fig. 1). Recently, a number of researchers have suggested the use of anti-adhesive agents for preventing postoperative adhesion of the cervical area after thyroid or neck surgery [9-12].

Since its release in 1990, the use of an oxidized, regenerated cellulose adhesion barrier (Interceed, Ethicon Inc., Somerville, NJ, USA) as an adjuvant for adhesion prevention has increased in a variety of gynecological and general surgical procedures [13-17]. After thyroid surgery, patients complain about various adhesion-related symptoms, such as neck discomfort, skin adhesion to the trachea, and vocal cord palsy [5,18]. Postoperative adhesions include various symptoms such as neck discomfort, neck tightness and skin scarring from adhesive reaction. With regard to the increased incidence of papillary thyroid carcinoma as well as the number of thyroid operations, it has been requested to study the safety and usefulness of anti-adhesive agents in thyroid surgery [9,10]. To date, how-

ever, no prospective, randomized, controlled trials have been performed on film-type anti-adhesive agents for use during thyroid surgery.

The goal of this study was to investigate the safety and efficacy of Interceed in the prevention of postoperative adhesions such as neck discomfort and skin adhesion to the trachea.

METHODS

Patient selection and follow-up

We prospectively included patients who were diagnosed and surgically treated for thyroid neoplasm at the department of surgery at Seoul National University Hospital.

We excluded patients with a history of previous neck surgeries and previous history of keloid or hypertrophic scar. We also excluded patients who were administered nonsteroidal anti-inflammatory drugs (NSAIDs) or anti-platelet agents within 1 week before surgery and patients with a history of previous neck surgeries or medical diseases such as thyroiditis, hyperthyroidism, diabetes, and hypertension. Randomized treatment assignments of

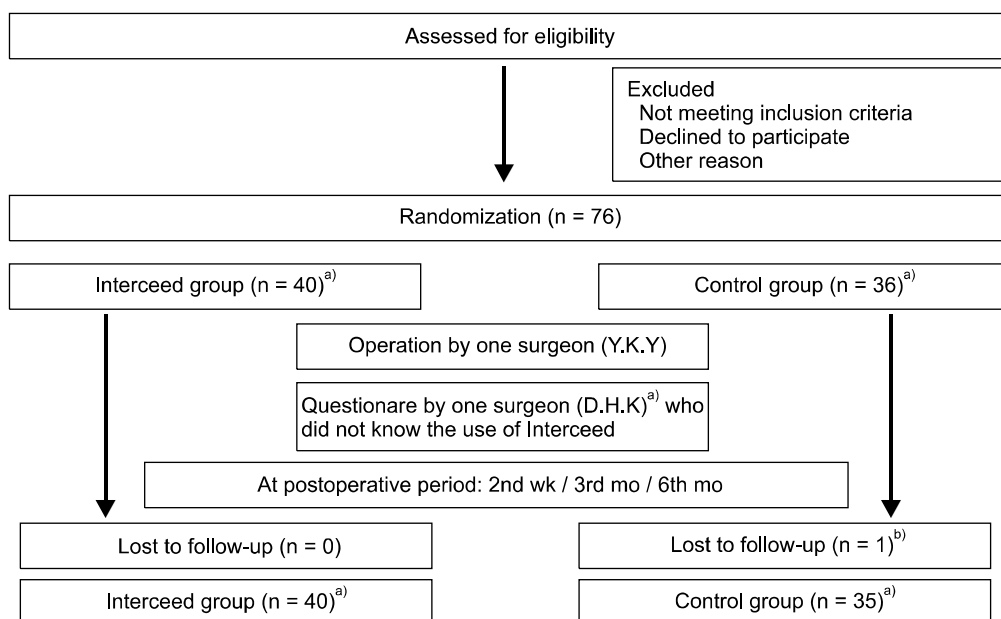


Fig. 1. Flowchart of trial design. ^{a)}Both patients and investigator did not know the use of Interceed. ^{b)}Due to regional problem: so far to follow-up.

Interceed were performed according to the Web-based randomized study protocol of Clinical Research Collaborating Center at Seoul National University Hospital.

We reviewed that the incidence of post-thyroidectomy

adhesion has been reported from 50% to 100% [10]. After considering the alpha, beta error, power of test and drop rate, we calculated the appropriate sample size was about 38 persons in each group. Of the 76 patients who enrolled

Table 1. Items used to evaluate the postoperative adhesion after a thyroidectomy

	Assessment items
Patient's scoring	1. How much difficulty do you have swallowing your saliva? 2. How much difficulty do you have swallowing water? 3. How much difficulty do you have swallowing solid foods? 4. Do you think your neck wrinkles are unnatural?
Physician's scoring	5. The symmetry and naturalness of neck wrinkles when the patient rests. 6. The symmetry and naturalness of neck wrinkles when the patient extends his/her neck. 7. The degree of inflammatory reaction and scar formation in the surgical wound. 8. The degree of skin adhesion to trachea on swallowing saliva.

Each item was scored from 0 to 10 with increasing severity.

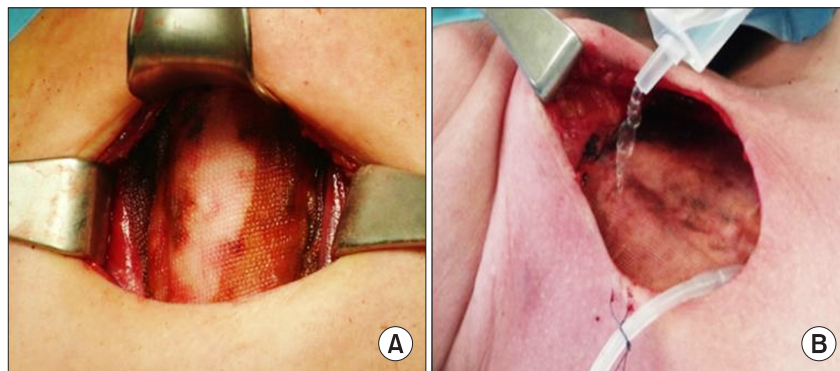


Fig. 2. Application of Interceed. After considering hemostasis, Interceed was applied to cover the trachea (A) and strap muscle (B) to prevent adhesion between overlying subcutaneous fat and the strap muscle fascia.



Fig. 3. Skin changes on the cervical area after thyroid surgery. Physicians primarily observed the symmetry and natural aspects of wrinkles and skin changes, such as inflammatory reaction and scar formation in the surgical wound of the neck. For example, since the relative width of skin to show inflammatory reaction such as redness or swelling was about 50%, we scored the patient a "5" in the visual analog scale scoring system (A). During swallowing, a patient showed skin adhesion to the trachea covering about 50% of dissected area 2 weeks after thyroidectomy (B). Since the relative width of skin adherent to the trachea was about 50%, we scored the patient a "5" in the visual analog scale scoring system.

in the study, 75 completed the study except one patient who was lost in follow up between June 2008 and February 2009 (Fig. 1).

This study was approved by the Institutional Review Board of the Seoul National University Hospital. Additionally, written and informed consent was obtained from each patient.

Surgical procedure and application of Interceed

We performed total thyroidectomy with central lymph node dissection and modified radical neck dissection (MRND) in cases of cervical lymph node metastasis. Careful attention was paid to meticulous hemostasis to prevent hematoma formation. Prior to skin closure, Interceed was applied to cover the trachea and the strap muscle (Fig. 2) to block adhesion between the overlying, subcutaneous fat layer and the strap muscle fascia. We also inserted a Jackson Pratt drain into the thyroid operative bed into every patient.

Postoperative follow-up and measurement of the Postthyroidectomy adhesion

All patients were monitored during the perioperative period for any adverse reactions, such as hematoma, fluid collection, and infection. The mobility of the vocal cord was also examined in every patient at the outpatient department postoperatively, using a direct laryngoscope. Follow-up measurements of any adhesion-related symptoms and signs were executed at the 2nd week, 3rd month, and 6th month after surgery. Postoperative adhesion was measured by one of the authors (D.H.K) who was blinded to the surgical procedure.

The degree of neck discomfort in swallowing and cosmetic problems were measured using a questionnaire that included four questions about subjective symptoms reported by the patient and four questions that focused on physician observations using a visual analog scale (0, no discomfort or best finding; 10, worst discomfort or finding) (Table 1). For example, since the relative width of skin to show inflammatory reaction such as redness or swelling was about 50%, we scored the patient a "5" in the scoring system (Fig. 3A). During swallowing, a patient showed skin adhesion to the trachea covering about 50% of dis-

sected area 2 weeks after thyroidectomy (Fig. 3B). Since the relative width of skin adherent to the trachea was about 50%, we scored the patient a "5" in the scoring system.

Statistical analysis

Statistical analysis was performed using the DBSTAT computer program ver. 4.5 (DBSTAT Co., Chuncheon, Korea).

The relationship between the application of Interceed and other clinical factors such as age, sex, body mass index (BMI), and adhesion-related symptoms and signs of the patients, were analyzed using the Student's t-test, Fisher's exact test, chi-square test, and Mann Whitney U-test. Each follow-up result between 2 weeks, 3 months, and 6 months after surgery was compared using repeated measures analysis of variance. The Cronbach's alpha was calculated to determine the internal consistency and reliability of the questionnaire items; $P < 0.05$ was considered statistically significant.

RESULTS

Clinical characteristics and postoperative complications

Forty patients were assigned to Interceed group and 35 patients were assigned to control group. We collected clinical data, such as age, sex, body weight, height, BMI, operative type, operative duration, days of hospitalization, and amount of Jackson Pratt drain and seventy-five patients were finally analyzed in Table 2. Mean age of patients was 48.5 years (range, 28 to 67 years). Ten of the patients were male and 65 were female. The mean body weights, heights, and body mass indices of the patients were not significantly different between the groups. There were no differences in histologic factors between the groups. All patients underwent total thyroidectomy, and 29 patients were submitted to neck dissection (i.e., neck nodes II, III, and/or IV). There were no differences in the use of NSAIDs between the groups and no significant differences in the drain amount.

Postoperative outcomes related to complications were

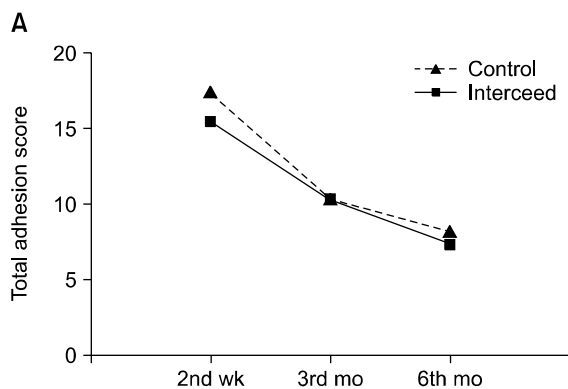
similar between the groups and summarized at Table 2.

We observed transient vocal cord palsy in 3 patients in each group, but they recovered at the sixth month except one patients of Interceed group. Although the patient re-

Table 2. Comparison of the adhesion score of each item between the control and the Interceed groups at each postoperative time point

Postoperative time	Item no.	Control group	Interceed group	P-value
2nd wk	1	2 (0-8)	1 (0-8)	0.10
	2	2 (0-10)	1 (0-10)	0.047
	3	2 (0-6)	1 (0-8)	0.50
	4	2 (0-10)	2 (0-10)	0.70
	5	2 (1-7)	2 (0-6)	0.94
	6	2 (0-6)	2 (0-8)	0.82
	7	0 (0-3)	0 (0-4)	0.85
	8	2 (1-7)	2 (1-6)	0.84
3rd mo	1	1 (0-6)	0 (0-4)	0.34
	2	1 (0-4)	0 (0-4)	0.30
	3	0 (0-3)	0 (0-3)	0.70
	4	2 (0-8)	1 (0-8)	0.75
	5	2 (0-4)	1 (0-4)	0.71
	6	1 (0-3)	1 (0-5)	0.23
	7	0 (0-3)	0 (0-0)	0.17
	8	2 (1-5)	2 (0-5)	0.93
6th mo	1	1 (0-6)	1 (0-2)	0.33
	2	0 (0-3)	0 (0-3)	0.71
	3	0 (0-3)	0 (0-1)	0.29
	4	1 (0-10)	1 (0-7)	0.33
	5	2 (0-4)	1 (0-3)	0.53
	6	1 (0-2)	1 (0-4)	0.03
	7	0 (0-0)	0 (0-0)	0.16
	8	2 (1-6)	2 (0-4)	0.02

Values are presented as median score (range).



covered normal voice, they did not recover the full motility of vocal cord compared to preoperative status at the 9th month follow-up.

Neck discomfort and cosmetic outcomes

We summarized all data from 8 items according to the time course (Table 3). Total adhesion scores for both groups showed no significant differences but significantly decreased with time ($P < 0.001$) (Fig. 4A). We also compared data between each group at each time point. There were three items showing significant differences. The median score for swallowing discomfort for water (item no. 2) was significantly lower in the Interceed group (1.00; range, 0 to 6) than in the control group (2.00; range, 0 to 10) 2 weeks after surgery ($P = 0.047$) (Table 3 and Fig. 5A). Fig. 5A shows the difference in median value and interquartile range (IQR) (control group: median, 2; IQR, 1 to 4 vs. Interceed group: median, 1; IQR, 0 to 2). Although the

Table 3. Reliability of the adhesion score of each item between the control and the Interceed groups at each postoperative time point

	Postoperative time	Cronbach's alpha coefficient
Patient's scoring (items 1, 2, 3, 4)	2nd wk	0.74
	3rd mo	0.67
	6th mo	0.59
Physician's scoring (items 5, 6, 7, 8)	2nd wk	0.52
	3rd mo	0.66
	6th mo	0.63

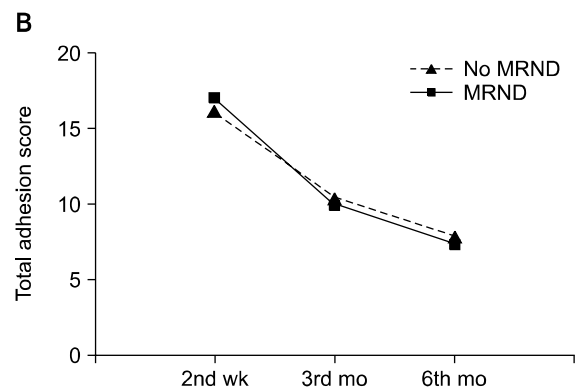


Fig. 4. Comparison of total adhesion scores. The scores significantly decreased with time in both Interceed and control groups ($P < 0.001$) (A), but there were no significant different between the groups. Comparison of the total adhesion scores according whether modified radical neck dissection (MRND) was performed (B). There were no significant differences in total adhesion scores with regard to MRND at any time after surgery.

score for swallowing liquid showed a significant difference in the early postoperative period, the scores improved along the time line.

In addition, the score for severity of skin adhesion to the trachea (item no. 8) was reduced in the Interceed group (2.00; range, 0 to 4) compared with the control group (2.00; range, 1 to 6) 6 months after surgery ($P = 0.02$) (Fig. 5B). In detail, median values are the same between the two groups, but IQR showed a difference. Fig. 5B shows the difference in IQR, but not in median value (control group: median, 2; IQR, 1 to 2 vs. Interceed group: median, 2; IQR, 1 to 3). The score for skin adhesion to the trachea on swallowing in the control group tended to remain stable over time, but the corresponding score in the Interceed group decreased significantly 6 months after thyroidectomy. However, the score for wrinkle symmetry and naturalness during neck extension (item no. 6) was higher in the Interceed group (1.00; range, 0 to 4) compared with the control group (1.00; range, 0 to 2) 6 months after surgery ($P = 0.03$).

Since there were longer skin incisions and broader surgical flaps after modified neck dissection, we analyzed scores according to whether MRND was performed. There were 50 patients who did not have MRND performed and 25 patients who had MRND performed. There were no significant differences in the number of MRND among each group. There were also no significant differences in total

adhesion scores at any time after surgery as to whether MRND was performed or not (Fig. 4B).

In the subgroup analysis for the 25 patients who had MRND performed, the total adhesion scores of those in the Interceed group did not differ from the control group.

DISCUSSION

The nature, severity and progression of postthyroidectomy adhesion are debated and recently have been investigated [5-11,18-21].

The aim of this study was to evaluate the antiadhesive effects and safety of Interceed in thyroid surgery. The significant findings of our study are two-such as decrease of neck discomfort and prevention of skin adhesion to trachea (Fig. 5). The score for swallowing difficulty during water drinking was found to be satisfactory 2 weeks after surgery in Interceed group, indicating that Interceed reduced discomfort at early stages after thyroid surgery (Fig. 5A). Additionally, physician's observations revealed no differences either at 2 weeks or 3 months after surgery, but significant differences were found 6 months after surgery regarding skin adhesion to the trachea during the swallowing of saliva (Fig. 5B). That is, skin adhesion to the trachea was found to be significantly lower in the Interceed group than control group 6 months after surgery, im-

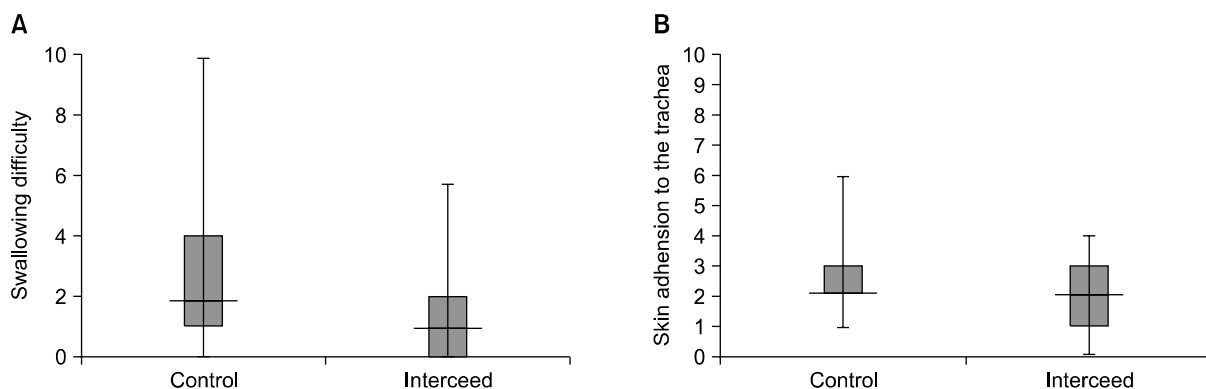


Fig. 5. Box plots of scores for swallowing difficulty and skin adhesion to the trachea. The swallowing discomfort scores for liquids were significantly lower in the Interceed group than in the control group 2 weeks after surgery (A) ($P = 0.047$). Fig. 5A showed the difference in median value and interquartile range (IQR): control group (median, 2; IQR, 1 to 4) vs. Interceed group (median, 1; IQR, 0 to 2). Comparison of the scores for skin adhesion to the trachea on swallowing (B). The scores for severity of adhesion to the trachea were reduced in the Interceed group compared with the control group 6 months after surgery ($P = 0.02$). Fig. 5B showed the difference in IQR, but not in median value; control group (median, 2; IQR, 1 to 2) vs. Interceed group (median, 2; IQR, 1 to 3).

plying that adhesion around the trachea occurred late in recovery; and suggesting that Interceed elicits a long-term protective effect against adhesion.

In addition to these major benefits, Table 1 shows that the drainage amount from patients with Interceed was insignificant, indicating that there was no waste of Interceed, and that it could function at full capacity. Liquid types of adhesion barrier products are likely to leak out through a drain after application. On the other hand, Interceed, a fabric type of barrier, was not only easy to locate on the surgical site but is also absorbed in 4 weeks. Thus, we expect the effectiveness of Interceed as an adhesion barrier would be stable for at least 4 weeks after thyroid surgery. As a matter of drainage of Interceed, we thought that the effect of drainage would be trivial because Interceed is resolved and absorbed 3 to 4 weeks after application. And so, we did not plan to analyze the difference between drain insertion and noninsertion groups.

We also know that there are often subtle changes to the voice that cannot be explained by injury to the recurrent or external branch of the superior laryngeal nerves [18,20].

Perhaps this is related to scarring of the strap muscles and other extrinsic muscles used in the production of sound from the larynx. There are several objective parameters for measuring the quality of the voice that could be looked at pre and post surgery and then compared. So, we examined all the patients' vocal cords by indirect laryngoscope. We observed transient vocal cord palsy in 3 patients in each group, but they recovered at the sixth month, except one patient. Although not statistically significant, we described that there was 1 case of vocal cord palsy even after 6th month in this study without any intraoperative event. The patient recovered normal voice pattern at the 9th month follow-up, but did not recover full motility of vocal cords compared to preoperative status. In addition to skin adhesion to cricothyroid muscle, the adhesion

Table 4. Clinical characteristics and perioperative variables of enrolled patients

Characteristic	Control group (n = 35)	Interceed group (n = 40)	P-value
Age (yr), mean \pm SD (range)	49.4 \pm 9.4 (28–68)	47.8 \pm 7.7 (26–74)	0.42
Gender (male:female)	2:33	8:32	0.14
Height (cm)	158.4 \pm 4.81	160.1 \pm 8.30	0.29
Weight (kg)	58.8 \pm 10.9	62.5 \pm 10.8	0.14
Body mass index (kg/cm ²)	23.5 \pm 4.0	24.3 \pm 3.1	0.29
Postoperative diagnosis			0.68
Benign	4 (11.4)	7 (17.5)	
Malignant	31 (88.6)	33 (82.5)	
Tumor size (cm), median (range)	0.8 (0.30–3.00)	0.8 (0.30–4.60)	0.78
Operative variables			
Operative method			0.73
Total thyroidectomy	20 (57.1)	26 (65.0)	
Total thyroidectomy and MRND	15 (42.9)	14 (35.0)	
Duration of operation (min)	82.4 \pm 25.8	92.7 \pm 22.3	0.07
Amounts of NSAIDs (tablets)	4.6 \pm 3.5	4.3 \pm 3.3	0.88
Postoperative hospitalization (day)	3.3 \pm 1.0	3.4 \pm 1.1	0.89
Drain removal (day)	3.3 \pm 0.8	3.2 \pm 1.0	0.79
Drain amount (mL)	86 \pm 21.4	103 \pm 30.7	0.41
Postoperative complication			
Postoperative bleeding	0 (0)	0 (0)	
Infection	0 (0)	0 (0)	
Transient hypocalcemia	16 (45.7)	20 (50.0)	0.89
Permanent hypocalcemia	3 (8.6)	2 (5.0)	0.88
Transient vocal cord palsy	3 (8.6)	3 (7.5)	0.88
Permanent vocal cord palsy	0 (0)	1 (2.5)	0.95

Values are presented as mean \pm standard deviation or number (%) unless otherwise indicated.

MRND, modified radical neck dissection; NSAIDs, nonsteroidal anti-inflammatory drugs.

around the recurrent laryngeal nerve could be the cause of postoperative voice problems. There is an experimental study in which no functional or histological deleterious effects were noted from placing antiadhesive agents such as Seprafilm on intact nerves or cut and repaired nerves [22]. In this study, there were also no significant differences in vocal cord paralysis.

Our study has several limitations, such as small number of cases and histologic consideration. At present, there is no reliable method for grading the adhesive symptoms and signs, and we could not do anything other than using a questionnaire with a visual analogue scale as noted above. The adhesion score of this study is a scoring system for evaluating the symptoms and signs related to the postoperative adhesive scoring system, yet its validity and reliability have not been established fully but is accepted by some authors. For the purpose of further evidence, we examined the data of this study and calculated the Cronbach's alpha coefficients (Table 4). The Cronbach's alpha coefficients of the items indicate that the items have an acceptable internal consistency and validity except physician's scoring during the 2nd week. However, their external validity has yet to be investigated. The questionnaire itself, evaluating items such as skin adhesion to trachea, was an objective score measured by independent surgeon, but inadequate in measuring the histologic adhesion to trachea directly. Peritoneal adhesion relates to the onset of a fibrin band, which appears during mesothelial repair after peritoneal injury. However, there have been few studies based on the theoretical background of cervical surgeries. To date, there have been two experimental studies on the relationship between neck surgery and the efficacy of adhesion barriers. An animal study showed that Interceed and Seprafilm (Genzyme Co., Cambridge, MA, USA) effectively prevent adhesion in subtotal thyroidectomy. In the other study, although Seprafilm had the best mean score, this was statistically insignificant and Seprafilm and Interceed had no effect on esophagus dissection [12].

An additional study is needed to investigate the possible benefit of Interceed in reoperative thyroid surgery, since there is a higher risk of nerve injury and other complications in this situation. In this study, however, we

could only follow up for 6 months after surgery. So, this endpoint was not included in the scope of this study. With regard to the problem with reoperative neck surgery, we should have long-term follow-up where reoperation might be done.

In conclusion, these results provide evidence that Interceed appears to be safe during thyroid surgery and could relieve patient discomfort at early stage post-surgery, and reduce skin adhesion to the trachea during long-term follow-up after thyroid surgery.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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