Adhesion Reduction Agent Guardix-SG® Versus MegaShield® for Postoperative Swallowing Function Analysis in Thyroidectomy Patients

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ABSTRACT

BACKGROUND: Antiadhesion products are essential for postoperative care in patients after thyroidectomy by providing a physical barrier to cover the exposed tissue and thus preventing abnormal adhesion of adjacent tissues. Since thyroidectomy may result in swallowing difficulties arising from damage or inflammation of the surrounding tissues, the use of antiadhesion agents such as MegaShield® or Guardix-SG® will help reduce scar formation. This may thus improve postoperative swallowing function in patients.

METHODS: Patients were enrolled and followed up between October 4, 2018, and March 26, 2020. Patients during the postoperative follow-up sessions were randomly allocated to the standard care with Guardix-SG® and clinical trial medical device application group with MegaShield® (test group) in a 1:1 ratio by the permuted block randomization method. Patient performance on penetration aspiration scale (PAS), National Institutes of Health-Swallow Safety Scale (NIH-SSS), videofluoroscopic dysphagia scale (VDS), Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) based on Videofluoroscopic swallowing study (VFSS) were collected. Nonadhesion-reducing agent patient data were used as a control group.

RESULTS: No statistical significance was shown ($P > .05$) between the 2 groups of MegaShield® and Guardix-SG® in various phases from thick semisolid, thin semisolid to liquid for both PAS and NIH-SSS. Several statistical significances were reported in the results comparing various criteria of PAS, NIH-SSS, VDS at different oral and pharyngeal phases, and DIGEST in all 3 stages among MegaShield®, Guardix-SG®, and nonadhesion-reducing agent group.

CONCLUSIONS: These results prove the noninferiority of MegaShield® compared with Guardix-SG® as an antiadhesion agent in postthyroidectomy care.

KEYWORDS: thyroid cancer, antiadhesive agent, noninferiority test, thyroidectomy, swallowing, dysphagia

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Introduction

With the advancement of diagnostic imaging, thyroid cancer (TC) has emerged to become one of the most common types of cancer that affects both men and women.[1,2] There have been 586 000 new cases estimated in 2020 alone, accounting for 3% of all cancers worldwide.[3] The cause of TC remains unknown, and the incidence is on a steady rise.[4] The mortality rate has not shown a correlative increase.[5] Patients with TC exhibit a range of clinical presentations based on the stage of malignancy and their specific forms.[6,7] Physicians manage TC with various types of treatments including thyroidectomy.[7] However, surgical interventions are not without complications. Permanent complications such as recurrent laryngeal nerve injury, vocal cord/fold paralysis, and hypoparathyroidism significantly reduce the patient's quality of life.[7-9]

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Both the superior and recurrent laryngeal nerves are involved in swallowing.[10] The internal branch of the superior laryngeal nerve is responsible for sensory at supraglottic space and vocal cords. Injury of this nerve can result in aspiration and dysphagia.[10] Conversely, the external branch of the superior laryngeal nerve is in charge of motor control of the cricothyroid muscle and therefore gives tension to the vocal cords.[10] Recurrent laryngeal nerve contributes to all intrinsic laryngeal muscles, except the cricothyroid muscle and sensory innervation for the upper esophagus. Previous literature reports that patients with unilateral inferior laryngeal nerve palsy experience swallowing disorders in approximately 30% of cases, whereby the inability to close the glottis completely is one of the reasons for correlation between swallowing impairment and recurrent laryngeal nerve injury.[10] The study confirmed several key factors involved in swallowing disorders: (1) injuries to extrinsic perithyroidal neural plexus which innervates the pharynx, (2) injuries to the thin anastomoses connecting the recurrent laryngeal nerve and the external branch of the superior laryngeal nerve, and (3) injuries to the sympathetic cervical chain with both the recurrent laryngeal nerve and superior laryngeal nerve.[10] The extensive dissection of recurrent laryngeal nerve results in shortening and thinning of the preserved section of nerve fiber, breaching the nerve integrity.[11] Depending on the extent of involvement of TC on the recurrent laryngeal nerve, the response of the vocal cord against electric stimulation to recurrent laryngeal nerve may be lost.[11] While some cases of swallowing dysfunction can be transient and only occur in the first week of postoperation, occasional cases of long-term dysphagia is also reported.[10] This can be due to orotracheal intubation, surgical trauma, scar and surgical site adhesions, and psychosocial reaction to the operation. A previous study has highlighted that the most commonly reported symptoms are hoarseness, sensation of a "lump," a foreign body, a "too-tightly-buttoned shirt collar," sensation of being strangled, cough, effort, and/or obstacle during swallowing.[10] It is thus crucial to clarify if scarring of tissues in the absence of timely antiadhesion agent intervention could have possibly contributed to such symptoms related to swallowing impairment. Consequently, patients often experience swallowing disorders arising from inferior pharyngeal constrictor muscle (IPCM) dysfunction.[12] Laryngeal tract elevation disorders also contribute to dysphasic conditions as tissue adhesions occur in a postoperative phase when the laryngeal tract unit undergoes abnormal attachment to adjacent superficial soft tissues.[13] While postoperative adhesion is a natural and common phenomenon in the self-healing process of TC, abnormal adhesion often results in anatomical deformation of the affected area and functional deterioration. This tissue adhesion impedes upper esophageal motility, hampers parathyroid gland and posterior laryngeal nerve fiber functions, and triggers neck muscle stiffness at certain orientations.[14,15] Such debilitating condition worsens over time and is irreversible. Thus, it is crucial to ensure that the cause of discomfort, abnormal adhesion of the operative site, is prevented.[16]

The clinical practice in preventing tissue adhesion involves 3 distinct stages. The first stage is to ensure sophistication of surgical process in minimizing tissue damage that may mechanically discompose the affected tissue and thus proliferate scar formation at the dissected area.[17] The second stage is to suppress the cascade of tissue formation with anti-inflammatory drugs and anticoagulant preadhesion drugs.[18] The third stage involves reducing contact area by postoperative mechanical blockage of surrounding tissues by covering or wrapping the wound area with an antiadhesion barrier.[19] These protocols, however, do not present a complete prevention of adhesion.[20] In recent years, previous studies have highlighted this limitation and have instead suggested the use of antiadhesion agents to prevent postoperative adhesion.[21]

Antiadhesion barriers come in many different forms including gels, solutions, and films.[20,22] Considering its purpose of usage, antiadhesion barrier should hold excellent biocompatibility, biodegradability, supported by effectiveness and safety.[22] In addition to the need for it to be an injectable formulation appropriate in minimally invasive or laparoscopic surgeries, it must retain its structure on the damaged tissue during the healing period and prevent excessive formation of fibrous tissue at and adjacent to the wound.[22] Videofluoroscopic swallowing study (VFSS) was considered as the parameter as it is one of the most commonly utilized instrumental assessment tools to determine the nature and degree of oropharyngeal swallowing disorder.[23] VFSS is a specialized X-ray fluoroscopy examination designed to evaluate the dynamics of swallowing components such as the mouth, pharynx, larynx, and esophagus.[23] Through the analysis of VFSS data, abnormalities in swallowing function can be identified using both spot film and video, allowing for detailed frame-by-frame and slow playback analysis.[23] Widely employed and well-established, this examination is a reliable technique in clinical practice for directly observing dynamic changes in the functioning of the involved organs during swallowing.[23]

There are 2 types of antiadhesion agent formulations: natural and synthetic polymers.[24-26] Guardix-SG®, a temperature-sensitive hydrogel natural polymer product, is composed of poloxamer, sodium alginate, and $CaCl_2$.[27,28] In contrast, the new product of MegaShield® is an antiadhesion material that contains human extract-derived particle-type acellular dermal matrix (ADM).[29] This study aimed to evaluate the effectiveness of the anti-adhesion products MegaShield® and Guardix-SG®. Patients with TC who underwent thyroidectomy were allocated to 2 different test groups; those using Guardix-SG® antiadhesion product and those using MegaShield® antiadhesion product. We therefore certified the

noninferiority of MegaShield® product performance as an antiadhesion barrier used in patients with TC with thyroidectomy as compared with that of Guardix-SG® as well as against the nonadhesion-reducing agent group.

Methods

Study design

This is a retrospective clinical study, based on the database of patients who underwent total thyroidectomy in a single-blind, randomized controlled clinical trial with a noninferiority design from our previous study, was conducted from October 4, 2018, to March 26, 2020, in Severance Hospital, Seoul, Republic of Korea.[30] A total of 156 patients had been assessed in the previous multicenter clinical trial.[30] Of 156 patients, 16 patients were excluded. Thus, 140 patients were randomized and completed the previous clinical trial. These 16 patients excluded comprised of 3 patients not meeting inclusion criteria, 11 declined to participate, 8 lost to follow-up and/or failed to complete the set of examinations, and 1 for other reasons. This previous study did not involve masking of group allocation for physicians.[30]

Out of 140 patients, this study evaluated 71 patient data for postoperative VFSS, with 8 patients excluded. These 8 excluded patients comprised of 5 patients who refused Videofluoroscopic dysphagia scale (VDS), 2 patients who failed screening test, and 1 patient without the video record. Thus, 63 patients were analyzed for their data. The product used was MegaShield® (L&C BIO, Seongnam, Korea). Patients were then randomized between the standard care with Guardix-SG® and the clinical trial medical device application group with MegaShield® (test group) in a 1:1 ratio by the permuted block randomization method.[30] Patient recruit was conducted using the SAS 9.4 software by an independent research coordinator assigning random numbers generated from the software to individual patients.[30] These random numbers were presented in codes to ensure masking of patients and evaluators.[30] The study protocol was approved by the Institutional Review Board of Yonsei University Health System (Approval No. 4-2021-0413). Patients during the post-operative follow-up sessions were randomly allocated to the standard care composed of 2 groups: between the standard care with Guardix-SG® and the clinical trial group with MegaShield® (test group).[30] Herein, standard care is defined as receiving conventional anti-adhesion treatment with Guardix-SG®.[30]

Study participants

Individuals of at least 19 years of age, diagnosed with thyroid cancer and thus underwent surgical interventions including thyroidectomy, were eligible for the study.[30] Patients were excluded if they were pregnant, moribund, or had been treated with anti-adhesion agents other than Guardix-SG® or MegaShield®.[30] Nine patients who underwent the same surgical procedure but without the use of antiadhesive agents, were selected as control and assigned as the nonadhesion reducing agent group. Their data were extracted from the Electronic Medical System.

Materials

MegaShield® and Guardix-SG® are temperature-sensitive antiadhesive agents that change phase from solution to gel at normal human body temperature.[30] MegaShield® is composed of ADM, poloxamer 407, hyaluronic acid, and 1,4-BDDE.[30] However, Guardix-SG® is composed of poloxamer, sodium alginate, and calcium chloride.[30] The patients were prescribed with 5 g of either MegaShield® or Guardix-SG® in accordance with their assigned group.[30]

Surgical procedure

All patients underwent standard bilateral total thyroidectomy with central lymph node dissection by a single surgeon.[30] After total thyroidectomy, 2 mL of either MegaShield® or Guardix-SG® was applied between the tracheal wall and strap muscle.[30] After closing the midline of the strap muscles, 3 mL of identical anti-adhesive agent was applied in between the overlying subcutaneous fat layer and strap muscle fascia.[30]

Data collection and interventions

Clinical visits were conducted for 30 days from 0 day before the surgery (first visit), day of the surgery (second visit), postoperative week 1 (third visit), and week 6 (fourth visit). During the first visit, the baseline demographic characteristics and clinical and laboratory assessments were thoroughly recorded after obtaining written informed consent. During the second visit, the investigational device (MegaShield® or Guardix-SG®) was applied in the operating environment. Patients were followed up twice on their third and fourth visits after application of the device. Clinical and laboratory variables and adverse events were also evaluated in all visits.

Outcome measures

Patient demographic findings including sex, age, and body mass index (BMI) were recorded.[30] The primary outcome measures are as follows: Penetration aspiration scale (PAS), National Institutes of Health-Swallow Safety Scale (NIH-SSS), VDS, and Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) based on VFSS.

Penetration aspiration scale. This scale provides a multidimensional and reliable quantification of selected penetration and aspiration events observed during VFSS.[31] Examiners can identify how far the airway material passes and whether it is expelled or not.[31] This scale thus helps examiners differentiate

normal and abnormal swallowing process on an 8-point scale.[31] Point 1 indicates normal swallowing function, points 2 to 5 indicate penetration, and points 6 to 8 indicate aspiration.[31]

National Institutes of Health-Swallow Safety Scale. This scale provides a numerical quantification of swallowing safety based on the observations derived from VFSS.[32] Higher scores indicate more severe impairment in factors such as food residue, laryngeal penetration, aspiration response, maximal esophageal entry, and multiple swallows.[32]

Videofluoroscopic dysphagia scale. This scale provides a quantification of oropharyngeal function during swallowing based on the following criteria: lip closure, bolus formation, mastication, apraxia, tongue-to-palate contact, premature bolus loss, oral transit time, pharyngeal swallow triggering, vallecular residue, laryngeal elevation, pyriform sinus residue, and coating of pharyngeal wall, pharyngeal transit time, and aspiration.[32] With a maximum score of 10, higher scores indicate poorer swallowing function.[32]

Dynamic Imaging Grade of Swallowing Toxicity. This scale provides a quantification of pharyngeal bolus transit during pharyngeal phase swallowing function using 2 components: safety profile and efficiency profile.[33] With a maximum score of 4, higher scores indicate poorer safety and efficiency profile of pharyngeal wallowing function.[33]

Statistical analysis

SPSS Statistics 27 (IBM Corp., Armonk, NY, USA) was used to analyze the efficacy of antiadhesion agents MegaShield® and Guardix-SG® in swallowing function of patients enrolled in this study. Product efficacy was compared among trial groups and nonadhesion-reducing agent group using chi-square test and One-way analysis of variance (ANOVA) with post-hoc Bonferroni comparisons with a P value $< .05$ indicating statistical significance. Independent variables used in this study are as follows: PAS and NIH-SSS, oral phase and pharyngeal phase in VDS, and safety grade, efficiency grade, and total grade in DIGEST based on VFSS.

Results

Patient characteristics

Individuals were screened for inclusion from October 4, 2018, to March 26, 2020, at Severance Hospital, Seoul, Republic of Korea. Of these 71 screened individuals, 8 were excluded for not meeting the inclusion criteria. These 63 patients were then randomized into 2 groups, with 32 of them allocated to intervention MegaShield® and 31 of them allocated to intervention Guardix-SG®. Nine patients who did not receive any antiadhesion product intervention were selected from the Electronic Medical System and were assigned as a nonadhesion-reducing agent control group. None from the 3 groups failed to receive allocated intervention (Figure 1). Similarly, none from the 3 groups were lost from failure to follow-up (Figure 1). Baseline characteristics are as reported in Table 1.

Of 32 patients allocated to MegaShield® group, 7 (21.9%) were men and 25 (78.1) were women. Their mean age was 47.4 ± 10.43 years, average weight 66.6 ± 14.11 kg, and BMI 24.9 ± 3.94 kg/m^2. Of 31 patients allocated to the Guardix-SG® group, 8 (25.8%) were men and 23 (74.2%) were women. Their mean age was 50.0 ± 12.29 years, average weight 67.6 ± 16.69 kg and BMI 25.0 ± 4.65 kg/m2. Of 9 patients from the nonadhesion-reducing agent group, 2 (22.2%) were men and 7 (77.8%) were women. Their mean age was 64.77 ± 12.67 years, average weight 67.77 ± 12.67 kg and BMI 24.43 ± 4.52 kg/m2. The mean age, mean weight, BMI, and sex ratio were similar in all 3 groups, not showing any statistical difference by chi-square test and One-way ANOVA with post-hoc Bonferroni comparisons.

Swallowing function

Swallowing function of patients using MegaShield® and Guardix-SG® was evaluated via PAS and NIH-SSS. Nonadhesion-reducing agent group was also assessed of their swallowing function via PAS and NIH-SSS. This examination involved 3 types of materials with different viscosities, and patients were thus tested with thick semisolid, thin semisolid and liquid of less than 5 mL each. The material was tracked of its pathway to be classified of the depth upon penetration or aspiration into trachea, through vocal cord and larynx. Response to airway invasion via reflux was also observed and recorded.

MegaShield® and Guardix-SG® groups attained a lower PAS compared with nonadhesion-reducing agent group, with statistical significance demonstrated by chi-square with Bonferroni post-hoc analysis of thick-semisolid, thin-semisolid, and liquid are all $\chi^2 = 7.099$, $P = .029$. Both MegaShield® and Guardix-SG® groups' normal proportion is 100% in all, thick semisolid, thin semisolid, and liquid (Table 2). However, nonadhesion-reducing agent group's normal proportion is 88.9%, and mild proportion is 11.1% (Table 2).

The NIH-SSS scores showed comparable results between MegaShield® and Guardix-SG® for thick semisolid and thin semisolid (Table 3). MegaShield® (0.56 ± 0.669) and Guardix-SG® (0.55 ± 0.624) groups attained a lower NIH-SSS score with liquid compared with nonadhesion-reducing agent group (1.67 ± 1.414), with statistical significance demonstrated by One-way ANOVA with Bonferroni post-hoc analysis ($F = 8.075$, $P = .001$; MegaShield® vs nonadhesion reducing agent, $P = .001$; Guardix-SG® vs nonadhesion reducing agent, $P = .001$) (Table 3). There was no statistical difference between MegaShield® group, Guardix-SG® group, and nonadhesion-reducing agent group shown in NIH-SSS scores for thick semisolid ($F = 0.516$, $P = .599$) and thin semisolid ($F = 1.420$, $P = .249$) (Table 3).

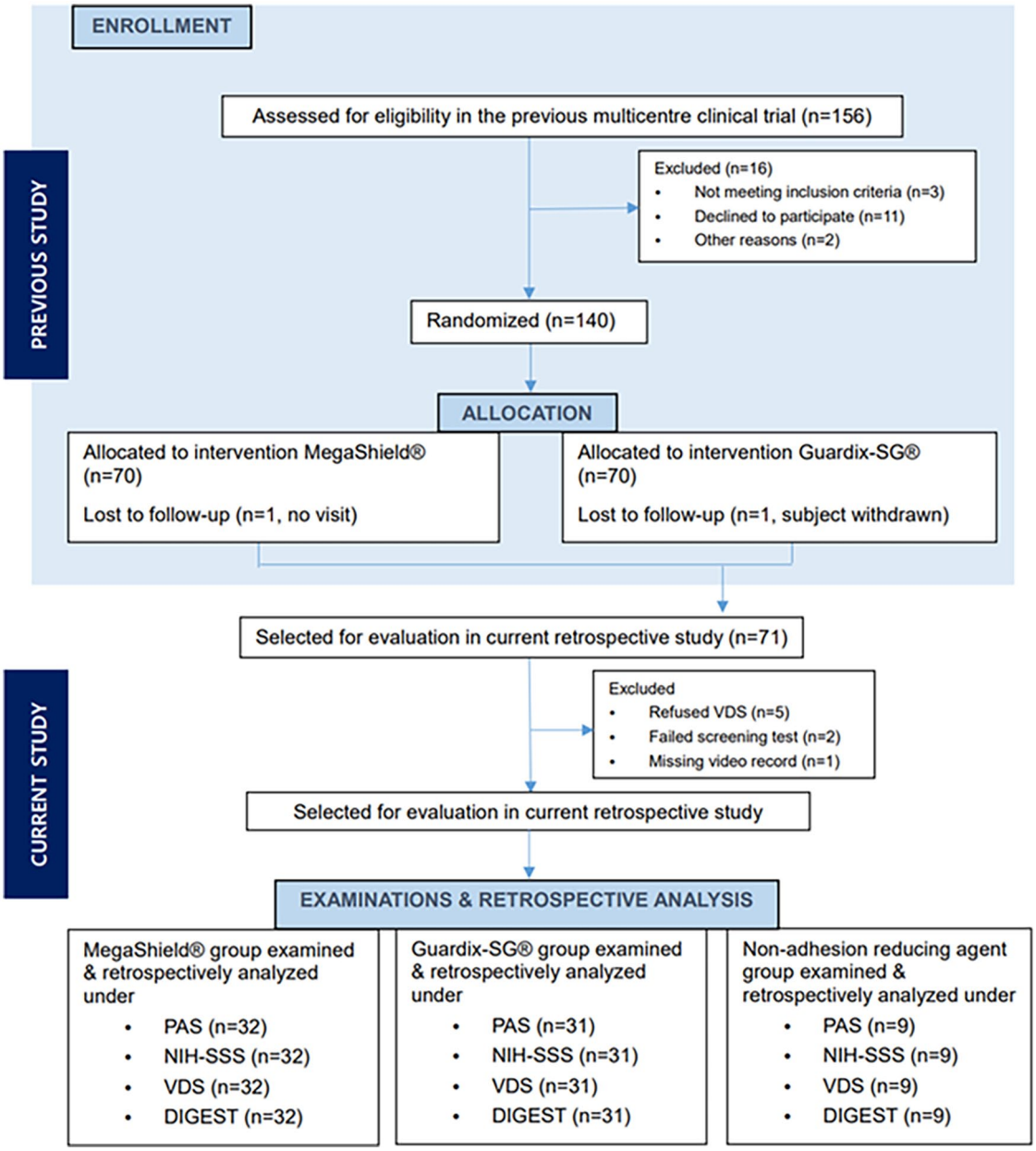

Figure 1. Patient disposition.

The DIGEST scale was used to compare the safety and efficiency grade among MegaShield®, Guardix-SG®, and nonadhesion-reducing agent groups (Table 4). MegaShield® and Guardix-SG® groups attained a lower DIGEST score in safety-grade compared with nonadhesion-reducing agent group, with statistical significance demonstrated by chi-square with Bonferroni post-hoc analysis ($\chi^2 = 14.589$, $P = .006$) (Table 4). Similarly, MegaShield® and Guardix-SG® groups attained a lower total DIGEST score compared with nonadhesion-reducing agent group, with statistical significance demonstrated by chi-square with Bonferroni post-hoc analysis ($\chi^2 = 14.589$, $P = .006$) (Table 4). There was no statistical difference among MegaShield®, Guardix-SG®, and nonadhesion-reducing agent groups shown in DIGEST efficiency scores when compared by chi-square with Bonferroni post-hoc analysis (MegaShield® vs nonadhesion-reducing agent, $P = .014$; Guardix-SG® vs nonadhesion-reducing agent, $P = .016$; MegaShield® vs Guardix-SG®, $P = .982$) (Table 4).

Videofluoroscopic dysphagia scale

Patients were tested on swallowing 3 different food formulations in VDS. Each parameter of VDS was analyzed to identify the specific phase at which it is influenced by the materials. Total scores were measured for both oral phase and pharyngeal phase for the 3 respective materials (Table 5). Oral phase included "Lip Closure," "Bolus Formation," "Mastication," "Apraxia," "Tongues to palate contact," "Premature bolus loss," and "Oral transit time" (Table 6). Pharyngeal phase included "Triggering pharyngeal swallow," "Vallecular residue,"

Table 1. Baseline characteristics of patients between MegaShield®, Guardix-SG®, and nonadhesion-reducing agent group.

CRITERIA		TOTAL	MEGASHIELD (N = 32)	GUARDIX-SG (N = 31)	NONADHESION-REDUCING AGENT (N = 9)	*F*	OVERALL *P* VALUE
Age	Mean	72	47.41 ± 10.432	50.10 ± 12.199	55.33 ± 10.198	1.820	.170
Sex						0.145	.930
Male	n (%)	17	7 (21.9)	8 (25.8)	2 (22.2)		
Female	n (%)	53	25 (78.1)	23 (74.2)	7 (77.8)		
Body weight	Mean	72	66.62 ± 14.11	67.59 ± 16.69	64.77 ± 12.67	0.126	.882
BMI	Mean	72	24.91 ± 3.94	24.98 ± 4.65	24.43 ± 4.52	0.059	.943

Age, body weight, BMI by One-way ANOVA, and sex by chi-square test.
Notes. Variables are presented as mean ± SEM or n (%).

"Laryngeal elevation," "Pyriform sinus residue," "Coating on the pharyngeal wall," "Pharyngeal transit time," and "Aspiration" (Table 6).

During pharyngeal phase of VDS test with thick-semisolid, there was a significant difference in the laryngeal elevation phase among MegaShield®, Guardix-SG®, and nonadhesion-reducing agent groups with statistical significance demonstrated by chi-square with post-hoc Bonferroni ($\chi^2 = 7.099$, overall $P = .029$) (Table 6). Similarly, MegaShield® and Guardix-SG® groups attained a lower VDS score during the pharyngeal transit time of the pharyngeal phase using thick-semisolid compared with nonadhesion-reducing agent group, with statistical significance demonstrated by chi-square with post-hoc Bonferroni ($\chi^2 = 7.099$, overall $P = .029$) (Table 6). MegaShield® and Guardix-SG® groups attained a lower VDS score during the "mastication" phase of the oral phase using thick-semisolid compared with nonadhesion-reducing agent group, with statistical significance demonstrated by chi-square with post-hoc Bonferroni ($\chi^2 = 37.612$, overall $P = .001$) (Table 6). Ultimately, MegaShield® (3.88 ± 4.621) and Guardix-SG® groups (4.79 ± 4.161) attained a lower total VDS score using thick-semisolid compared with nonadhesion-reducing agent group (12.06 ± 16.973), with statistical significance demonstrated by One-way ANOVA with Bonferroni post-hoc analysis ($F = 4.788$, $P = .011$; MegaShield® vs nonadhesion-reducing agent, $P = .010$; Guardix-SG® vs nonadhesion-reducing agent, $P = .026$) (Table 5).

During pharyngeal phase of VDS test with thin-semisolid, there was a significant difference in the laryngeal elevation phase among MegaShield®, Guardix-SG®, and nonadhesion-reducing agent groups with statistical significance demonstrated chi-square with post-hoc Bonferroni ($\chi^2 = 7.099$, overall $P = .029$) (Table 6). Similarly, MegaShield® and Guardix-SG® groups attained a lower VDS score during the pharyngeal transit time of the pharyngeal phase using thin-semisolid compared with nonadhesion-reducing agent group, with statistical significance demonstrated by chi-square with post-hoc Bonferroni ($\chi^2 = 7.099$, overall $P = .029$) (Table 6). MegaShield® and Guardix-SG® groups attained a lower VDS score during the "aspiration" phase of the pharyngeal phase using thin-semisolid compared with nonadhesion-reducing agent group, with statistical significance demonstrated by chi-square with post-hoc Bonferroni ($\chi^2 = 0.099$, overall $P = .029$) (Table 6). Ultimately, MegaShield® (5.30 ± 5.179) and Guardix-SG® groups (4.58 ± 4.707) attained a lower total VDS score using thin-semisolid compared with nonadhesion-reducing agent group (19.06 ± 20.434), with statistical significance demonstrated by One-way ANOVA with Bonferroni post-hoc analysis ($F = 10.733$, $P = .000$; MegaShield® vs nonadhesion-reducing agent, $P < .001$; Guardix-SG® vs nonadhesion-reducing agent, $P < .001$) (Table 5).

During pharyngeal phase of VDS test with liquid, there was a significant difference in the vallecular residue among MegaShield®, Guardix-SG®, and nonadhesion-reducing agent group with statistical significance demonstrated chi-square with post-hoc Bonferroni ($\chi^2 = 8.397$, overall $P = .015$) (Table 6). Similarly, MegaShield® and Guardix-SG® groups attained a lower VDS score during the pharyngeal transit time of the pharyngeal phase using liquid compared with nonadhesion-reducing agent group, with statistical significance demonstrated by chi-square with post-hoc Bonferroni ($\chi^2 = 7.099$, overall $P = .029$) (Table 6). MegaShield® and Guardix-SG® groups attained a lower VDS score for coating on the pharyngeal wall of the pharyngeal phase using liquid compared with nonadhesion-reducing agent group, with statistical significance demonstrated chi-square with post-hoc Bonferroni ($\chi^2 = 15.419$, overall $P < .001$) (Table 6). Score during the pharyngeal transit time also showed a significant difference between MegaShield®, Guardix-SG®, and nonadhesion-reducing agent groups, with statistical significance demonstrated by chi-square with post-hoc Bonferroni ($\chi^2 = 7.099$, overall $P = .029$) (Table 6). MegaShield® and Guardix-SG® groups attained a lower VDS score for aspiration of the pharyngeal phase using liquid compared with nonadhesion-reducing agent group, with statistical

Table 2. Comparison of Penetration Aspiration Scale among MegaShield®, Guardix-SG®, and nonadhesion-reducing agent groups.

TEST	VARIABLES	MEGASHIELD (N=32)	GUARDIX-SG (N=31)	NONADHESION-REDUCING AGENT (N=9)	χ^2	OVERALL *P* VALUE	POST-HOC *P* VALUE		
							MEGASHIELD VS GUARDIX-SG	GUARDIX-SG VS NONADHESION-REDUCING AGENT	MEGASHIELD VS NONADHESION-REDUCING AGENT
PAS	Thick semisolid				7.099	.029*	-	.062	.058
	Normal (PAS: 1)	32 (100)	31 (100)	8 (88.9)					
	Mild (PAS: 2)	0 (0)	0 (0)	1 (11.1)					
	Moderate (PAS: 3-5)	0 (0)	0 (0)	0 (0)					
	Severe (PAS: 6-8)	0 (0)	0 (0)	0 (0)					
	Thin semisolid				7.099	.029*	-	.062	.058
	Normal (PAS: 1)	32 (100)	31 (100)	8 (88.9)					
	Mild (PAS: 2)	0 (0)	0 (0)	1 (11.1)					
	Moderate (PAS: 3-5)	0 (0)	0 (0)	0 (0)					
	Severe (PAS: 6-8)	0 (0)	0 (0)	0 (0)					
	Liquid				7.099	.029*	-	.062	.058
	Normal (PAS: 1)	32 (100)	31 (100)	8 (88.9)					
	Mild (PAS: 2)	0 (0)	0 (0)	1 (11.1)					
	Moderate (PAS: 3-5)	0 (0)	0 (0)	0 (0)					
	Severe (PAS: 6-8	0 (0)	0 (0)	0 (0)					

Notes. Variables are presented as observed frequency (%).
*$P < .05$ by chi-square test with post-hoc Bonferroni.

Table 3. Comparison of National Institutes of Health Swallowing Safety Scale among MegaShield®, Guardix-SG®, and nonadhesion-reducing agent groups.

TEST	VARIABLES	MEGASHIELD (N = 32)	GUARDIX-SG (N = 31)	NONADHESION-REDUCING AGENT (N = 9)	F	OVERALL *P* VALUE	POST-HOC *P* VALUE		
							MEGASHIELD VS GUARDIX-SG	GUARDIX-SG VS NONADHESION-REDUCING AGENT	MEGASHIELD VS NONADHESION-REDUCING AGENT
NIH-SSS	Thick-semisolid	0.81 ± 0.780	0.74 ± 0.815	1.11 ± 1.764	0.516	.599	1.000	.941	.000
	Thin-semisolid	1.00 ± 0.762	1.06 ± 0.772	1.56 ± 1.509	1.420	.249	1.000	.443	.303
	Liquid	0.56 ± 0.669	0.55 ± 0.624	1.67 ± 1.414	8.075	.001**	1.000	.001**	.001**

Note. Thick-semisolid, thin-semisolid, liquid variables for respective groups are presented as mean ± SEM.
*$P < .05$ by One-way ANOVA with post-hoc Bonferroni. **$P < .01$ by One-way ANOVA with post-hoc Bonferroni.

Table 4. Comparison of dynamic imaging grade of swallowing toxicity scale between MegaShield®, Guardix-SG®, and nonadhesion-reducing agent groups.

TEST	VARIABLES	MEGASHIELD (N = 32)	GUARDIX-SG (N = 31)	NONADHESION-REDUCING AGENT (N = 9)	χ^2	OVERALL *P* VALUE	POST-HOC *P* VALUE		
							MEGASHIELD VS GUARDIX-SG	GUARDIX-SG VS NONADHESION-REDUCING AGENT	MEGASHIELD VS NONADHESION-REDUCING AGENT
Digest total	Grade 0	0 (0)	0 (0)	0 (0)	14.589	.006**	.982	.016*	.014*
	Grade 1	31 (96.9)	30 (96.8)	7 (77.8)					
	Grade 2	1 (3.1)	1 (3.2)	0 (0)					
	Grade 3	0 (0)	0 (0)	2 (22.2)					
	Grade 4	0 (0)	0 (0)	0 (0)					

Notes. Variables for respective groups are presented as observed frequency (%).
*$P < .05$. **$P < .01$ by chi-square test with post-hoc Bonferroni.

Table 5. Comparison of videofluoroscopic dysphagia scale between MegaShield®, Guardix-SG®, and nonadhesion-reducing agent groups.

TEST	VARIABLES	PHASE	MEGASHIELD (N = 32)	GUARDIX-SG (N = 31)	NONADHESION-REDUCING AGENT (N = 9)	F	OVERALL *P* VALUE	POST-HOC *P* VALUE		
								MEGASHIELD VS GUARDIX-SG	GUARDIX-SG VS NONADHESION-REDUCING AGENT	MEGASHIELD VS NONADHESION-REDUCING AGENT
VDS	Thick-semisolid	Oral-phase Total	0.75 ± 0.852	0.73 ± 0.855	4.44 ± 4.687	16.955	<.001***	1.000	<.001***	<.001***
		Pharyngeal Phase Total	3.03 ± 4.386	4.02 ± 3.809	7.61 ± 13.626	2.020	.140	1.000	.362	.145
		Thick-semisolid total score	3.88 ± 4.621	4.79 ± 4.161	12.06 ± 16.973	4.788	.011*	1.000	.026*	.011*
	Thin-semisolid	Oral-phase Total	0.89 ± 0.840	0.92 ± 0.923	7.56 ± 11.004	11.355	<.001***	1.000	<.001***	<.001***
		Pharyngeal Phase Total	4.25 ± 4.740	8.45 ± 27.867	11.50 ± 12.460	0.648	.515	1.000	1.000	.995
		Thin-semisolid total score	5.30 ± 5.179	4.58 ± 4.707	19.06 ± 20.434	10.733	<.001***	1.000	<.001***	<.001***
	Liquid	Oral-phase Total	0.61 ± 0.749	0.34 ± 0.638	3.56 ± 8.647	4.167	.020*	1.000	.019*	.035*
		Pharyngeal Phase Total	1.66 ± 3.096	1.44 ± 1.978	9.78 ± 12.413	11.189	<.001***	1.000	<.001***	<.001***
		Liquid total score	2.31 ± 3.419	1.82 ± 2.204	13.33 ± 18.578	10.580	<.001***	1.000	<.001***	<.001***

*$P < .05$. **$P < .01$. ***$P < .001$ by One-way ANOVA with post-hoc Bonferroni.

Table 6. Comparison of Videofluoroscopic dysphagia scale between MegaShield®, Guardix-SG®, and nonadhesion-reducing agent groups.

TEST	VARIABLES	PHASE	SPECIFICS		MEGASHIELD (N = 32)	GUARDIX-SG (N = 31)	NONADHESION-REDUCING AGENT (N = 9)	χ^2	OVERALL *P* VALUE	POST-HOC *P* VALUE		
										MEGASHIELD VS GUARDIX-SG	GUARDIX-SG VS NONADHESION-REDUCING AGENT	MEGASHIELD VS NONADHESION-REDUCING AGENT
VDS	Thick-semisolid	Oral-phase	Lip closure	Intact	32 (100)	31 (100)	9 (100)	-	-	-	-	-
				Inadequate	0 (0)	0 (0)	0 (0)					
				None	0 (0)	0 (0)	0 (0)					
			Bolus formation	Intact	32 (100)	31 (100)	8 (88.9)	7.099	.029*	-	.062	.058
				Inadequate	0 (0)	0 (0)	0 (0)					
				None	0 (0)	0 (0)	1 (11.1)					
			Mastication	Intact	32 (100)	31 (100)	4 (44.4)	37.612	<.001***	-	<.001***	<.001***
				Inadequate	0 (0)	0 (0)	5 (55.6)					
				None	0 (0)	0 (0)	0 (0)					
			Apraxia	None	32 (100)	31 (100)	9 (100)	-	-	-	-	-
				Mild	0 (0)	0 (0)	0 (0)					
				Moderate	0 (0)	0 (0)	0 (0)					
				Severe	0 (0)	0 (0)	0 (0)					
			Tongues to palate contact	Intact	32 (100)	31 (100)	8 (88.9)	7.099	.029*	-	.062	.058
				Inadequate	0 (0)	0 (0)	0 (0)					
				None	0 (0)	0 (0)	1 (11.1)					
			Premature bolus loss	None	16 (50)	16 (51.6)	5 (55.6)	9.709	.046*	.9059	.540	.465
				<10%	16 (50)	14 (45.2)	2 (22.2)					
				10–50%	0 (0)	1 (3.2)	2 (22.2)					
				>50%	0 (0)	0 (0)	0 (0)					
			Oral transit time	<1.5	31 (96.9)	31 (100)	8 (88.9)	3.214	.200	.329	.062	.338
				>1.5	1 (3.1%)	0 (0%)	1 (11.1%)					

(Continued)

Table 6. (Continued)

TEST	VARIABLES	PHASE	SPECIFICS		MEGASHIELD (N=32)	GUARDIX-SG (N=31)	NONADHESION-REDUCING AGENT (N=9)	χ^2	OVERALL *P* VALUE	POST-HOC *P* VALUE		
										MEGASHIELD VS GUARDIX-SG	GUARDIX-SG VS NONADHESION-REDUCING AGENT	MEGASHIELD VS NONADHESION-REDUCING AGENT
		Pharyngeal Phase	Triggering of pharyngeal swallow	Normal	32 (100)	30 (96.8)	8 (88.9)	3.252	.197	.3135	.352	.058
				Delayed	0 (0)	1 (3.2)	1 (11.1)					
			Vallecular residue	None	16 (50)	16 (51.6)	6 (66.7)	9.785	.134	.7284	.771	.925
				<10%	15 (46.9)	15 (48.4)	2 (22.2)					
				10-50%	1 (3.1)	0 (0)	0 (0)					
				>50%	0 (0)	0 (0)	1 (11.1)					
			Laryngeal elevation	Normal	32 (100)	31 (100)	8 (88.9)	7.099	.029*	-	.062	.058
				Impaired	0 (0)	0 (0)	1 (11.1)					
			Pyriform sinus residue	None	22 (68.8)	19 (61.3)	7 (77.8)	0.966	.617	.5422	.374	.609
				<10%	10 (31.3)	12 (38.7)	2 (22.2)					
				10–50%	0 (0)	0 (0)	0 (0)					
				>50%	0 (0)	0 (0)	0 (0)					
			Coating on the pharyngeal wall	No	30 (93.8)	27 (87.1)	7 (77.8)	1.991	.369	.3766	.503	.161
				Yes	2 (6.3)	4 (12.9)	2 (22.2)					
			Pharyngeal transit time	<1.0 s	32 (100)	31 (100)	8 (88.9)	7.099	.029*	-	.062	.058
				>1.0 s	0 (0)	0 (0)	1 (11.1)					
			Aspiration	None	32 (100)	31 (100)	8 (88.9)	7.099	.029*	-	.062	.058
				Penetration	0 (0)	0 (0)	0 (0)					
				Aspiration	0 (0)	0 (0)	1 (11.1)					

(Continued)

Table 6. (Continued)

TEST	VARIABLES	PHASE	SPECIFICS		MEGASHIELD (N = 32)	GUARDIX-SG (N = 31)	NONADHESION-REDUCING AGENT (N = 9)	χ^2	OVERALL *P* VALUE	POST-HOC *P* VALUE		
										MEGASHIELD VS GUARDIX-SG	GUARDIX-SG VS NONADHESION-REDUCING AGENT	MEGASHIELD VS NONADHESION-REDUCING AGENT
	Thin-semisolid	Oral-phase	Lip closure	Intact	32 (100)	31 (100)	9 (100)	-	-	-	-	-
				Inadequate	0 (0)	0 (0)	0 (0)					
				None	0 (0)	0 (0)	0 (0)					
			Bolus formation	Intact	32 (100)	31	6 (66.7)	21.913	<.001***	-	.001**	<.001***
				Inadequate	0 (0)	(100)	2 (22.2)					
				None	0 (0)	0 (0)0 (0)	1 (11.1)					
			Mastication					45.818	<.001***	-	<.001***	<.001***
				Intact	32 (100)	31 (100)	3 (33.3)					
				Inadequate	0 (0)	0 (0)	5 (55.6)					
				None	0 (0)	0 (0)	1 (11.1)					
			Apraxia	None	32 (100)	31 (100)	8 (88.9)	7.099	.029*	-	.062	.058
				Mild	0 (0)	0 (0)	0 (0)					
				Moderate	0 (0)	0 (0)	0 (0)					
				Severe	0 (0)	0 (0)	1 (11.1)					
			Tongues to palate contact	Intact	31 (96.9)	31 (100)	8 (88.9)	8.339	.080	.329	.062	.145
				Inadequate	1 (3.1)	0 (0)	0 (0)					
				None	0 (0)	0 (0)	1 (11.1)					
			Premature bolus loss	None	15 (46.9)	13 (41.9)	5 (55.6)	11.540	.073	.4219	.637	.335
				<10%	17 (53.1)	16 (51.6)	2 (5.7)					
				10–50%	0 (0)	2 (6.5)	1 (11.1)					
				>50%	0 (0)	0 (0)	1 (11.1)					
			Oral transit time	<1.5	31 (96.9)	31 (100)	8 (88.9)	3.214	.200	.329	.062	.338
				>1.5	1 (3.1)	0 (0)	1 (11.1)					

(Continued)

Table 6. (Continued)

TEST	VARIABLES	PHASE	SPECIFICS		MEGASHIELD (N=32)	GUARDIX-SG (N=31)	NONADHESION-REDUCING AGENT (N=9)	χ^2	OVERALL *P* VALUE	POST-HOC *P* VALUE		
										MEGASHIELD VS GUARDIX-SG	GUARDIX-SG VS NONADHESION-REDUCING AGENT	MEGASHIELD VS NONADHESION-REDUCING AGENT
		Pharyngeal Phase	Triggering of pharyngeal swallow	Normal	31 (96.9)	31 (100)	8 (88.9)	3.214	.200	.329	.062	.338
				Delayed	1 (3.1)	0 (0)	1 (11.1)					
			Vallecular residue	None	10 (31.3)	8 (25.8)	2 (22.2)	8.710	.191	.850	.231	.228
				<10%	21 (65.6)	23 (74.2)	6 (66.7)					
				10–50%	1 (3.1)	0 (0)	0 (0)					
				>50%	0 (0)	0(0)	1 (11/1)					
			Laryngeal elevation	Normal	32 (100)	31 (100)	8 (88.9)	7.099	.029*	-	.062	.058
				Impaired	0 (0)	0 (0)	1 (11.1)					
			Pyriform sinus residue	None	23 (71.9)	21 (67.7)	5 (55.6)	0.863	.650	.726	.512	.365
				<10%	9 (28.1)	10 (32.3)	4 (44.4)					
				10–50%	0 (0)	0 (0)	0 (0)					
				>50%	0 (0)	0 (0)	0 (0)					
			Coating on the pharyngeal wall	No	27 (84.4)	28 (90.3)	5 (55.6)	6.115	.047*	.486	.015	.067
				Yes	5 (15.6)	3 (9.7)	4 (44.4)					
			Pharyngeal transit time	<1.0 s	32 (100)	31 (100)	8 (88.9)	7.099	.029*	-	.062	.058
				>1.0 s	0 (0)	0 (0)	1 (11.1)					
			Aspiration	None	32 (100)	31 (100)	8 (88.9)	7.099	.029*	-	.062	.058
				Penetration	0 (0)	0 (0)	0 (0)					
				Aspiration	0 (0)	0 (0)	1 (11.1)					
	Liquid	Oral-phase	Lip closure	Intact	32 (100)	31 (100)	9 (100)	-	-	-	-	-
				Inadequate	0 (0)	0 (0)	0 (0)					
				None	0 (0)	0 (0)	0 (0)					

(Continued)

Table 6. (Continued)

TEST	VARIABLES	PHASE	SPECIFICS		MEGASHIELD (N = 32)	GUARDIX-SG (N = 31)	NONADHESION-REDUCING AGENT (N = 9)	χ^2	OVERALL *P* VALUE	POST-HOC *P* VALUE		
										MEGASHIELD VS GUARDIX-SG	GUARDIX-SG VS NONADHESION-REDUCING AGENT	MEGASHIELD VS NONADHESION-REDUCING AGENT
			Bolus formation	Intact	32 (100)	31 (100)	7 (77.8)	14.400	.006**	-	.010*	.008**
				Inadequate	0 (0)	0 (0)	1 (11.1)					
				None	0 (0)	0 (0)	1 (11.1)					
			Mastication	Intact	32 (100)	31 (100)	8 (88.9)	7.099	.029*	-	.062	.058
				Inadequate	0 (0)	0 (0)	1 (11.1)					
				None	0 (0)	0 (0)	0 (0)					
			Apraxia	None	32 (100)	31 (100)	8 (88.9)	7.099	.029*	-	.062	.058
				Mild	0 (0)	0 (0)	1 (11.1)					
				Moderate	0 (0)	0 (0)	0 (0)					
				Severe	0 (0)	0 (0)	0 (0)					
			Tongues to palate contact	Intact	32 (100)	31 (100)	8 (88.9)	7.099	.029*	-	.062	.058
				Inadequate	0 (0)	0 (0)	0 (0)					
				None	0 (0)	0 (0)	1 (11.1)					
			Premature bolus loss	None	18 (56.3)	23 (74.2)	7 (66.7)	19.753	.003**	.139	.235	.648
				<10%	14 (43.8)	8 (25.8)	0 (0)					
				10–50%	0 (0)	0 (0)	1 (11.1)					
				>50%	0 (0)	0 (0)	1 (11.1)					
			Oral transit time	<1.5	32 (100)	31 (100)	9 (100)	-	-	-	-	-
				>1.5	0 (0)	0 (0)	0 (0)					
		Pharyngeal Phase	Triggering of pharyngeal swallow	Normal	32 (100)	31 (100)	9 (100)	-	-	-	-	-
				Delayed	0 (0)	0 (0)	0 (0)					

(Continued)

Table 6. (Continued)

TEST	VARIABLES	PHASE	SPECIFICS		MEGASHIELD (N = 32)	GUARDIX-SG (N = 31)	NONADHESION-REDUCING AGENT (N = 9)	χ^2	OVERALL *P* VALUE	POST-HOC *P* VALUE		
										MEGASHIELD VS GUARDIX-SG	GUARDIX-SG VS NONADHESION-REDUCING AGENT	MEGASHIELD VS NONADHESION-REDUCING AGENT
			Vallecular residue	None	19 (59.4)	20 (64.5)	1 (11.1)	8.397	.015*	.680	.003**	.009**
				<10%	0 (0)	0 (0)	0 (0)					
				10–50%	13 (40.6)	11 (35.3)	8 (88.9)					
				>50%	0 (0)	0 (0)	0 (0)					
			Laryngeal elevation	Normal	32 (100)	31 (100)	8 (88.9)	7.099	.029*	-	.062	.058
				Impaired	0 (0)	0 (0)	1 (11.1)					
			Pyriform sinus residue	None	28 (87.5)	26 (83.9)	5 (55.6)	4.981	.083	.686	.076	.033*
				<10%	4 (12.5)	5 (38.5)	4 (44.4)					
				10–50%	0 (0)	0 (0)	0 (0)					
				>50%	0 (0)	0 (0)	0 (0)					
			Coating on the pharyngeal wall	No	31 (96.9)	31 (100)	6 (66.7)	15.419	<.001***	.329	<.001	.006**
				Yes	1 (3.1)	0 (0)	3 (33.3)					
			Pharyngeal transit time	<1.0 s	32 (100)	31 (100)	8 (88.9)	7.099	.029*	-	.062	.058
				>1.0 s	0 (0)	0 (0)	1 (11.1)					
			Aspiration	None	32 (100)	31 (100)	8 (88.9)	7.099	.029*	-	.062	.058
				Penetration	0 (0)	0 (0)	0 (0)					
			total	Aspiration	0 (0)	0 (0)	1 (11.1)					

*$P < .05$, **$P < .01$, and ***$P < .01$ by chi-square with post-hoc Bonferroni.
Note. Variables are presented as observed frequency (%).

significance demonstrated by chi-square with post-hoc Bonferroni ($\chi^2 = 7.099$, overall $P = .029$) (Table 6). MegaShield® (1.66 ± 3.096) and Guardix-SG® groups (1.44 ± 1.978) attained a lower total VDS score of pharyngeal phase sing liquid compared with nonadhesion-reducing agent group (9.78 ± 12.413), with statistical significance demonstrated by One-way ANOVA with Bonferroni post-hoc analysis ($F = 11.189$, $P < .001$; MegaShield® vs nonadhesion-reducing agent, $P < .001$; Guardix-SG® vs nonadhesion-reducing agent, $P < .001$) (Table 5). Ultimately, MegaShield® (2.31 ± 3.419) and Guardix-SG® groups (1.82 ± 2.204) attained a lower total VDS score using thick-semisolid compared with nonadhesion-reducing agent group (13.33 ± 18.578), with statistical significance demonstrated by One-way ANOVA with Bonferroni post-hoc analysis ($F = 10.580$, $P = .000$; MegaShield® vs nonadhesion-reducing agent, $P = .000$; Guardix-SG® vs nonadhesion-reducing agent, $P < .001$) (Table 5). This suggests MegaShield® has successfully helped maintain swallowing function by preventing tissue scarring, especially in the pharyngeal phase.

Discussion

While it is true that more patients suffer from dysphagia when the operation is more invasive, patients can still experience postoperative swallowing changes even after uncomplicated surgery without laryngeal nerve injuries. Previous literature reported that about 20% of patients who underwent conventional bilateral thyroid resection with or without lymph node dissection faced long-lasting dysphagia.[34] Causes for the long-term dysphagia after uncomplicated thyroidectomy include lesions of the perithyroidal neural plexus, changes in the laryngeal vascular supply, postoperative adhesions, decreased pressure of the upper esophageal sphincter, or changed position after thyroidectomy.[34] As evident from the PAS result differences between the test groups and nonadhesion-reducing agent group, it can be implied that patients in the nonadhesion-reducing agent group did experience postoperative dysphagia (Table 2). Minimally invasive surgical procedures including laparoscopy significantly reduce trauma to the tissue as well as exposure to foreign materials. This allows effective coagulation of the microvessels in the affected tissue, and reduces dehydration in the adjacent pneumoperitoneum tissue that may possibly lead to abnormal adhesion. However, these surgical techniques carry a limitation antiadhesion is not completely preventable. Antiadhesive agents are thus valuable in addressing these limitations. Pharmaceutical options to treat abnormal tissue adhesion at surgical site include fibrinolytic agents, anticoagulation agents, anti-inflammation agents, antibiotics and hormonal agents. Antiadhesive barriers, on the other hand, consist of solid (intrinsic and extrinsic) and gel forms. While there are a variety of anti-adhesion alternatives in the market, there is no single dominantly effective option.[35]

Antiadhesive solutions currently in clinical use present a serious limitation that it is not fixated the moment it is applied onto the surgical site, the agent flows away or undergo lysis prior to showing therapeutic effects. Film- or membrane-type antiadhesion agents hold a low adhesive quality when applied onto internal organs, or induce severe immune reaction from being recognized as a foreign object. Due to its easily foldable nature, film and membrane type of antiadhesive agents are not suitable for minimally invasive surgical procedures as they wrap around surgical equipment in the application process. Gel typed antiadhesion agents are lysed and excreted from the system, before they take effect on the affected tissue. Without ample time to attach onto the affected area, a minimal therapeutic effect is often expected. This may also lead to immune reaction from being recognized as foreign object if they are composed of nonbiomolecules.[36] Recent adhesive agents manufactured in the current market are therefore composed of temperature sensitive polymer, overcoming the aforementioned limitations.

These antiadhesive agents are composed in the following combination: Poloxamer 407 (Pluronic F-127) and Poloxamer 188 (Pluronic F-68) serve as the main temperature sensitive polymers, compound composed of temperature-sensitive polymers and sodium alginate, or compound composed of temperature-sensitive polymers and gelatin or chitosan. Poloxamers show thermoreversible properties whereby they are in fluid state at room temperature facilitating administration and gel state above sol-gel transition temperature at body temperature promoting prolonged release of pharmacological agents.[37] They are also highly biocompatible and carry less toxins as compared with other pharmaceutical options.[38] Sodium alginate form a cross-linkage with different ions, resulting in a structural stability. It does not trigger immune response nor are lysed by animal cells. With close monitoring over the usage, antiadhesive agents thus need to be evaluated of its function and sustainability in human tissues.[39,40]

MegaShield® comprises hyaluronic acid, temperature-sensitive polymers and micronized ADM with collagen as the main component. As a temperature-sensitive antiadhesive agent, MegaShield® presents strong advantages including stable application on the affected tissue, excellent biocompatibility and sustainability from thermoreversible nature in a range of temperatures, tissue adhesiveness, and biodegradability. Acellular dermal matrix, one of the key components of MegaShield®, functions to minimize abnormal adhesion in postsurgical phase, and thyroidectomy upon transplantation.[41] These antiadhesive efficacy has been proven in a rat model as well.[41]

Guardix-SG®, currently the predominant product in the market, is mainly composed of sodium hyaluronate and cabroxymethylcellulose. Hyaluronate is a long linear anionic polysaccharide composed of D-glucuronic acid and N-acetyl-D-glucosamine and makes up synovial fluid, vitreous incarceration and extracellular matrix. Guardix-SG® is a proprietary composition of aforementioned materials. It is a large molecule that is highly biocompatible and highly absorbable. By

providing a physical barrier over the exposed tissue, it prevents the formation of cellulose.

Similar to Guardix-SG®, MegaShield® is relatively long-lasting due to their highly viscous and elastic nature as compared with typical antiadhesion gel/solutions. Both products thus can remain in place for an extended period of time over the recovery process, reducing the need for additional procedures that may trigger further inflammatory or immune response. With MegaShield® proving its competency against Guardix-SG®, this study has shown that MegaShield® is not inferior to its counterpart in terms of its antiadhesion effect. This product will thus allow a wider range of anti-adhesion options for the physicians to choose from. Given the different molecular composition of MegaShield® and Guardix-SG®, physicians can better tailor postsurgical antiadhesion therapy for each individual patients by taking into account factors including efficacy, side effects, cost, and drug interactions. This increase in pharmaceutical option arising from the distribution of MegaShield® into the market may also lead to lowering of prices for antiadhesion products in the long run, serving particular cost benefit for patients with limited access to healthcare resources. Ultimately, the study design may be favorable to be replicated in other institutions, especially when there is high proportion of postoperative patients for noninvasive evaluations including VFSS. However, the possible limitation of this study is that patients from both MegaShield® and Guardix-SG® groups showed no initial symptoms of dysphagia. Patients enrolled in our study were either those who complained of swallowing difficult or those who indicated their interest in taking the swallowing function examinations due to difficulty in swallowing. While it may not be common for clinically severe dysphagia to occur after thyroid surgery without tracheostomy, the study had been designed to cater to the needs of our patients to the best of our ability.

Conclusion

This study has ultimately elucidated the noninferiority in performance of MegaShield® against Guardix-SG® as a promising postsurgical antiadhesive pharmaceutical option, presenting physicians with greater flexibility in treating the patients.

Acknowledgements

Not applicable.

Author Contributions

HKL and JH designed the model and the framework of the study, wrote the manuscript and analyzed the data. HKL and SJ analyzed the data and compiled the results. SRC supervised the project and were in charge of overall direction and planning. JH drafted the revised manuscript. All authors were involved in the intellectual discussion of the study. All authors read and approved the final manuscript.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

All participants in this study were provided with sufficient explanation prior to receiving any interventions mentioned in this study. Their written consent was obtained. The study protocol was approved by the Institutional Review Board of Yonsei University Health System (approval no. 4-2021-0413).

Consent for Publication

Not applicable.

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REFERENCES

1. Guo W-P, Tang D, Pang Y-Y, et al. Immunohistochemical basigin expression level in thyroid cancer tissues. *World J Surg Oncol*. 2020;18:240. doi:10.1186/s12957-020-01975-9
2. Vigneri R, Malandrino P, Vigneri P. The changing epidemiology of thyroid cancer: why is incidence increasing. *Curr Opin Oncol*. 2015;27:1-7. doi:10.1097/cco.0000000000000148
3. Miranda-Filho A, Lortet-Tieulent J, Bray F, et al. Thyroid cancer incidence trends by histology in 25 countries: a population-based study. *Lancet Diabetes Endocrinol*. 2021;9:225-234. doi:10.1016/s2213-8587(21)00027-9
4. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209-249. doi:10.3322/caac.21660
5. López Gavilanez E, Bautista Litardo N, Navarro Chávez M, Hernández Bonilla M, Segale Bajaña A. Thyroid cancer in Ecuador. *BMC Cancer*. 2020;20:637. doi:10.1186/s12885-020-07137-0
6. Nabhan F, Ringel MD. Thyroid nodules and cancer management guidelines: comparisons and controversies. *Endocr Relat Cancer*. 2017;24:R13-R26. doi:10.1530/erc-16-0432
7. Pace-Asciak P, Russell JO, Tufano RP. The treatment of thyroid cancer with radiofrequency ablation. *Tech Vasc Interv Radiol*. 2022;25:100825. doi:10.1016/j.tvir.2022.100825
8. Rossi L, Materazzi G, Bakkar S, Miccoli P. Recent trends in surgical approach to thyroid cancer. *Front Endocrinol (Lausanne)*. 2021;12:699805. doi:10.3389/fendo.2021.699805
9. Dhepnorrarat RC, Witterick IJ. New technologies in thyroid cancer surgery. *Oral Oncol*. 2013;49:659-664. doi:10.1016/j.oraloncology.2013.03.445
10. Scerrino G, Inviati A, Di Giovanni S, et al. Esophageal motility changes after thyroidectomy; possible associations with postoperative voice and swallowing disorders: preliminary results. *Otolaryngol Head Neck Surg*. 2013;148:926-932. doi:10.1177/0194599813482299
11. Masuoka H, Miyauchi A. Intraoperative management of the recurrent laryngeal nerve transected or invaded by thyroid cancer. *Front Endocrinol*. 2022;13:884866. doi:10.3389/fendo.2022.884866
12. Lombardi CP, Raffaelli M, D'Alatri L, et al. Voice and swallowing changes after thyroidectomy in patients without inferior laryngeal nerve injuries. *Surgery*. 2006;140:1026-32; discussion 1032. doi:10.1016/j.surg.2006.08.008
13. Arakawa-Sugueno L, Ferraz AR, Morandi J, et al. Videoendoscopic evaluation of swallowing after thyroidectomy: 7 and 60 days. *Dysphagia*. 2015;30:496-505. doi:10.1007/s00455-015-9628-z
14. Cho JG, Byeon HK, Oh KH, et al. Objective assessment of postoperative swallowing difficulty through ultrasound in patients undergoing thyroidectomy. *Dysphagia*. 2020;35:253-260. doi:10.1007/s00455-019-10020-1
15. Scerrino G, Inviati A, Di Giovanni S, et al. Long-term esophageal motility changes after thyroidectomy: associations with aerodigestive disorders. *G Chir*. 2017;37:193-199. doi:10.11138/gchir/2016.37.5.193
16. Kim H-K, Kim SM, Chang H, et al. Anti-adhesive agent (Guardix-SG) does not influence the drainage volume after thyroid cancer surgery. *Korean J Endocr Surg*. 2013;13:251-256.
17. Aref-Adib M, Phan T, Ades A. Preventing adhesions in laparoscopic surgery: the role of anti-adhesion agents. *The Obstet Gynecol*. 2019;21:185-192. doi:10.1111/tog.12588
18. Fatehi Hassanabad A, Zarzycki AN, Jeon K, et al. Prevention of post-operative adhesions: a comprehensive review of present and emerging strategies. *Biomolecules*. 2021;11:1027.
19. Arung W, Meurisse M, Detry O. Pathophysiology and prevention of postoperative peritoneal adhesions. *World J Gastroenterol*. 2011;17:4545-4553. doi:10.3748/wjg.v17.i41.4545

20. Park H, Baek S, Kang H, Lee D. Biomaterials to prevent post-operative adhesion. *Materials (Basel)*. 2020;13(14):3056. doi:10.3390/ma13143056
21. Park WS, Chung YS, Lee KE, et al. Anti-adhesive effect and safety of sodium hyaluronate and sodium carboxymethyl cellulose solution in thyroid surgery. *Asian J Surg*. 2010;33:25-30. doi:10.1016/s1015-9584(10)60005-x
22. Baek S, Park H, Park Y, Kang H, Lee D. Development of a lidocaine-loaded alginate/CMC/PEO electrospun nanofiber film and application as an anti-adhesion barrier. *Polymers (Basel)*. 2020;12(3):618. doi:10.3390/polym12030618
23. Cui Q, Wei B, He Y, et al. Findings of a videofluoroscopic swallowing study in patients with dysphagia. *Front Neurol*. 2023;14:1213491. doi:10.3389/fneur.2023.1213491
24. Gunatillake PA, Adhikari R. Biodegradable synthetic polymers for tissue engineering. *Eur Cell Mater*. 2003;5:1; discussion 16-116. doi:10.22203/ecm.v005a01
25. Kulkarni V, Butte K, Rathod S. Natural polymers: a comprehensive review. *Int J Res Pharm Biomed Sci*. 2012;3:1597-1613.
26. Pişkin E. Biodegradable polymers as biomaterials. *J Biomater Sci Polym Ed*. 1995;6:775-795. doi:10.1163/156856295x00175
27. Kim SG, Song KY, Lee HH, et al. Efficacy of an antiadhesive agent for the prevention of intra-abdominal adhesions after radical gastrectomy: a prospective randomized, multicenter trial. *Medicine (Baltimore)*. 2019;98:e15141. doi:10.1097/md.0000000000015141
28. Park JW, Bak KH, Cho TK, Chun HJ, Ryu JI. Effects of a temperature-sensitive, anti-adhesive agent on the reduction of adhesion in a rabbit laminectomy model. *J Korean Neurosurg Soc*. 2016;59:250-258. doi:10.3340/jkns.2016.59.3.250
29. Macadam SA, Lennox PA. Acellular dermal matrices: use in reconstructive and aesthetic breast surgery. *Can J Plast Surg*. 2012;20:75-89. doi:10.1177/229255031202000201
30. Kim JK, Lee CR, Kang SW, et al. Efficacy and safety of temperature-sensitive acellular dermal matrix in prevention of postoperative adhesion after thyroidectomy: a randomized, multicenter, double-blind, non-inferiority study. *PLoS ONE*. 2022;17:e0273215. doi:10.1371/journal.pone.0273215
31. Rosenbek JC, Robbins JA, Roecker EB, Coyle JL, Wood JL. A penetration-aspiration scale. *Dysphagia*. 1996;11:93-98. doi:10.1007/BF00417897
32. Ko EJ, Chae M, Cho SR. Relationship between swallowing function and maximum phonation time in patients with parkinsonism. *Ann Rehabil Med*. 2018;42:425-432. doi:10.5535/arm.2018.42.3.425
33. Hutcheson KA, Barrow MP, Barringer DA, et al. Dynamic Imaging Grade of Swallowing Toxicity (DIGEST): scale development and validation. *Cancer*. 2017;123:62-70. doi:10.1002/cncr.30283
34. Hillenbrand A, Cammerer G, Dankesreiter L, Lemke J, Henne-Bruns D. Postoperative swallowing disorder after thyroid and parathyroid resection. *Pragmat Obs Res*. 2018;9:63-68. doi:10.2147/por.S172059
35. Oh A. Trends of anti-adhesion adjuvant: review. *Biomater Res*. 2013;17:138-145.
36. Dumortier G, Grossiord JL, Agnely F, Chaumeil JC. A review of poloxamer 407 pharmaceutical and pharmacological characteristics. *Pharm Res*. 2006;23:2709-2728. doi:10.1007/s11095-006-9104-4
37. Russo E, Villa C. Poloxamer hydrogels for biomedical applications. *Pharmaceutics*. 2019;11(12):671. doi:10.3390/pharmaceutics11120671
38. Shim HS, Lee Y, Lee YM, et al. Evaluation of resorbable materials for preventing surgical adhesion on rat experiment. *J Korean Surg Soc*. 2002;63:179-186.
39. Oh SH, Kim JK, Song KS, et al. Prevention of postsurgical tissue adhesion by anti-inflammatory drug-loaded pluronic mixtures with sol–gel transition behavior. *J Biomed Mater Res A*. 2005;72A:306-316. doi:10.1002/jbm.a.30239
40. Kim DY, Kang SW, Kim DS, et al. Preventive effect of human acellular dermal matrix on post-thyroidectomy scars and adhesions: a randomized, double-blinded, controlled trial. *Dermatol Surg*. 2015;41:812-820. doi:10.1097/dss.0000000000000410
41. Jeong JJ, Lee DW, Song SY, et al. Development of novel biocompatible thermosensitive anti-adhesive agents using human-derived acellular dermal matrix. *PLoS ONE*. 2019;14:e0212583. doi:10.1371/journal.pone.0212583