Int Surg 2018;**103:**452–460
DOI: 10.9738/INTSURG-D-17-00065.1

Prospective, Randomized, Double Blind, Multicenter Study for an Autocrosslinked Polysaccharide Gel to Evaluate Antiadhesive Effect and Safety Compared to Poloxamer/ Sodium Alginate After Thyroidectomy

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The aim of the study was to compare the efficacy and safety between an autocrosslinked polysaccharide (ACP) gel (Hyalobarrier) and a poloxamer/sodium alginate (P/SA: Guardix-SG) in preventing adhesions after thyroidectomy and demonstrate the non-inferiority of ACP gel to P/SA. To identify differences of antiadhesive efficacy and safety between the ACP gel and P/SA, we investigated various variables such as the proportion of normal esophageal motility as assessed using marshmallow esophagography,

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swallowing impairment, adhesion severity and so on. This prospective, randomized, double-blinded, multicenter, phase III study investigated the antiadhesive efficacy and safety of ACP gel compared with those of P/SA for 12 weeks. Subjects were randomly assigned to receive either ACP gel (n = 97) or P/SA (n = 96). The primary endpoint was the proportion of normal esophageal motility as assessed using marshmallow esophagography, while the secondary endpoints included swallowing impairment, adhesion severity, laryngoscopic assessment of the vocal cords, and voice range profile. Safety endpoints included adverse events. There was no significant difference between the ACP gel and P/SA groups in the proportion of normal esophageal motility as the primary endpoint ($P = 0.7428$). In addition, there were no differences in the secondary or safety endpoints between the 2 groups. It was demonstrated that ACP gel was not inferior to P/SA. ACP gel appears both effective and safe for use in preventing adhesions after thyroidectomy.

Key words: Sodium hyaluronate – Surgery-induced tissue adhesions – Thyroid

Postoperative adhesions consist of residual collagen fibers that appear during fibrosis, which is activated after surgical trauma.[1] Postoperative adhesions after thyroidectomies can lead to voice changes, swallowing difficulties, a pulling sensation during neck extension, and surgical difficulties due to anatomic changes in a secondary operation.[2–5] Numerous strategies have been introduced to improve surgical techniques and manufacture pharmacologic agents that create mechanical barriers. Hyaluronic acid (HA), a naturally occurring component of the extracellular matrix and peritoneal fluid, has been used as an adhesion prevention adjuvant in a variety of surgical procedures. Native HA has a high degree of biocompatibility and a favorable safety profile.[6] Indeed, several authors in various experimental and clinical settings have proposed that HA deposition around surgically treated tissues reduces postoperative adhesion.[7,8] Hyalobarrier (Anika Therapeutics Inc, Bedford, Massachusetts) is a developed highly viscous gel derivative of HA that was obtained using an autocrosslinking process that does not introduce foreign bridge molecules.[9]

Autocrosslinked polysaccharide (ACP) is an inter- and intramolecular ester of HA in which a proportion of the carboxyl groups is esterified with hydroxyl groups, thus forming a mixture of lactones and intermolecular ester bonds. The absence of foreign bridge molecules ensures the release of native HA only during degradation, while the autocrosslinking process improves the viscoelastic properties of the gel, resulting in its higher adhesiveness and prolonged residence time at the injured surface compared with unmodified HA solutions of the same molecular weight.[10] Preclinical trials in animal models and clinical trials in humans have shown that the ACP gel reduces the incidence and severity of postoperative adhesions.[10–13] Poloxamer/sodium alginate (P/SA: Guardix-SG, Genewel, Dongsung company, Sungnam, Gyeonggi, South Korea) is a temperature-sensitive adhesion barrier composed of poloxamer, a biocompatible polymer and alginate, which was approved for use in thyroidectomy by the Ministry of Food and Drug Safety and appeared to effectively prevent adhesions after thyroidectomy.[14] Poloxamer is currently widely used in the pharmaceutical industry because it is both suitable for drug delivery and is nontoxic and safe for use in total thyroidectomies.[15] At room temperature, P/SA is liquid (viscosity of approximately 3000 centipoise [cP] at 21°C), thus enabling easy injection and application around the incision. At body temperature, the material forms a gel with a high viscosity (viscosity of approximately 90,000–95,000 cP at 37°C). We performed a prospective, randomized, double-blinded, multicenter study to compare the efficacy and safety between ACP gel (Hyalobarrier) and P/SA (Guardix-SG) for reducing adhesions after thyroidectomy.

Materials and Methods

Ethical considerations

The trial is registered at ClinicalTrials.gov (number, NCT01696305). The study protocol was reviewed and approved by the institutional review boards of each referral center (MD12012001, MD1117003, and

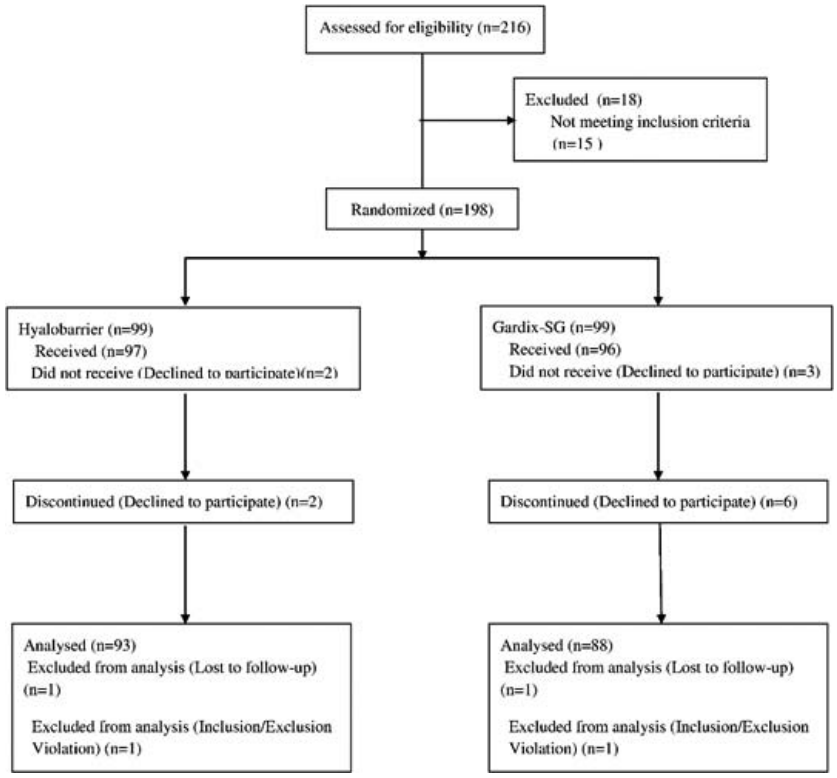

Fig. 1 Flowchart of the patients through the study.

KUH1020049). Written informed consent was obtained from all study subjects.

Trial design

The trial was conducted using a randomized controlled double-blind phase III design at 3 surgery referral centers between December 2012 and February 2014. The study was carried out in compliance with good clinical practice and the Consolidated Standards for Reporting of Trials (CONSORT) statement.[16] After providing informed consent, eligible subjects that met inclusion/exclusion criteria based on the screening evaluation were randomized at a 1:1 ratio into the test group (Hyalobarrier; ACP gel) and the control group (Guardix-SG; P/SA) by an interactive web response system. We implemented the random allocation sequence by use of the numbered containers in the refrigerator reserved for the trial.

Subjects

Subjects aged 18–79 years were included in the study. All subjects required a total thyroidectomy with or without cervical lymph node dissection for treatment of thyroid diseases. We excluded currently pregnant or breastfeeding women, abnormal coagulation, abnormal laboratory tests, inappropriate general health conditions, medication history for hyperthyroidism, current regular anticoagulant use, uncontrolled hypertension or diabetes mellitus, chronic renal failure, cardiovascular diseases, any drug or chronic alcohol abuse, participation in other clinical trials within 30 days of this study, history of esophageal diseases, history of thyroid surgery, and other inappropriate conditions.

Interventions

Clinical visits were conducted at 0 weeks (visit 1, including screening day, operation day, and 1 day after the operation day); postoperative week 1 (visit 2); week 6 (visit 3); and week 12 (visit 4). The demographic characteristics and clinical and laboratory assessments were recorded after informed consent was obtained during visit 1. The investigational device (ACP gel or P/SA) was applied sufficiently with complete coverage of the surgical field prior to closing the operative wound (visit 1). Participants were followed up 3 times (visits 2, 3, and 4) after device application. Clinical and laboratory variables as well as adverse events (AEs) were evaluated at all visits.

Table 1 Demographic characteristics

	Hyalobarrier (N = 97)	Guardix-SG (N = 96)	Total (N = 193)	*P* value
Sex, male/female	22/75	21/75	43/150	0.839
Age, y, mean ± SD	49.58 ± 10.57	47.46 ± 11.28	48.52 ± 10.95	0.180
Weight, kg, mean ± SD	65.15 ± 11.38	62.71 ± 11.46	63.94 ± 11.46	0.120
Height, cm, mean ± SD	160.90 ± 0.89	160.83 ± 8.21	160.86 ± 8.03	0.781
Thyroid cancer, N (%)	92 (94.85)	90 (93.75)	182 (94.30)	0.537
Thyroid cancer type, N				
Papillary	91	89	180	0.743
Medullary	0	1	1	
Papillary + medullary	1	0	1	
TNM stage, N				
I	41	37	78	0.448
II	1	3	4	
III	31	28	59	
IVA	0	3	3	
Others[a]	19	19	38	
Operation time, min	116.95 ± 34.64	126.53 ± 58.44	121.72 ± 48.09	0.949

TNM, tumor-node-metastasis.

[a]Nx (no cervical lymph node dissection).

Outcome measures

The primary endpoint was the proportion of normal esophageal motility as assessed using marshmallow esophagography at visit 3, which was classified as normal if the esophageal transit time in the supine position occurred within 30 seconds. The secondary endpoints included changes in swallowing discomfort (SW); hypesthesia or paresthesia at the operative site (SN); swallowing impairment index-6 (SII-6); adhesion severity on the visual analog scale (VAS); voice handicap index-30 (VHI-30) assessed using a questionnaire; laryngoscopic finding of vocal cords for an assessment of recurrent laryngeal nerve injury performed by an otolaryngologist; voice range profile (VRP) frequencies and intensities at all visits; and grades of postoperative sore throat (POST) assessed using a questionnaire within 24 hours after thyroidectomy. The safety endpoints included adverse events, changes in hematology, blood chemistry, blood coagulation, urinalysis, thyroid function, vital signs, and physical examinations. All data of these endpoints were measured and collected by independent assessors.

Statistical analysis

We calculated the sample size based on an α error level of 0.025, β error level of 0.20, and estimated dropout rate of 20%. A sample size of 79 subjects per group was required. This was increased to at least 99 subjects per group to account for the expected dropout rate. The analysis sets consisted of intent-to-treat (ITT), per protocol (PP), and safety populations. The intent-to-treat set consisted of any subjects who were treated with the investigational device, while the PP set included any subject who belonged to the ITT set and completed the trial without any major protocol violations. A safety analysis was performed on the safety set, which consisted of any subject on whom the device was applied. The efficacy analysis was performed primarily on the ITT population.

The proportion of normal esophageal motility (a score of 3 was considered normal) at visit 3 was evaluated and calculated as the primary efficacy outcome for the 97.5% 1-sided confidence intervals (CIs) of the changes in both groups. Noninferiority of the ACP gel would be confirmed in the primary efficacy outcome when the calculated lower limit of the 1-tailed CI exceeded the prespecified noninferiority margin of –9.2. The size of the margin was specified statistically using an efficacy difference for the control device (P/SA) based on a previously published placebo-controlled (no application of the device) trial. All endpoints were analyzed by independent *t*-test or Mann-Whitney *U*-test using statistical software (SAS System 9.3, SAS Institute, Cary, North Carolina). Values of $P < 0.05$ were accepted as statistically significant.

Results

Subjects

Recruitment began in December 2012 and finished February 2014, after the sample size goal was

Table 2 Esophageal motility, grades of esophageal motility, mean scores of esophageal motility, transit time assessed by marshmallow esophagography at the postoperative week 6 visit

	Hyalobarrier	Guardix-SG	Difference [97.5% 1-sided CI]
ITT set	N = 91	N = 87	
Normal esophageal motility, N (%)	87 (95.60)	82 (94.25)	1.35%
95% CI	[89.13, 98.79]	[87.10, 98.11]	[–5.10, –]
P value			0.743
PP set	N = 80	N = 74	
Normal esophageal motility, N (%)	76 (95.00)	69 (93.24)	1.76%
95% CI	[87.69, 98.62]	[84.93, 97.77]	[–5.69, –]
P value			0.739
Mean scores of esophageal motility (mean ± SD)	2.96 ± 0.21	2.94 ± 0.23	0.685
Esophageal transit time (mean ± SD)	13.59 ± 12.07	15.22 ± 11.16	0.066

reached. A total of 198 subjects were enrolled, and among them, 5 subjects were withdrawn due to nonapplication of the device for declines to participate this study (Fig. 1). The data from the 193 enrolled subjects who underwent surgery and completed the postoperative assessments were analyzed. The mean age was 48.52 ± 10.95 years, and there were 150 women and 43 men. The demographic characteristics are shown in Table 1.

Efficacy results

The proportions of subjects with normal esophageal motility as measured using marshmallow esophagography for the test group and the control group at visit 3, as the primary efficacy outcome, were 95.60% and 94.25%, respectively, and the difference between the groups was 1.35% ($P = 0.743$). The 97.5% 1-sided CI of the difference was [–5.10, –], and the calculated lower limit of the 1-sided CI exceeded the prespecified noninferiority margin of –9.2, demonstrating the noninferiority of the ACP gel. Similarly, the noninferiority of the ACP gel was also confirmed for the PP set. The proportions were 95.0% (the test group) and 93.24% (the control group), and the difference between the groups was 1.76% ($P = 0.739$). The 97.5% 1-sided CI of the difference was [–5.69, –], which also exceeded the noninferiority margin of –9.2 (Table 2).

Table 3 Summary of secondary endpoint

Visit	N, mean ± SD	SW	SN	SII-6	VAS, cm
Visit 1	Hyalobarrier	97,2.86 ± 0.41	97, 2.98 ± 0.20	97, 0.51 ± 1.57	97, 0.66 ± 2.72
	Guardix-SG	96, 2.84 ± 0.39	96, 2.92 ± 0.40	95, 0.59 ± 1.75	96, 0.66 ± 2.21
	P value[a]	0.681	0.098	0.919	0.610
Visit 2	Hyalobarrier	96, 1.99 ± 0.69	96, 2.33 ± 0.95	95, 4.79 ± 5.30	96, 8.72 ± 9.79
	Guardix-SG	92, 2.17 ± 0.70	92, 2.50 ± 0.79	92, 2.77 ± 3.56	92, 5.45 ± 6.38
	P value[a]	0.073	0.288	0.001	0.026
Visit 3	Hyalobarrier	96, 2.40 ± 0.73	96, 2.46 ± 0.85	96, 3.26 ± 4.27	95, 5.65 ±7.16
	Guardix-SG	88, 2.45 ± 0.66	88, 2.44 ± 0.88	88, 2.05 ± 3.18	88, 4.68 ± 6.60
	P value[a]	0.701	0.968	0.051	0.351
Visit 4	Hyalobarrier	94, 2.67 ± 0.49	94, 2.65 ± 0.58	94, 1.03 ± 1.86	93, 1.69 ± 3.83
	Guardix-SG	88, 2.80 ± 0.48	88, 2.67 ± 0.60	88, 1.15 ± 3.41	87, 1.49 ± 3.02
	P value[a]	0.037	0.708	0.152	0.863
Changes between visits 1 and 2	Hyalobarrier	96, –0.86 ± 0.75	96, –0.65 ± 0.94	95, 4.27±5.25	96, 8.06 ± 9.62
	Guardix-SG	92, –0.68 ± 0.74	92, –0.46 ± 0.80	91, 2.35 ± 3.74	92, 4.95 ± 6.62
	P value[a]	0.081	0.172	0.002	0.015
Changes between visits 1 and 3	Hyalobarrier	96, –0.46 ± 0.79	96, –0.52 ± 0.83	96, 2.75 ± 4.29	95, 4.98 ± 6.95
	Guardix-SG	88, –0.41 ± 0.77	88, –0.53 ± 0.88	87, 1.57 ± 3.39	88, 4.16 ± 6.63
	P value[a]	0.739	0.877	0.073	0.426
Changes between visits 1 and 4	Hyalobarrier	94, –0.18 ± 0.62	94, –0.33 ± 0.59	94, 0.52 ± 2.07	93, 1.01 ± 3.75
	Guardix-SG	88, –0.07 ± 0.66	88, –0.31 ± 0.63	87, 0.70 ± 3.67	87, 0.96 ± 3.36
	P value[a]	0.142	0.730	0.049	0.653

The proportions of subjects assigned to each grade based on marshmallow esophagography, mean grades of esophageal transit dysfunction as assessed using marshmallow esophagography, and mean esophageal transit time were supportively analyzed to assess the robustness of the primary efficacy outcomes. In the test group, the proportions of subjects assigned to each grade were 95.60% and 4.40% for normal and mild esophageal motility dysfunction, respectively, and no subject had either severe or moderate grade dysfunction. Similarly, in the control group, the proportions were 94.25% and 5.75% for normal and mild esophageal motility dysfunction, respectively, and no subject had either severe or moderate grade dysfunction ($P = 0.743$). The mean grades of esophageal motility dysfunction were 2.96 ± 0.21 and 2.94 ± 0.23 for the test and control groups, respectively ($P = 0.685$). Mean esophageal transit times were 13.59 ± 12.07 seconds and 15.22 ± 11.16 seconds for the test and control groups, respectively ($P = 0.066$; Table 2).

The secondary endpoints were assessed for changes in SW scores, SII-6 scores, and adhesion severity in VAS scores. There were significant differences in mean score for SW scores ($P = 0.037$); VHI-30 ($P = 0.047$) at visit 4; mean score for SII-6 scores ($P = 0.001$); and adhesion severity VAS scores ($P = 0.0258$) at visit 2. Moreover, there were significant differences for the mean score for SII-6 scores between visit 1 and visit 2 ($P = 0.002$) and between visits 1 and 4 ($P = 0.049$) as well as adhesion severity VAS scores between visits 1 and 2 ($P = 0.015$) and VHI-30 between visits 1 and 4 ($P = 0.029$). However, no significant differences were detected for VRP frequencies and intensities (Table 3); laryngoscopic findings of vocal cords (Table 4); or POST grades (data not shown, after operation; $P = 0.8593$, at recovery room; $P = 0.1601$, 24 hours after operation; $P = 0.8359$).

Safety results

Mean changes of the laboratory test parameters were not significantly different between the groups, with the exceptions of C-reactive protein (CRP; $P = 0.043$); erythrocyte sedimentation rate (ESR; $P = 0.018$); and fibrinogen ($P = 0.045$; Table 5). During the course of the trial, severe adverse events occurred in 6 (3.1%) of the 193 subjects; however, no adverse device effects (ADE) occurred. Adverse events were 261, 61, and 11 cases for mild, moderate, and severe intensity, respectively. Across the groups, 172 and 161 adverse events were reported in 96 (98.97%) subjects of the test group and in 96 (100.00%) subjects of the control group. Almost all adverse events were postoperative pain and swallowing discomfort. There was no significant difference in the incidence of adverse events between the groups ($P > 0.9999$). Eight serious adverse events (SAEs) occurred in 6 subjects. All SAEs resulted in

Table 3 Extended

Lowest frequencies in the VRP, Hz	Highest frequencies in the VRP, Hz	Lowest intensities, dB, in the VRP	Highest intensities, dB, in the VRP	VHI-30
97, 169.72 ± 56.24	97, 323.31 ± 149.95	97, 78.20 ± 8.84	97, 90.27 ± 16.25	97, 0.70 ± 3.24
96, 170.86 ± 56.06	96, 333.82 ± 170.24	96, 77.52 ± 10.03	96, 91.34 ± 17.37	96, 2.35 ± 12.16
0.904	0.964	0.767	0.620	0.311
96, 164.61 ± 65.81	96, 248.48 ± 96.61	96, 78.54 ± 8.97	96, 88.99 ± 15.37	96, 20.03 ± 28.71
92, 169.04 ± 57.20	92, 266.25 ± 119.23	92, 78.51 ± 8.70	92, 89.45 ± 14.99	92, 12.26 ± 19.95
0.423	0.416	0.979	0.882	0.121
96, 159.86 ± 55.93	96, 257.36 ± 94.54	96, 77.63 ± 9.08	96, 89.30 ± 15.20	95, 17.97 ± 26.87
86, 167.45 ± 55.41	86, 266.34 ± 106.25	86 75.76 ± 9.60	86, 86.86 ± 16.14	88, 12.17 ± 21.31
0.344	0.745	0.229	0.325	0.150
89, 163.39 ± 52.70	89, 265.73 ± 111.74	89, 76.63 ± 9.21	89, 87.67 ± 16.41	94, 6.43 ± 14.57
88, 169.80 ± 56.74	88, 289.30 ± 144.52	88, 76.26 ± 9.94	88, 86.73 ± 16.29	88, 4.36 ± 11.04
0.424	0.375	0.921	0.744	0.047
96, –4.68 ± 53.17	96, –75.94 ± 124.04	96, 0.29 ± 7.71	96, –1.42 ± 6.77	96, 19.32 ± 28.46
92, –3.63 ± 38.56	92, –65.89 ± 115.43	92, 1.11 ± 10.64	92, –1.25 ± 6.92	92, 11.01 ± 19.51
0.354	0.420	0.318	0.867	0.056
96, –9.43 ± 48.20	96,–67.05 ± 111.61	96, –0.62 ± 7.93	96, –1.10 ± 6.36	95, 17.25 ± 26.00
86, –8.59 ± 45.43	86, –53.03 ± 92.25	86, –1.39 ± 11.23	86, –2.42 ± 7.64	88, 10.86 ± 21.44
0.587	0.348	0.360	0.206	0.068
89, –9.00 ± 37.90	89, –50.54 ± 98.05	89, –1.39 ± 8.66	89, –1.65 ± 7.46	94, 5.70 ± 13.86
88, –4.85 ± 43.21	88, –34.96 ± 77.79	88, –1.10 ± 11.26	88, –3.12 ± 8.98	88, 3.06 ± 12.43
0.066	0.327	0.851	0.238	0.029

Table 4 Normal/abnormal findings of vocal cords assessed by laryngoscopy

Normal, n (%)/abnormal, n (%)	Vocal fold movement	Vocal fold mucosal lesion	Vocal fold gap in phonation
Visit 2			
Hyalobarrier	80 (85.1)/14 (14.9)	93 (98.9)/1 (1.0)	87 (92.6)/7 (7.5)
Guardix-SG	82 (89.1)/10 (10.9)	91 (98.9)/1 (1.1)	90 (97.8)/2 (2.2)
P value	0.303	>0.999	0.169
Visit 3			
Hyalobarrier	8 4 (88.4)/11 (11.6)	92 (9 6.8)/3 (3.2)	92 (96.8)/3 (3.2)
Guardix-SG	82 (93.2)/6 (6.8)	8 6 (97.7)/2 (2.3)	84 (95.5)/4 (4.5)
P value	0.165	>0.999	0.711
Visit 4			
Hyalobarrier	87 (93.6)/6 (6.4)	92 (98.9)/1 (1.1)	91(97.9)/2 (2.2)
Guardix-SG	83 (94.4)/5 (5.6)	88 (100.0 0)/0 (0.0)	86 (97.7)/2 (2.3)
P value	0.748	>0.999	>0.999

admission to the hospital or prolonged hospitalization (Table 6). Neither death nor life-threatening SAEs occurred.

Discussion

HA is a ubiquitous substance that is normally present in all human tissues. It is elevated during periods of rapid tissue regeneration or repair, and is present in the extracellular matrix of fetal wounds, which are well known for their ability to avoid scar formation and prevent postoperative adhesion formation.[16] HA controls and regulates cell behavior and cell–cell interactions, especially in the context of tissue healing, which involves immune response activation and modulation, promotion of angiogenesis, and cell proliferation and migration.[16] Moreover, HA is known to improve re-epithelialization,[17,18] and rapid wound healing by re-epithelialization minimizes the risk of adhesion and infection. In addition, since previous studies and meta-analyses revealed that HA derivatives have antiadhesive effects in human abdominal, facial, and breast surgeries as well as in animal models, we postulated that ACP gel, like P/SA, is particularly suitable for preventing adhesion formation and promoting tissue regeneration after thyroidectomy in human.[8,10,13,14,19–22]

Table 5 Summary of ESR, CRP, fibrinogen

	Hyalobarrier	Guardix-SG	*P* value
ESR, mm/h			
Preoperative	12.68 ± 9.73	14.23 ± 12.37	0.591
Last visit	13.30 ± 10.85	16.89 ± 13.73	0.050
Changes between preoperative and last visit	0.24 ± 8.33	2.78 ± 11.71	0.018
CRP, mg/L			
Preoperative	1.28 ± 2.45	1.12 ± 1.91	0.498
Last visit	1.64 ± 4.33	1.84 ± 3.59	0.647
Changes between preoperative and last visit	0.34 ± 4.83	0.75 ± 3.97	0.043
Fibrinogen, mg/dL			
Preoperative	292.37 ± 58.32	286.58 ± 54.49	0.510
Last visit	307.15 ± 67.52	320.40 ± 74.02	0.295
Changes between preoperative and last visit	13.38 ± 62.49	36.20 ± 68.22	0.045

We investigated the proportions of subjects with normal esophageal motility as measured using marshmallow esophagography, which is considered one of the objective measurements of swallowing difficulty after thyroidectomy because swallowing difficulty is one of the common complications related to postthyroidectomy adhesion. The abnormal pharyngeal and upper esophageal muscle movement that is induced by postthyroidectomy adhesion might trigger swallowing difficulty.[3] Marshmallow esophagography is more sensitive for identifying dysfunctional or anatomic symptoms associated with pharyngeal or esophageal diseases or disorders related to swallowing difficulty than conventional esophagography.[23] In addition, we used numerous methods for assessing postoperative adhesion to retain objectivity of results, whereas only 1 or 2 methods were used in other studies. In this study, postthyroidectomy adhesion symptoms were assessed using various methods including SW (inquiring about swallowing discomfort); SN (inquiring about paresthenia or hypesthenia at the operative site); SII-6 (inquiring about swallowing difficulty); adhesion severity VAS (inquiring about or examining swallowing, cosmesis, and postoperative inflammation); VHI-30 (inquiring about voice handicaps or changes); laryngoscopic findings of the vocal cords (examining vocal fold movement,

Table 6 Summary of overall AEs

	Hyalobarrier (N = 97)	Guardix-SG (N = 96)	Total (N = 193)
Subjects with at least 1 AE, n			
Overall AE	96 (98.97%)	96 (100.00%)	192 (99.48%)
95% CI	[94.39, 99.97]	[96.23, 100.00]	[97.15, 99.99]
P value		>0.9999	
SAE	5 (5.15%)	1 (1.04%)	6 (3.11%)
AE leading to premature termination	0 (0.00%)	1 (1.04%)	1 (0.52%)
AE occurrences, N	172	161	333
Severity			
Grade 1/mild	135	126	261
Grade 2/moderate	30	31	61
Grade 3/severe	7	4	11
SAE	6	2	8
AE leading to premature termination	0	1	1

phonation gaps, and mucosal lesions); VRP frequencies and intensities (examining voice changes); and POST grades (inquiring about throat soreness). Although there were statistical differences among the above mentioned results, because of no difference in marshmallow esophagography (as primary endpoint), voice range profile, and laryngoscopic finding of vocal cords—which were the ones of the most objective methods for assessing functional changes—it is presumed that ACP gel is not inferior to P/SA to prevent postthyroidectomy adhesion. For the laboratory parameters, the levels of ESR as well as CRP and fibrinogen are representative indicators for inflammatory and adhesive responses, respectively. ACP gel may have less inflammatory and adhesive responses compared with P/SA in that the levels of CRP, ESR, and fibrinogen in ACP gel declined further in P/SA significantly.

In 6 subjects, 8 SAEs occurred: 1 carotid body tumor, 6 temporary vocal cord palsy with or without respiratory discomfort, and 1 uterine leiomyoma. None was related to an ADE. These events were resolved using surgery and medication or were observed during a prolonged hospital stay, outpatient clinic follow-ups, and recovery monitoring.

Conclusion

There were no differences in postoperative adhesions after the application of either ACP gel or P/SA after thyroidectomy. Therefore, ACP gel has an equivalent antiadhesion effect to that of P/SA and can be used safely. This randomized, controlled, double-blinded, multicenter trial showed that the efficacy of ACP gel (Hyalobarrier) was not inferior to that of P/SA (Guardix-SG), and its safety was favorable.

Acknowledgments

This study was sponsored by a study grant from Green Cross Corporation (Korea).

Conflict of interest: The authors have no conflicts of interest to disclose.

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