공학석사 학위논문

Efficacy and Safety of a New Hyaluronic Acid Filler containing lidocaine compared to Conventional HA Fillers in the treatment of moderate to severe Nasolabial fold Wrinkles

성인의 안면부 코입술주름(nasolabial fold)에 대한 라스뷰 스트롱 (LASBEAU Strong) 및 레스틸렌® 리프트 리도카인(Restylane® Lyft Lidocaine)의 일시적인 주름 개선 효과와 안전성을 비교 평가하기 위한 다기관, 무작위배정 피험자와 평가자 눈가림, 짝대응 설계, 비교, 확증 임상시험

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의과학과

조지영

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조지영

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국문요약

연구배경: 비수술적 주사 치료는 미적 목적으로 널리 사용되는 방법이 되었다. 요즘 리도카인을 함유하는 가교 히알루론산 충전제가 팔자 주름의 교정에 사용되고 있다. 팔자주름을 회복시키기 위해 리도카인을 함유한 가교 히알루론산 필러를 사용한 최근 연구는 거의 없다.

재료 및 방법: 총 72명의 피험자가 등록되어 얼굴의 왼쪽 또는 오른쪽에 새로운 히알루론산 필러(시험군) (24 mg/mL) 또는 기존 히알루론산 필러(대조군)를 주사하도록 무작위 배정되었습니다. 새로운 히알루론산 필러(시험군) 또는 기존 히알루론산 필러(대조군) 필러들은 모두 주사 시 통증감소를 목적으로 리도카인이 포함되어 있다. 1차 효능은 치료 후 24주차에 주름 심각도 등급 점수의 평균 차이 변화로 평가되었다. 2차 효능은 치료 후 8주차, 16주차, 24주차 및 48주차에 주름 심각도 등급 점수 및 글로벌 미용 개선 척도 평가에 의해 평가되었으며 안전성은 부작용, 실험실 혈액검사 및 방문 시 활력 징후 확인으로 평가되었다.

결과: 1차 효능은 기저점으로부터 24주차에 연구자에 의해 기저점과 비교, 평가된 주름 심각도 등급 점수의 평균 변화로 측정되었다. 시험군의 경우 2.00±0.71, 대조군의 경우 2.26±0.66이었다. 두 군의 차이는 -0.26±0.69였다. 구간의 상한선은 -0.0101로 비열등성에 대해 미리 정의된 마진(0.29)보다 작았으며, 이는 치료 후24주차에 시험군의 효능이 대조군에 비해 열등하지 않음을 나타낸다.

결론: 시험군(새로운 히알루론산 필러, LASBEAU Strong)은 치료 후 24주차에 중등도 내지 중증의 팔자주름의 일시적 치료에서 대조군(기존 히알루론산 필러, Restylane Lyft)보다 열등하지 않았다. 치료 후 48주차에 장기 안전성 평가가 확인되었다. WSRS 점수가 1점 이상 개선된 피험자의 비율은 시험군 31.37%(참가자 16/51명), 대조군 32.76%(여성 19/58명)로 통계적으로 유의한 차이는 없었다. 이물질 육아종 형성이나 염증과 같은 지연성 이상반응 관찰하기 위해 보다 장기적인 추가연구가 필요하나 본 48주간의 임상시험을 통해 새로운 히알루론산 필러는 안전성과 효능이 보장되는 충분한 제품이 될 수 있음이 확인되었다.

중심어: 새로운 히알루론산 필러, 히알루론산, 리도카인, 코입술주름

표 및 그림 차례

ABSTRACT

Background: Nonsurgical injectable treatments have become popular for aesthetic purposes. In recent years, cross-linked hyaluronic acid (HA) fillers containing lidocaine have been used to correct the nasolabial folds. Recently, there have been few studies using cross-linked HA fillers containing lidocaine to restore nasolabial folds.

Aim: The aim of this study was to demonstrate the efficacy and safety of a new HA filler (LASBEAU Strong) (24 mg/mL) containing lidocaine compared with a conventional HA filler (Restylane Lyft) for the temporary restoration of nasolabial folds.

Patients/methods: A total of 72 subjects were enrolled and randomized to receive injections of the new HA filler containing lidocaine (test group) or the conventional HA filler (control group) on the left or right side of the face. The mean value difference in the Wrinkle Severity Rating Scale (WSRS) scores at week 24 evaluated primary efficacy. The WSRS and the Global Aesthetic Improvement Scale (GAIS) at weeks 8, 16, 24, and 48 evaluated secondary efficacy. Adverse events, laboratory tests, and a check of vital signs at every visit assessed safety.

Results: The mean value in the WSRS scores evaluated by investigators at week 24, the primary efficacy measure, was 2.00 ± 0.71 for the test group and 2.26 ± 0.66 for the control group. The mean value difference between the device groups was -0.26 ± 0.69. The upper limit of the interval was -0.0101, which was smaller than the predefined margin for noninferiority (0.29), indicating that the efficacy in the test group at week 24 was comparable to that of the control group. At week 48, the proportion of subjects with an improvement in WSRS score of one or more points was 31.37% (16/51 participants) in the test group and 32.76% (19/58 women) in the control group and there was no statistically significant difference.

Conclusion: The test group (LASBEAU Strong) was not inferior to the control group (Restylane Lyft) in the temporary improvement of moderate to severe nasolabial folds at week 24 following the HA filler injections. Further research is required to ensure long-term safety.

Keywords: new HA filler (LASBEAU Strong); hyaluronic acid; lidocaine; nasolabial fold.

Ⅰ. Introduction

Hyaluronic acid (HA) is a type of glycosaminoglycan that has a repeating structure of sodium glucuronate and N-acetylglucosamine unit sugar and that is known as a component of connective tissue such as joint fluid, oculovitreous fluid, umbilical cord, dermis surface layer, etc. HA is a form of polymer with the same structure in all species. The main function of HA in the extracellular matrix is to stabilize the extracellular structure and form matrix fluid. HA has strong hydrophilicity and functions as a natural supply of moisture to the skin, contributing to its flexibility and swelling. In view of its structural role in tissues, protective effect on cell membranes, and viscoelasticity. HA is ideal as a skin filler [1]. Cross-linking is a process in which HA in a liquid state is transformed into a soft solid or gel by chemically combining each chain of HA. By slowing down HA metabolism in the human body, cross-linked HA can have a long-lasting effect in terms of beauty [1]. Among non-surgical procedures for wrinkle improvement, soft tissue augmentation using an injectable filler is one of the most frequently performed cosmetic procedures and is widely applied [3]. However, there has been a risk of a serious hypersensitivity reaction due to an immune response caused by various substances. Among them, HA began to be used clinically about 20 years ago, cross-linked and nonanimal-stabilized HA derivatives have longer-lasting power and less immune response compared with unprocessed HA [1,2].

The new HA filler is a biomaterial that contains nonanimal-stabilized HA derived from bacterial fermentation and lidocaine, a local anesthetic that reduces pain during the procedure [7].

This product is a cross-linked HA gel containing Lidocaine, a biomaterial for tissue repair, and was developed to temporarily improve facial wrinkles in the adult's face and relieve

pain during the procedure. The aim of this trial was to demonstrate that the new HA filler consisting of 24 mg/mL cross-linked HA containing lidocaine was not inferior to the conventional HA filler, which contains the same ingredient for the temporary restoration of nasolabial folds with moderate to severe Wrinkle Severity Rating Scale (WSRS) scores..

Ⅱ. Materials and methods

1. Trial design

This multicenter, randomized, double-blind, split-face clinical trial was conducted from November 2019 to February 2021 at two investigational sites (Asan Medical Center and Nowon Eulji Medical Center) in the Republic of Korea. The trial protocol was approved by the institutional review board of both institutions and followed the guidelines of the 1975 Declaration of Helsinki. All the subjects provided written informed consent, including a signed photographic consent form, before participation in the trial.

2. Trial population

From November 2019 to June 2020, among subjects who desired temporary improvement of the nasolabial folds on both sides, those who had a WSRS of 3 or 4 points (they didn't have to have the same score on both sides) were enrolled in the trial. Subjects aged over 19 years were included in the trial. The subjects agreed not to have any other treatment for facial wrinkle correction during the trial period. The exclusion criteria were administration of antithrombotic agents(excluding low-dose aspirin therapy (100mg ; maximum 300mg/day)) from 2 weeks before to 2 weeks following the HA filler injections, administration Vitamin E preparations or NSAID preparations from 1 week before to 1 week following the HA filler injections; previous or current bleeding disorder, Calcium Hydroxyapatite(CaHA) or Poly L-Lactide(PLLA) filler treatment within 1 year after the screening date; use of topical agents (steroids, retinoids: only for pharmaceuticals, excluding cosmetics) on the face within 4 weeks after the screening date or planning to use them during the clinical trial period (however, for treatment purposes, steroid ointments could be used for a short period within 14 consecutive days); administration of

antiwrinkle therapy, acne scar treatment, plastic surgery (including botulinum toxin injection), facial abrasion or skin rejuvenation within the past 24 weeks; permanent skin expansion implant, such as soft form and silicon on the face; skin disorders; wound infections on the face; and a history of keloid or hypertrophic scar. Other exclusion criteria were disagreement to contraception by a medically allowed method for the trial period following the HA filler injections among female subjects who were probably pregnant; pregnancy or lactation; and clinically significant findings considered inappropriate for this test by the investigator.

3. Materials

LASBEAU Strong (ExocoBio, Inc., Seoul, Korea), an investigational device filled with a colorless transparent liquid filler consisting of 24 mg/mL cross-linked HA containing lidocaine, was used as a test device in the trial.

Restylane Lyft (GalDerma a Korea, Inc., Seoul, Korea), a filler filled with cross-linked HA containing lidocaine, was used as a control device.

4. Trial protocol

At the first treatment visit (Week 0), the subjects were randomized to determine into which nasolabial fold the test device would be applied; the control device was applied into the other nasolabial fold. Following the HA filler injections, the subject was kept under observation for 30 min to check for adverse events (AEs). The subjects received a subject diary and recorded the occurrence and disappearance of AEs in the subject diary for 2 weeks; the subjects returned the subject diary at second visit after the HA filler injections. The response to the injection of test device and control devices was documented at weeks

8, 16 and 24. The call visit at week 36, performed additional safety assessment. At week 48, subjects completed the trial, and evaluated the safety and efficacy of the treatment.

5. Treatment procedure

Before the injection of the HA fillers, the treatment site was cleansed with disinfecting fluid. Subjects were applied to the test device to one side of the face and the control device to the contralateral side. The injection sites were massaged as needed following the HA filler injection.

6. Method of randomization and blinding

A random-number table was used for randomization. The investigator opened the randomization envelopes in the order in which the subjects were registered, and the HA fillers were injected. To maintain blindfolding between the subjects and the independent investigators until the end of the trial, the subjects and the independent investigators didn't know into which side of the nasolabial fold the test device and control device were applied. The investigator opened the randomization envelope immediately before the injection of the HA fillers, so that the investigator knew the fillers to be injected for each nasolabial fold. Before the injection of the HA fillers and at each follow-up visit, high-quality digital photographs including the left and right nasolabial folds, were taken. It was necessary to ensure that the left and right sides were symmetrical from the beginning of the nose lip fold to the tip of the chin, centering on the center line of the lips. Any information about the subjects was removed from the photographs, which were then sent to independent investigators to assess the efficacy of the treatment.

7. Method of split -face comparison

To minimize the differences between individuals according to the depth and degree of wrinkles for each subject, the difference in the procedure situation of the practitioner (time, condition, injection time, etc.), and the degree of recovery, it was considered most appropriate to apply both the test device and the control device to one subject. In addition, since the components of the test device and the control device are the same, and the effect following the HA filler injections is expected to be similar, the design of the pair-corresponding comparison method was adopted. It is possible to measure local safety by comparing local adverse events of the injection site to the left and right sides to check the local adverse events of the test device and that of the control device. Therefore, if new adverse events collected as data and serious adverse events appear, it is judged to be a clinical trial design technique that needs to investigate the correlation.

8. Efficacy Assessment

The primary efficacy measure was mean value differences in the WSRS assessed by three independent investigators between baseline and 24 weeks (Table 1). WSRS scores were first evaluated by the independent investigators. If the WSRS scores were the same among independent investigators, they were accepted. If the WSRS scores were different, they were evaluated by different independent investigators, and results of the same values were adopted and interpreted. The difference in the mean values of WSRS scores between the test group and the control group was then calculated. As secondary measures, WSRS and GAIS (Global Aesthetic Improvement Scale) scores were determined at each of the follow-

up visits by the investigator. The subjects evaluated the level of improvement at each of the follow-up visits even by GAIS (Table 2).

The subjects' pretreatment photograph served as reference images for assessing improvement.

Additional visits were performed at weeks 36(call visit) and 48 following the HA filler injections. At week 36, a call visit was made to check for AEs and concomitant medications; at week 48, the subjects visited the hospital and WSRS and GAIS evaluation were performed through photography of the injection sites.

9. Safety Assessment

Adverse events (AEs) and serious adverse events (SAEs) that occurred following the HA filler injections were presented as numbers of subjects, percentages, and incidences.

10. Statistical Analyses

The primary efficacy endpoint was the mean value difference in WSRS scores between the test group and the control group, as determined by the independent investigators at week 24. The mean value difference between the test group (LASBEAU Strong) and the control group (Restylane Lyft) was calculated with a one-sided 97.5% confidence interval; the test group was noninferior compared with the control group if the upper limit of the one-sided 97.5% confidence interval was much smaller than the predefined margin for noninferiority (0.29) in both the full analysis set (FAS) and the per-protocol set (PPS).

The secondary efficacy endpoints included the followings: (1) The investigators calculated the mean value differences in the WSRS scores between the test group and the control group at weeks 8, 16, 24, and 48 after the filler injections; (2) The investigators calculated

the mean value differences in the GAIS scores between the test group and the control group at weeks 8, 16, 24, and 48 after the filler injections; (3) The independent investigators calculated whether the ratio of subjects whose WSRS scores improved by one or more points in the test group and the control group compared with those before the filler injections at weeks 24 and 48.

The two-sample t-test and Wilcoxon's rank sum test were used for the analyses of endpoints (1) and (2). The chi-square test and Fisher's exact test were used for the analysis of endpoints (3). The chi-square test and Fisher's exact test were used for the safety analysis. The comparisons were subjected to two-tailed tests with a 5% significance level. The paired t-test, Wilcoxon's signed rank test and McNemar's test analyzed the laboratory test results, vital signs, and physical examinations.

Ⅲ. Results

1.Subjects and efficacy outcomes

A total of 72 subjects agreed to participate in this trial and were randomized after a screening period; of these, 72 had at least one HA filler injected and had a safety set of 72 subjects. Four subjects were excluded from the safety set: 2 withdraw consent (01-S030, 01-S038) and 2 failed follow-up (02-S026, 02-S028), resulting in a FAS of 68. An analysis was performed on 62 subjects in the PPS: 1 who dropped out (02-S008), 3 who violated the window period (01-S006, 01-S010, 01-S029), 1 random assignment code error (01-S001), and 1 photo randomization code error (01-S005) out of the FAS. In the long-term safety evaluation, 68 subjects were analyzed by FAS and 59 subjects were further analyzed, excluding 3 subjects by long-term safety evaluation in the PPS: 1 dropout (02-S003), 1 subject for window period violation (01-S031), and 1 error in photo randomization code (02-S005). A representative two-dimensional image of subjects is shown in Figures 1.

1.1 Primary Efficacy Endpoint

The primary efficacy measure was the mean value difference in the WSRS scores evaluated by three independent investigators at week 24. The mean value of WSRS score in the test group was 2.02 ± 0.71, the mean value of WSRS score in the control group was 2.27 ± 0.68, and the mean value difference between the filler injection groups (test group minus control group) was -0.26 ± 0.69, 97.5% one-sided confidence interval by t-distribution at week 24. The upper limit of the one-sided confidence interval was -0.0101, which was smaller than the noninferiority limit (0.29). Therefore, it was confirmed that the test group was noninferior to the control group (Figure 2). The corredponding results, along with

clinical photos, are presented in Figure 3.

1.2 Secondary Efficacy Endpoint

The mean value difference in WSRS scores in the test group and the control group evaluated by the independent investigators at week 8, 16, and 48 following the HA filler injections was -0.21±0.61 at week 8, -0.25±0.47 at week 16, and -0.11±0.56 at week 48, with no visits showing a statistically significant difference (Figure 4).

The mean value difference in WSRS scores in the test group and the control group evaluated by the investigators following the HA filler injections was 0.08±0.27 at week 8, 0.08±0.33 at week 16, and 0.15±0.40 at week 24, with no visits showing a statistically significant difference. At week 48, the mean value difference in WSRS scores between the test group and the control group evaluated by the investigators was -0.14±0.35, with no statistically significant difference (Figure 5 A).

The mean value differences in GAIS scores in the test group and the control group evaluated by the investigators following the HA filler injections was -0.06 ± 0.36 at week 8, -0.05 ± 0.28 at week 16, and -0.10 ± 0.35 at week 24, with no visits showing a statistically significant difference. The mean value difference in GAIS between the test group and the control group evaluated by the investigators was -0.08 ± 0.28 at week 48, with no statistically significant differences (Figure 5 B). The corredponding results, along with clinical photos, are presented in Figure 6.

The mean value differences in GAIS scores in the test group and the control group evaluated by subjects following the HA filler injections was -0.09±0.45 at week 8, -0.10±0.43 at week 16, and -0.13±0.38 at week 24, with no visits showing a statistically

significant difference. At week 48, the mean value difference in GAIS score in the test group and the control group assessed by subjects was -0.06±0.42, with no statistically significant difference (Figure 7).

The proportion of subjects with an improvement in WSRS scores of one or more points was evaluated by the independent investigators following the HA filler injections at weeks 24 and 48. The proportion of subjects with an improvement in WSRS scores of one or more points evaluated by the independent investigators among subjects who injected the two fillers was 41.94% (26 subjects) at week 24 in the test group and 30.65% (19 subjects) at week 24 in the control group. There was no statistically significant difference. At week 48, the proportion was 31.37% (16/51 subjects) and 32.76% (19/58 subjects) in the control group and there was no statistically significant difference (Figure 8).

The proportion of subjects with an improvement in WSRS scores of one or more points evaluated by the investigators was 64.52% (40 subjects) at week 24 in the test group and 62.91% (39 subjects) at week 24 in the control group. There was no statistically significant difference. The long-term safety assessment was 49.15% (29/59 subjects) in the control group and 49.15% (29/59 subjects) in the control group at week 48. There was no statistically significant difference (Figure 9).

1.3 Safety Outcomes

There were no systemic AEs related to investigational devices expressed during the long-term safety evaluation period at week 24. Systemic SAEs were limb injury and nervous system injury, which were not related to the investigational devices, and

all patients recovered. Local AEs were most common in the test and control groups (Table 3). The pain and swelling related to the product and injection were neither dominant nor statistically significant (P value: 0.1614 and 0.1168). Overall, the most reported symptoms in test group were pain (41.67%) and swelling (40.28%) following the HA filler injections. Both were the most common after the HA filler injections [13]. No local serious adverse events were in both the test group and control group.

IV. Discussion

The growing interest in volumetric facial rejuvenation has led to the development of various techniques, including fillers, autologous fat grafting, and surgical treatments. Nasolabial fold deepening is a midfacial aging process. Nasolabial folds respond well to filler injections, and several filling agents approved by the US Food and Drug Administration are now available, with further fillers under development [9]. Each filler has its own characteristics in terms of thickness, durability, efficacy, and safety [10]. Among fillers, HA is a hygroscopic molecule with the ability to bind 1000 times its volume in water. Due to this exceptionally strong water absorption property, HA can hydrate both the stratum corneum and the dermis [14]. In addition, Since the chemical structure of HA is the same in all species, the potential for immunological reactions and implant rejection is negligible, making HA a very suitable material for use as a dermal filler [15].

The effects of the new HA filler containing lidocaine with a colorless transparent liquid consisting of 24mg/mL cross–linked HA on the improvement of moderate to severe nasolabial folds were investigated and compared with those of the conventional HA filler in a split-face, double-blind study. We demonstrated that the new HA filler containing lidocaine was not inferior to the conventional HA filler for treating moderate to severe nasolabial folds with comparable WSRS scores, investigator- and subject-assessed GAIS scores, and the proportion of subjects whose WSRS scores improved at week 24.

This finding was supported by the result of the first endpoint, which showed that the new HA filler containing lidocaine was not inferior to the conventional HA filler at week 24. The upper limit of the one-sided confidence interval was -0.0101, which was smaller than the the predefined margin for noninferiority (0.29). Also, as shown on the WSRS graph [Figure

5 A], the scores for each visit following the HA filler injections were low relative to the baseline WSRS score. Notably, the WSRS score was the lowest after the HA filler injections at week 8. The WSRS scores in both groups returned to almost baseline levels by week 48.

Features that may contribute to the popularity of HA filler treatments include biocompatibility and degradability, overall safety and tolerability, high hydrophilicity, ease of administration, minimal recovery time, immediate results, and low incidence of immunologic reactions [10].

Regarding safety, AEs related to infection were pain, swelling, redness, pruritus, and erythema and all was predictable or mild and transient. Of these, pain and swelling were the most common following the HA filler injections. By week 48, there did not appear to be chronic AEs, and as SAEs, limb injury and nervous system injury occurred. This SAEs recovered without sequelae and were not related to either filler. For the trial period, there were no clinically significant differences in laboratory test results or vital sign results between the test group and the control group. In this study, the new HA filler containing lidocaine (LASBEAU Strong) was well tolerated, with no significant side effects by 48 months; however, delayed-onset AEs, such as foreign body granuloma formation or inflammation, may occur [12].

Therefore, further studies require with more subjects and a longer follow-up period are required to evaluate AEs and confirm the long-term safety of the new HA filler containing lidocaine.

Ⅴ. Conclusion

This 48-week clinical trial showed that the new HA filler containing lidocaine (LASBEAU Strong) was not inferior to the conventional HA filler (Restylane Lyft) in the temporary improvement of moderate to severe nasolabial folds. The new HA filler containing lidocaine (LASBEAU Strong) could be a sufficient product to ensure the safety and efficacy.

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Ⅶ. List of figures and tables

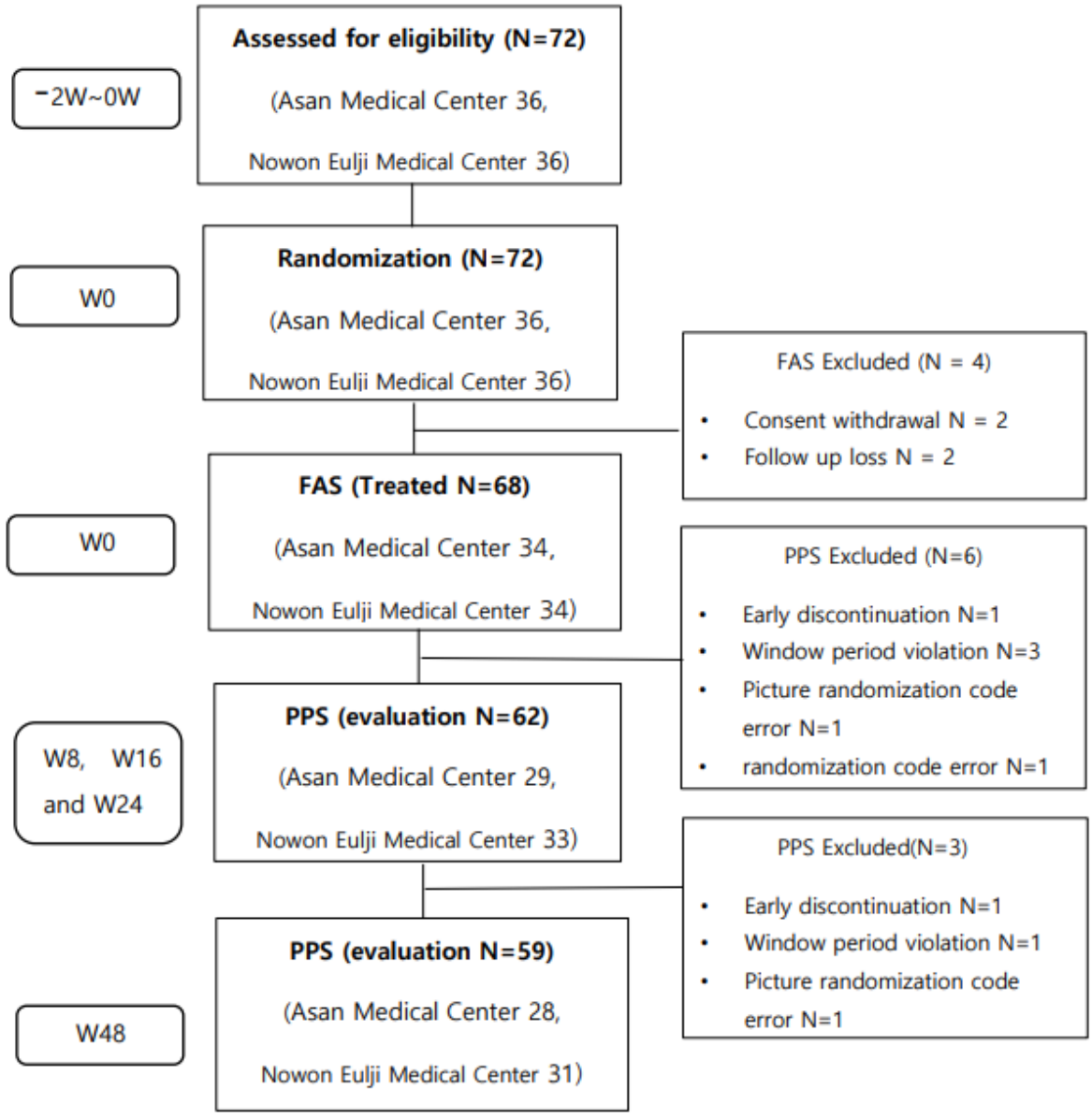


Figure 1

Flowchart of the subjects included in this trial.

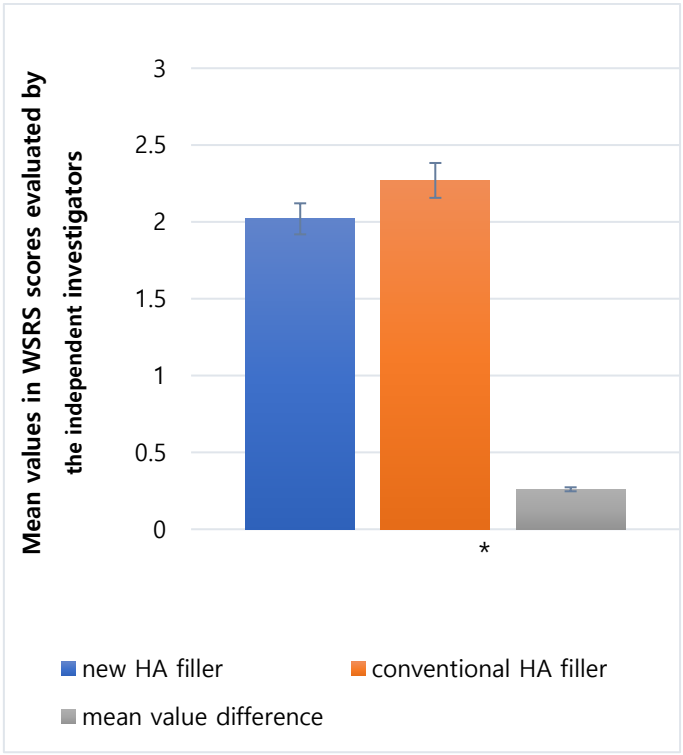
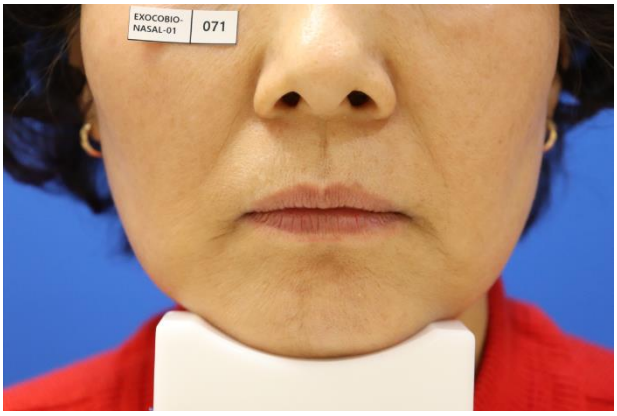


Figure 2

The mean values of WSRS scores evaluated by independent investigators at week 24.

The test device (the new HA filler) showed non-inferior compared to the control device (the conventional HA filler) because the upper limit (-0.0101) was smaller than the allowable noninferior margin limit (0.29).

(A)



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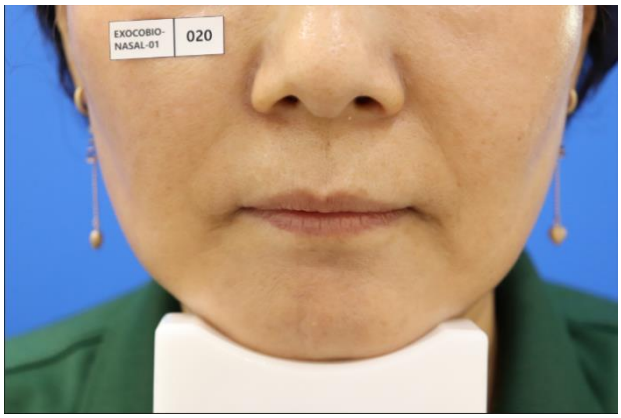


Figure 3

Aesthetic outcomes in a 45-year-old female subject

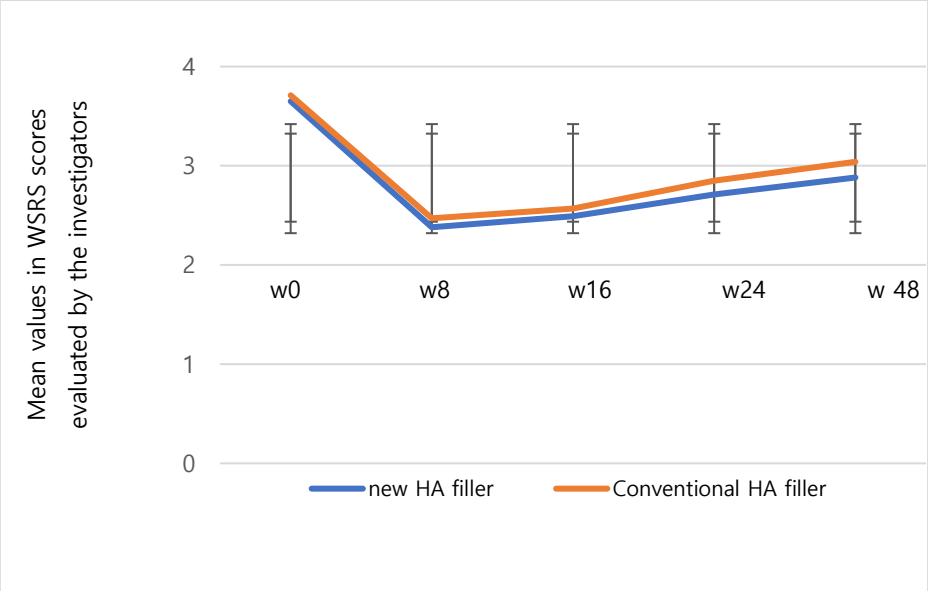
(A) at baseline, (B) at week 24 following the HA filler injections.

The subject's left mid-face was injected with the new HA filler containing lidocaine and right mid-face with the conventional HA filler.

Figure 4

The mean values of WSRS scores evaluated by the independent investigators at weeks 8, 16 and 48.

(A)



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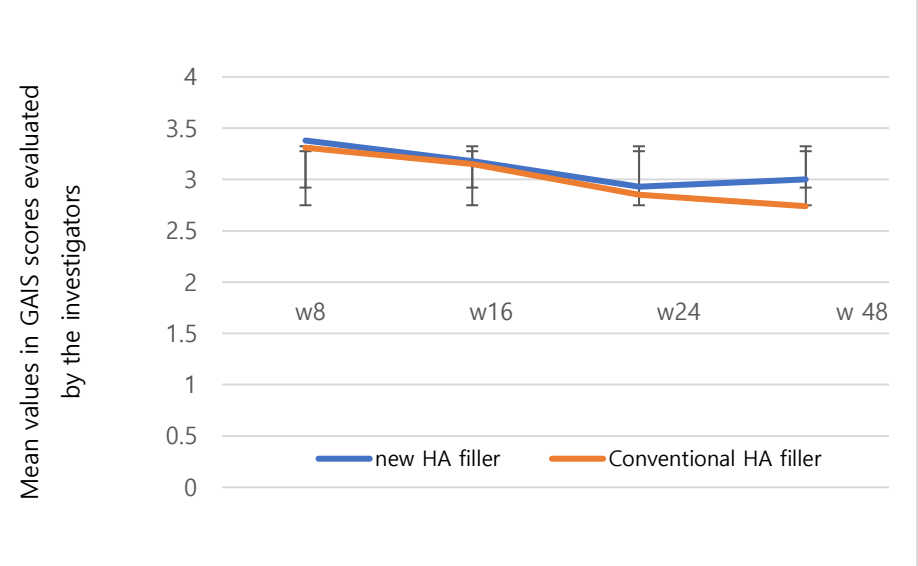
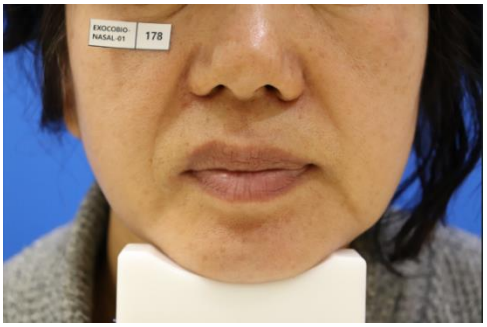


Figure 5 (A) The mean values in WSRS scores in the test group and the control group evaluated by the investigators.

(B) The mean values in GAIS scores in the test group and the control group evaluated by the investigators.

(A)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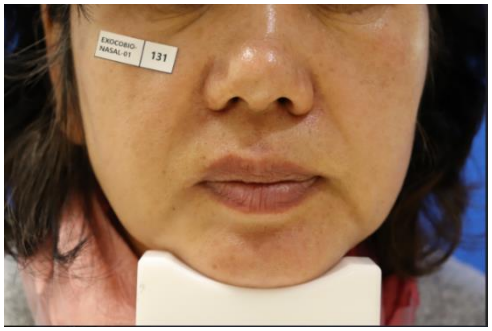
(B)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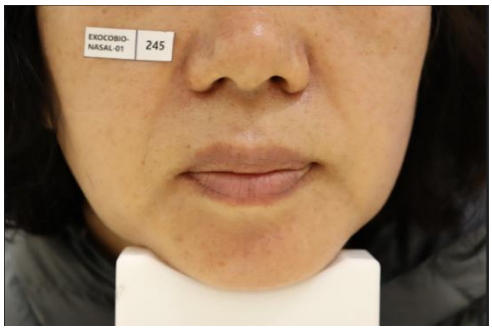
(c)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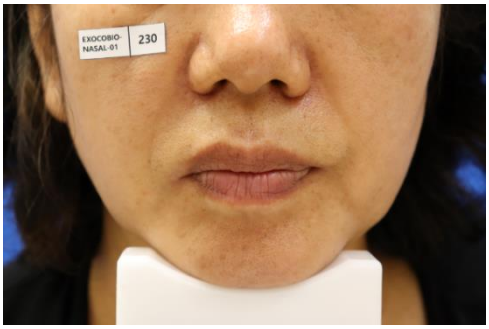
(D)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(E)

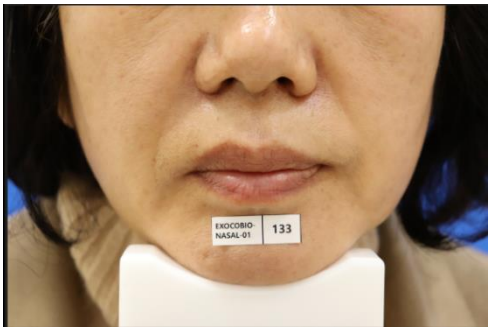
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Figure 6

Aesthetic outcomes in a 58-year-old female subject.

(A) at baseline, (B) week 8, (C) at week 16, (D) at week 24, and (E) at week 48 following the HA filler injections.

The subject's left mid-face was injected with the new HA filler containing lidocaine and right mid-face was injected with the conventional HA filler.

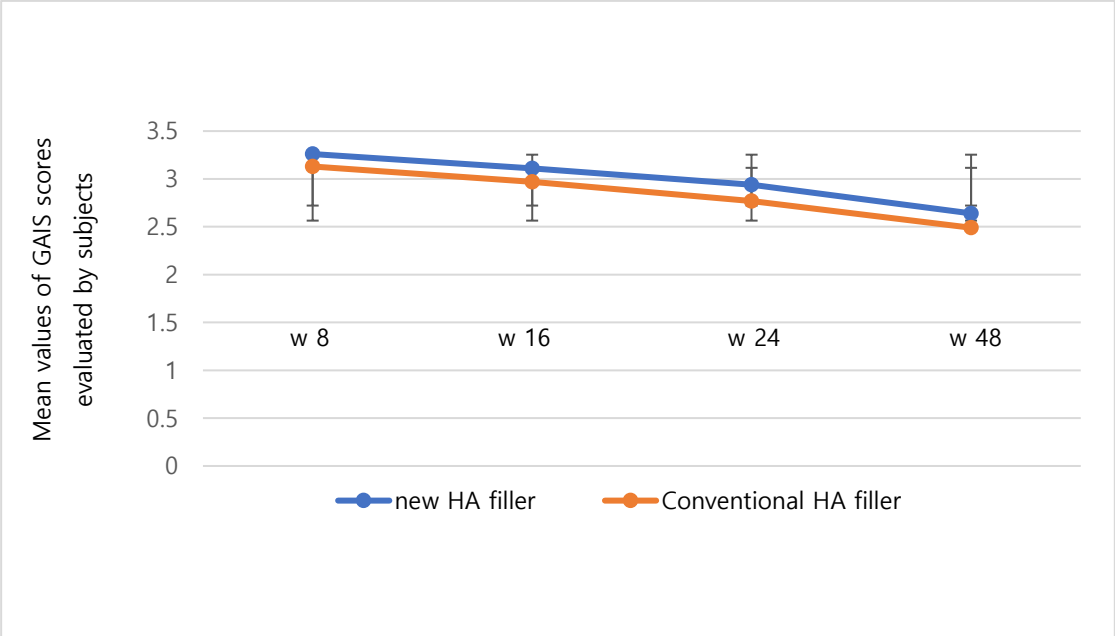

Figure 7

The mean values of GAIS scores evaluated by subjects at weeks 8, 16, 24 and 48.

The mean value difference in GAIS score in the test group and the control group evaluated by subjects was -0.06±0.42, with no statistically significant difference at week 48.

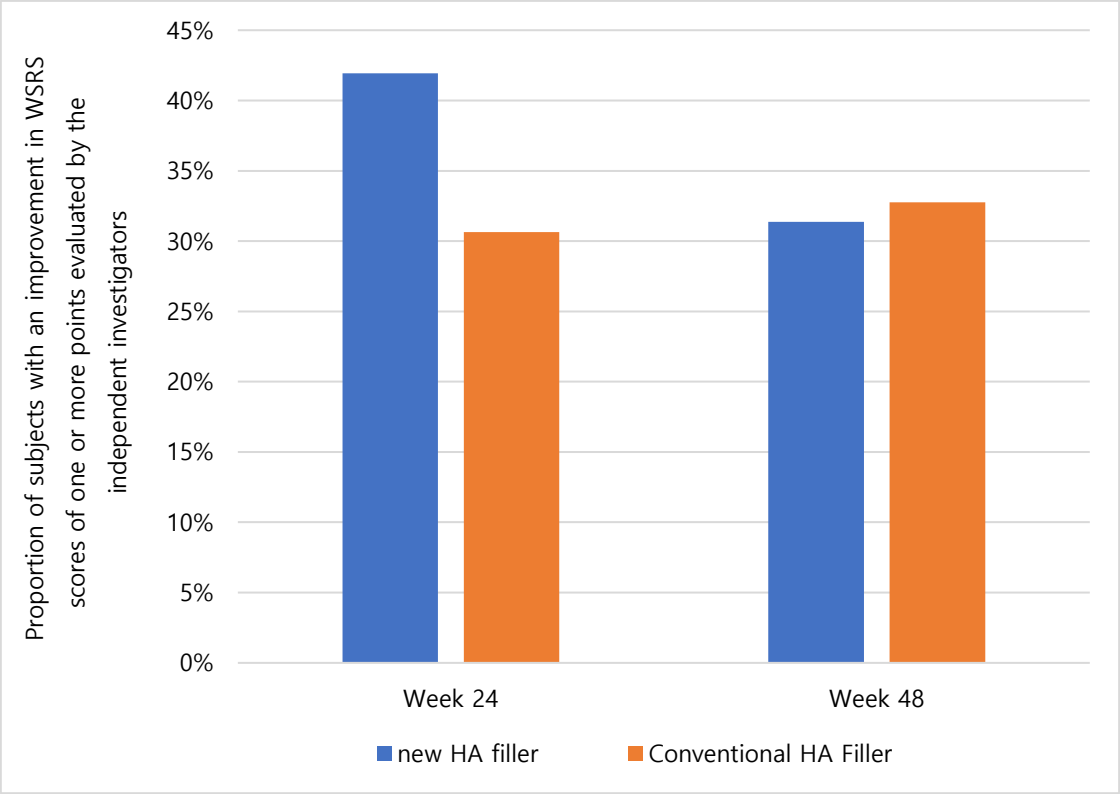

Figure 8

The proportion of subjects with an improvement in WSRS scores of one or more points evaluated by the independent investigators at weeks 24 and 48.

The new HA filler containing lidocaine showed a higher score than the conventional HA filler at week 24 and did not show a significant difference at week 48.

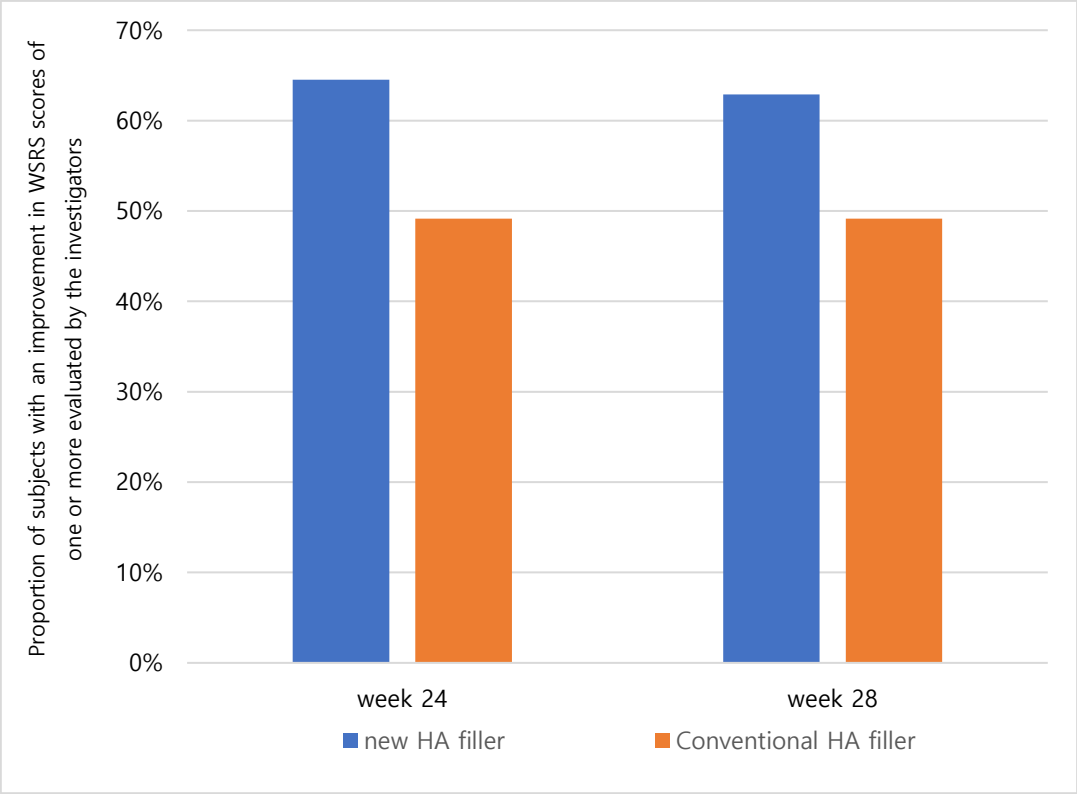

Figure 9

The proportion of subjects with an improvement in WSRS scores of one or more points evaluated by the investigators at weeks 24 and 48.

Grade	Notes
1	No flattening of the upper lip
2	Mild flattening of the upper lip
3	Moderate flattening of the upper lip, mild wrinkle mainly due to volume loss
4	Moderate wrinkling, moderate lengthening of the distance between nose and lip border due to volume loss, some yellowing and sun damage
5	Severe wrinkling and wizened appearance, marked lengthening of the distance between nose and lip border due to volume loss

Table 1

WSRS (Wrinkle Severity Rating Scale)

Grade	Notes
3	Very much improved
2	Much improved
1	Improved
0	No change
-1	Worse

Table 2

GAIS (Global Aesthetic Improvement Scale)

	Test group		Control group		p-value
pruritus	13	18.06%	10	13.89%	0.4950*
Bruise	17	23.61%	17	23.61%	1.0000*
swelling	29	40.28%	21	29.17%	0.1614*
tenderness	12	16.67%	11	15.28%	0.8221*
pain	30	41.67%	21	29.17%	0.1168*
erythema	18	25.00%	14	19.44%	0.4227*
Etc.	7	9.72%	6	8.33%	0.7712*
-redness	5	6.94%	4	5.56%	1.0000**
-conglomerate	1	1.39%	0	0.0%	1.0000**
-cellulite	1	1.39%	0	0.0%	1.0000**
-mild stinging	0	0.0%	1	1.39%	1.0000**
-white patch	0	0.0%	1	1.39%	1.0000**

Table 3

Local adverse events in the test group and the control group