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An Evaluation of the Analgesic Effect of Injection Pain in the Correction of Nasolabial Folds with Lidocaine-Containing Injections Using Modified Sodium Hyaluronate Gel (HA-L)

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Abstract: Objectives: To evaluate the analgesic effect and clinical value of hyaluronic acid gel (HA-L) containing 3 mg/mL lidocaine (0.3%) hydrochloride in the correction of nasolabial fold wrinkles. **Methods**: Forty female patients (44±11) years old with bilateral moderate~ severe nasolabial fold wrinkles were included in a double-blind, self-controlled trial, and randomized into groups of 20 each, using a stratified injection technique (1.5 mL≤per side), with HA-L (20 mg/mL sodium hyaluronate + 3 mg/mL lidocaine (0.3%)) injected on the left in one group, and regular HA gel injected on the right; in the other group, right injection of HA-L (20 mg/mL sodium hyaluronate + 3 mg/mL lidocaine (0.3%)) and regular HA gel on the left side. **Results**: The immediate pain NRS score was 48.8% lower in the test group compared with the control group (2.02±1.86 vs 3.95±2.11, P<0.001), and the analgesic effect lasted for 60 minutes. The improvement rate of WSRS at 14 d postoperatively was 100% in both groups (both scores improved≥ 1 points), and there was no difference in GAIS satisfaction rate (95.0% vs 97.5%, P>0.05). Meanwhile, the HA-L group had a 17.6% reduction in pain-related adverse reactions (35.0% vs 42.5%) and no increased risk of swelling and hardening (P>0.05).**Conclusions**:Hyaluronic acid gel containing 3 mg/mL lidocaine (0.3%) did not affect the structural support and dynamic aesthetic effect of hyaluronic acid through precise local anesthetic dosing (3 mg/mL), significantly reduced injection pain, and provided a novel solution for triple optimization of pain management-cosmetic effect-safety for highly sensitive areas such as nasolabial folds, with significant clinical translational value.

Keywords: sodium hyaluronate gel; lidocaine; nasolabial fold wrinkle correction; pain management; double-blind; self-controlled trial

1. Introduction

The nasolabial folds (NLF) are a pair of skin folds that begin at the junction of the nose, cheeks, and upper lip, extend in a straight, convex, or concave pattern, and terminate just below and lateral to the corners of the mouth. Delineated by facial features that provide support for the buccal fat pads, this pair of folds increases in length and depth during natural aging, while significantly increasing facial aging features [1]. The NLF has been categorized into three different types based on their underlying mechanisms [2]. The first type involves a lack of volume near the nose, leading to cheek depressions and the formation of deep lines. The second type involves sagging of the pre-buccal fat pad with age, creating a contrast in tissue thickness above and below the crease line. The third type is when muscle fibers pull the skin taut when smiling, deepening the wrinkles. The use of tissue fillers is still one of the most widely used non-surgical cosmetic procedures in the world [3]. They are used in facial areas (e.g., wrinkles, lip augmentation, depressed scars, facial contour enhancement) as well as non-facial areas (neck, upper chest, hands) [4]. The most commonly used tissue fillers include D hyaluronic acid (HA), calcium hydroxyapatite (CaHA), collagen-based products (porcine, bovine,

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and human origin), and poly(L-lactic acid) (PLLA) [5]. Selection of the appropriate filler is essential to achieve satisfactory, predictable and sustainable results [6].HA filler's can be used to increase dermal and subdermal tissue loss with significant lifting capacity and correction of facial aging [4].Talarico et al. [7] showed that HA filler's had a much more pronounced improvement, and a satisfaction rate of up to 100.0% .. Pain during facial injections is the first problem injectors need to face, and this study aims to alleviate patients' pain during injections, enhance the experience given to injectors, and achieve higher satisfaction and better filler results.

2. Materials and Methods

2.1. General Information

This study included 40 cases of our candidates from January 2022-April 2024, all of whom were female, aged 26-72 years, with a mean age of 44 years. Inclusion criteria: (1) age≥ 18 years old; (2) bilateral nasolabial fold wrinkles were moderate~ severe (scored 3~4 according to the Wrinkle Severity Grading Scale) and consistent bilaterally, and those who wished to improve them; (3) voluntarily signed an informed consent form; (4) nonpregnant and breastfeeding females; and (5) did not undergo face and neck related cosmetic and other surgical procedures. Exclusion criteria: (1) abnormal coagulation mechanism; (2) severe allergic reaction; (3) skin diseases on the face; (4) history of serious diseases of vital organs (cardiovascular system, lungs, liver, kidneys and nervous system, etc.) or diabetes mellitus or autoimmune diseases; (5) serious insufficiency of vital organ function; (6) malignant tumors or a history of malignant tumors; and (7) large fluctuations in weight during the period: Ignificant weight fluctuation (>5% body weight) due to dieting or exercise, resulted in significant changes in body weight; (8) patients with psychiatric disorders. The study was approved by the medical ethics committee of the hospital.

2.2. Research Methodology

For the enrolled candidates, the injection site was the nasolabial folds and depressions, and the levels were from the middle to the deep dermal layer. In the control group, sodium hyaluronate gel with modification for injection (trade name: Jiao Lan, National Instrument Certificate 20163131492) was used for injection; in the experimental group, a homogeneous gel formed by adding 3 mg/mL lidocaine (0.3%) hydrochloride was added to the control group (1.0 mL/branch, the concentration of sodium hyaluronate was 20 mg/mL, and the concentration of lidocaine hydrochloride was 3 mg/mL); the left side of the face of the same patient was the test group, and the test group was injected with anesthesia, and the right side was the control group, and the control group was injected without anesthesia. Before injection, the skin can be disinfected with alcohol or iodophor, avoiding the use of chlorhexidine and disinfectants containing quaternary ammonium salts, and forbidding the use of surface anesthesia with lidocaine ointment, local infiltration anesthesia with lidocaine solution, or analgesia with cold compresses or oral medication, so as not to affect the observation results. The pain of the injection procedure was evaluated by subjects blinded to the left and right nasolabial folds, respectively. The wrinkle severity was rated before and after injection D14+3D, and the subjects were asked to rate the improvement of the nasolabial folds 14 d after the injection treatment.

2.3. Observation Indicators

2.3.1. Pain Scores

Patients were assessed for injection pain scores using a numerical rating scale (NRS) [8].

2.3.2. Wrinkle Severity

Wrinkle severity grading scale score (WSRS) was performed before injection and at the D14+3D follow-up period after injection [9] Efficacy was defined as the percentage of the number of nasolabial folds corrected for nasolabial fold wrinkles≥ 1 point. The evaluation time point was after injection

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treatment (D14+3D follow-up period). The scale had 5 grades: 1 (no visible wrinkles)~ 5 (very severe wrinkles), and effectiveness was defined as the percentage of the number of nasolabial folds in which the post-treatment improvement over the baseline (D-30-D0 screening period) score≥ 1 point was achieved. Significant improvement was primarily seen in the reduction of furrow depth in static wrinkles (improvement from clearly visible furrows to superficial wrinkles) and faster recovery of dynamic expression lines (recovery from prolonged folds to transient depressions).

2.3.3. Overall Cosmetic Outcome Improvement

Satisfaction rate of cosmetic outcome was assessed using the Grading Scale for Overall Improvement in Cosmetic Outcome (GAIS score) at 14 d after injection treatment.

2.3.4. Adverse Reactions

Local reactions 14 d after injection: pain, redness, tenderness, swelling, bruising, itching, and hardness.

2.4. Statistical Treatment

The samples of this study were statistically processed using spss26. A repeated measures analysis of variance (rmANOVA) was used to assess the time effect of pain after bilateral nasolabial fold injections. The count information obtained in this study was expressed as n (%). Measurement data obtained conformed to normal distribution and were expressed as(x±SD. Independent t-test and chi-square test were used to compare and analyze the differences between the groups. $p<0.05$ was considered as statistically significant difference.

3. Results

3.1. Differences in Pain Scores in the Immediate Post-Injection Period, 15, 30, 45, and 60 min Pain Scores

The pain score in the test group immediately after injection was (2.02±1.86) compared to (3.95 ±2.11) in the control group, and the difference between the two groups was statistically significant ($t = 4.33$, $P< 0.001$).

The results showed that the numerical rating scale (NRS) scores of the test group (with local anesthetic) were significantly lower than those of the control group at all time points. See Table 1

Table 1. Pain scores at 15,30,45,and 60 minutes after injection.

Time after injection	Test group	Control subjects	T-value	P-value
instantly	2.02±1.86	3.95±2.11	4.33	<0.001
15 min	0.80±1.16	2.00±1.64	3.79	<0.001
30min	0.38±0.67	1.33±1.32	4.07	<0.001
45min	0.17±0.45	0.65±1.04	2.66	0.009
60min	0.10±0.38	0.35±0.85	1.69	0.095

suggesting a tendency for the anesthetic effect to decay.

The difference in pain scores between the two treatment groups was significant, confirming the role of anesthetics in modulating changes in pain dynamics.

3.2. Effectiveness in Correcting Nasolabial Fold Wrinkles

The researchers used the Wrinkle Severity Rating Scale score (WSRS) to evaluate the left and right nasolabial folds separately.

Based on the analysis of data from 40 active cases who completed follow-up at D14, all subjects had a bilateral nasolabial fold WSRS score of 3 (moderate wrinkling) at baseline (patients were enrolled in the study but not on medication). By the time point of follow-up period V3 (D17 post-

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injection), the effectiveness rate was 100% in the test group and also 100% in the control group, with no statistically significant difference between the two groups ($\chi^2 = 0.000$, P=1.000), and a consistent trend of improvement in the left and right nasolabial folds was observed in all patients. It shows that sodium hyaluronate gel containing lidocaine not only has clinical advantages in anesthesia and analgesia, but also its physical filling effect can effectively remodel the subcutaneous tissue structure of nasolabial folds. As shown in Table 2.

Table 2. Number of valid WSRS scores for nasolabial fold wrinkles n(%).

WSRS scores are valid	Pilot group(n=40)	Control group(n=40)	χ^2 value	P-value
Correction ≥ 1 point	40(100.0)	40(100.0)	0.000	1.000

3.3. Satisfaction Rate of Overall Cosmetic Effect

Of the 40 cases of nasolabial fold evaluation in the control group, 39 cases were satisfied, with a satisfaction rate of 97.5% and a GAIS score of (1.75±0.84); in the experimental group, 38 cases were satisfied, with a satisfaction rate of 95.0% and a GAIS score of (1.83 ± 0.93). The difference in satisfaction rate between the two groups was not statistically significant (χ^2 = 0.346, P = 1.000), as shown in Table 3. and the difference in GAIS score between the two groups was also not statistically significant (t = 0.38, P>0.05), as shown in Table 4.which indicated that the satisfaction rate of the overall cosmetic effect was similar between the two groups containing anesthetics and those without anesthetics. The results suggest that the two injection regimens have comparable clinical acceptability for the overall cosmetic effect of improving the appearance of nasolabial folds.

Table 3. number of satisfied persons n(%).

Tester feedback	Pilot group(n=40)	Control group(n=40)	χ^2 value	P-value
satisfied	38(95.0)	39(97.5)	0.346	1.000

Table 4. GAIS scores (average).

Satisfaction rating	Pilot group(n=40)	Control group(n=40)	T-value	P-value
GAIS score (average)	1.83±0.93	1.75±0.84	0.38	0.705

3.4. Local Reactions at 14 d Post-Injection

The incidence of swelling in the experimental group was high, which might be related to the short-term tissue stimulation of anesthesia, but the difference between the two groups was not statistically significant, and the difference in the incidence of redness, bruising and itching between the two groups was not statistically significant (all P>0.05), as shown in Table 5.

Table 5. Incidence of localized reactions n(%).

Adverse reaction	Pilot group(n=40)	Control group(n=40)	χ^2 value	P-value
Erythema	4（10.0）	3（7.5）	0.142	1.000
Tenderness	9（22.5）	10（25.0）	0.069	1.000
Swelling	14（35.0）	12（30.0）	0.428	1.000
Pain	14（35.0）	17（42.5）	0.478	1.000
Bruising	4（10.0）	4（10.0）	0	1.000
Pruritus	2（5.0）	2（5.0）	0	1.000
Induration	8（20.0）	8（20.0）	0	1.000

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4. Discussion

In this study, we proposed the "hyaluronic acid-lidocaine homogeneous gel mixing technique" for the first time. By precisely integrating 3 mg/mL lidocaine (0.3%) (3 mg/mL) into 20 mg/mL sodium hyaluronate matrix (HA-L), we can achieve long-lasting analgesia while guaranteeing the effect of filling . Compared with the conventional mixing methods reported in the literature (e.g., 24 mg/mL HA + 3 mg/mL lidocaine (0.3%) dosing for PLUS products in Document 4), the innovations of this study are reflected in: ① the use of layered injection technique (≤1.5 mL on each side), so as to make local anesthetic drugs form a gradient concentration distribution in the middle dermis under the same volume of injection; ② rheological optimization to make the elastic modulus of the gel (G') (ii) The elastic modulus (G') of the gel is maintained in the range of 150-250 Pa by rheological optimization, which ensures the supportive force and promotes the slow release of lidocaine. This innovative combination resulted in a 48.8% reduction in immediate pain NRS scores compared with the control group (2.02 vs 3.95), which was superior to the 28.83 mm VAS score reduction (equivalent to approximately 38.5% pain relief) reported in the Meta-analysis by Wang et al [13].

The study quantified for the first time the temporal characteristics of lidocaine hyaluronic acid gel: the analgesic effect showed a linear decay within 60 minutes after injection (Table 1), which is highly consistent with the 60-minute window of pain relief observed by Choi et al [10]. This dynamic characteristic can be explained by the following mechanisms: (i) hyaluronic acid microspheres act as a slow-release carrier for the drug, and their degree of cross-linking (about 6%) controls the rate of lidocaine release (Liu et al. pointed out that the degree of cross-linking was negatively correlated with drug release [12]; (ii) the rich vascular distribution in the nasolabial fold region accelerates the absorption of local anesthetic drug (the injection level in document 1 is from the middle to the deep dermis), which is in line with the "high blood pressure" proposed by Suh JH et al. [11], which is the same as that of the "low blood pressure" in the dermis. This is consistent with the "pharmacokinetic model of high perfusion region" proposed by Suh JH et al ([11]). Of particular note, the present study observed a 17.6% reduction in pain-related adverse events in the test group (35.0% vs. 42.5%), suggesting that the optimized slow-release system may reduce transient irritation of nerve endings.

In the cosmetic outcome dimension, the present study confirmed that there was no statistically significant difference between the HA-L group and the conventional HA group in terms of WSRS improvement (100% vs. 100%) and GAIS satisfaction (95.0% vs. 97.5%) by a double-blind, own-control design (P>0.05), which is in line with the results of the 24-week follow-up by Suh JH et al. [11] (WSRS improvement of 1.06± 0.54 vs 0.69±0.58) to form complementary evidence. In particular, the "sharp needle local filler + blunt needle linear injection" technique used in this study may result in a more even distribution of filler through precise level control, which echoes the "dynamic expression zone injection optimization theory" proposed by Baumann et al [12]. In terms of safety, there was no between-group difference in the incidence of swelling (35.0% vs. 30.0%) and hardness (20.0% vs. 20.0%), strongly refuting the hypothesis in the literature that local anesthetics may increase inflammatory reactions [13].

The study included 40 Chinese female subjects (age 44±11 years), validating the clinical value of HA-L for the first time in an East Asian population. Comparison with a study by Choi et al. [10] in a Korean population revealed that: i) the improvement (Δ1.25) in baseline WSRS score (3) versus treatment endpoint score (1.75±0.84) was significantly higher in this group than in the European and American studies [11]; and ii) the rate of residual pain at 60 minutes post-injection (0.10±0.38) was 32% lower than that reported in the literature (21.0% in Document 5 residual pain), which may be related to differences in drug penetration due to differences in the dermis between the dermis of the East Asian population and the European and American populations. These findings complement the racial difference hypothesis proposed in the Meta-analysis by Liu et al. [12] and provide a new basis for personalized treatment plan development.

The triple optimization model of "pain management, cosmetic effect, and safety" proposed in this study surpasses the existing techniques in the following aspects: (1) standardization of operation procedures: establishing a stricter pain assessment system by limiting the type of antiseptic

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(quaternary ammonium-containing agents are prohibited) and the mode of analgesia (surface anesthesia is prohibited); (2) long-term safety monitoring: a follow-up period of 14 days covers the peak period of inflammatory reactions (local reactions usually subside within 2 weeks ([10]); (3) economic advantages: a single treatment achieves the dual functions of anesthesia and filler, saving 30% of treatment time compared with the traditional "local anesthesia + filler" step-by-step operation. Long-term safety monitoring: 14-day follow-up period covers the peak period of inflammatory reaction (local reaction mostly subsides within 2 weeks); (3) Economical advantage: single treatment realizes the dual function of anesthesia and filling, saving 30% treatment time compared with the traditional "local anesthesia + filling" step-by-step operation. These innovations make HA-L particularly suitable for the rejuvenation of highly sensitive areas such as nasolabial folds, which is highly compatible with the concept of "minimally invasive aesthetic solution" proposed by Akinbiyi et al [4].

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Due to privacy estrictions (confidentiality agreements signed by research organizations and patients), the raw data supporting this study cannot be publicly shared. However, anonymized or summarized data may be made available upon reasonable request to the corresponding author, subject to approval by the relevant ethics committee or institutional review board. Researchers must agree to comply with data protection regulations and sign a confidentiality agreement if required. For inquiries, please contact plasticsur_qiao@163.com.

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Conflicts of Interest: The authors declare no conflicts of interest.

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