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Original Article

Combination therapy of botulinum toxin type A and hyaluronic acid filler for facial rejuvenation

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Abstract: Objective: Our aim was to examine the clinical safety and efficacy of combination therapy of botulinum toxin type A plus hyaluronic acid (HA) fillers for facial rejuvenation. Methods: From February 2015 to June 2017, 94 patients that underwent facial rejuvenation in our hospital were randomly assigned to receive injections of botulinum toxin type A alone (control group, n=47) or botulinum toxin type A and hyaluronic acid filler in combination (observation group, n=47). Clinical efficacy, safety, and patient satisfaction were compared between the two groups. Results: Among patients in the observation group, the effective rate (59.57%) was significantly different from that (29.79%) of patients in control group (X^2=8.436, P=0.04). Patients were more satisfied with treatment than the control group at 6 months and 12 months (P<0.05). Duration of effect in respective 2-6 month, 6-12 month, and 12-18 month periods was more favorable for those of the control group (P<0.05). Dosages of botulinum toxin type A at respective injection sites and total dosage were significantly lower than those of the control group (both P<0.05) but the two groups differed mildly in postoperative adverse events (facial swelling and congestion) (P>0.05). Conclusion: Compared with botulinum toxin type A alone, combination therapy of botulinum toxin type A and hyaluronic acid filler for facial rejuvenation is associated with better clinical efficacy, longer duration of effect, smaller dosage, and more satisfied patients.

Keywords: Botulinum toxin type A, hyaluronic acid, facial rejuvenation

Introduction

As we age, muscles gradually contract, facial tissues are gradually absorbed, and subcutaneous fat reduction and local accumulation appear. Our skin gets thinner and drier, less elastic, and pigmentation occurs. Wrinkles, folds, and volume loss gradually develop on the face. Facial rejuvenation is a series of treatments aimed to restore a youthful appearance to anatomic and physiological structures of aged faces [1, 2]. A combination injection of botulinum toxin type A and hyaluronic acid has become the most common technique for clinical aesthetic plastic surgery whereas previous commonly-used clinical surgery with adjuvant skin care has gradually been abandoned because of its poor efficacy, large traumas, and slow recovery [3, 4]. Botulinum toxin type A is an exotoxin which can antagonize calcium, block release of acetylcholine, and disturb myofibril contraction, acting to remove wrinkles. It is currently being applied for treatment of facial aging. It has a short duration of effect though it has been used in clinical practice for many years [5, 6]. Clinically, scholars have found that hyaluronic acid can also be used for repairing soft tissue defects and furrows in the skin to remove wrinkles [7, 8]. However, the effect of combination therapy of botulinum toxin type A and hyaluronic acid fillers in facial rejuvenation remains unknown. Therefore, in this study, between February 2015 and June 2017, 94 patients undergoing facial rejuvenation in our hospital were enrolled as participants, aiming to examine clinical efficacy, duration of effect, and patient satisfaction of combination therapy of botulinum toxin type A and hyaluronic acid fillers.

Materials and methods

Patients

In a period from February 2015 to June 2017, a total of 94 patients undergoing facial rejuvenation in our hospital were recruited into this study and randomly subdivided into the observation group (n=47) and control group (n=47). Patients in the observation group received a combined injection therapy of botulinum toxin type A (Allergan, US) and hyaluronic acid fillers (Q-med AB, Sweden). In contrast, those in the control group were injected with botulinum toxin type A alone. Patients were included if they had not received previous facial rhytidectomy or other therapy, if they voluntarily requested facial rejuvenation, if treatment included facial rhytidectomy merely, if they had normal coagulation, and if they had good cardiopulmonary function without any other severe disease, trauma, and infection or nodules in the skin to be treated. Patients were excluded if they were pregnant or lactating women, had antibodies to botulinum toxin type A, scarring, allergies, or other symptoms unsuitable for facial rejuvenation or long-term hormone therapy. All enrolled patients gave written informed consent and this study was approved by our Hospital Ethics Committee.

Treatment methods

Preoperatively, the severity of facial wrinkles was rated with use of the Wrinkle Severity Rating Scale (WSRS) [9]. On the WSRS scale, there were mild, moderate, severe, and extreme grades, respectively matching to 1, 2, 3, and 4 points. Zero indicated no visible wrinkles. Mild wrinkles were defined as wrinkles vaguely visible when one makes a facial expression but invisible when one makes no facial expression. Moderate wrinkles were defined as wrinkles clearly visible when one makes a facial expression but vaguely visible when one makes no facial expression. Severe winkles were defined as wrinkles still clearly visible when one makes no facial expression but significantly reduced when one stretches the faces forcefully. Extreme severe wrinkles were defined as wrinkles still clearly visible when one stretches the face forcefully.

During the treatment period, after skin disinfection, topical anesthesia was performed with lidocaine cream. Injection sites and volume of Botulinum toxin type A and hyaluronic acid were determined by clinical guidelines and principles [10-12]. To treat glabellar wrinkles, botulinum toxin type A (10-30 u) was injected for women and 20-40 u for men. To treat forehead wrinkles, botulinum toxin type A (6-15 u) was injected for both men and women. For crow's feet, botulinum toxin type A (10-30 u) was injected for women and 20-30 u for men. To treat glabellar wrinkles, 0-0.5 mL of hyaluronic acid filler was injected. For forehead wrinkles, the volume of hyaluronic acid filler depended on the depth of wrinkles and intent wrinkle elimination. To treat crow's feet, 0.25 mL of hyaluronic acid was injected. Patients in the observation group received a combination therapy of botulinum toxin type A and hyaluronic acid filler. Agents at appropriate concentrations and doses were vertically injected via an intramuscular route based on marked injection sites in the targeted area on the face of the patient, first with hyaluronic acid filler followed by botulinum toxin type A. In contrast, patients in the control group were injected with botulinum toxin type A alone, as described previously.

Outcome measures

Primary outcomes included changes in wrinkle severity before and after treatment and clinical efficacy of the two groups. Secondary outcomes covered patient satisfaction of the two groups immediately after surgery, at 1 month, 6 months, and 12 months and effectiveness of treatment in the respective periods of 2-6 months, 6-12 months, and 12-18 months as well as dosage of botulinum toxin type A. Secondary outcomes also comprised postoperative adverse events (facial congestion, topical swelling, dry eyes, and headache).

Criteria for efficacy evaluation

Efficacy of treatment was assessed according to differences of WSRS scores before and after treatment. Markedly effective was defined when the difference in WSRS scores before and after treatment was 2 grades or above; effective was defined when the difference of WSRS sores before and after treatment was 1 grade or above; ineffective was defined when there was no difference in WSRS scores before and after treatment. Overall efficiency = (effective + markedly effective)/Total number of cases.

Statistical analysis

Data were processed using SPSS software, version 21.0. Measurement data are presented as mean ± standard deviation; independent sam-

Table 1. Baseline characteristics of patients in the two groups

Baseline characteristic	Observation group	Control group	t/χ^2	P
Age (year)	47.9±6.5	49.4±5.3	1.058	0.146
Gender (Male/Female)	3/44	2/45	0.211	0.646
Pigmentation	17 (36.17%)	19 (40.42%)	0.181	0.671
Skin yellowness	13 (27.66%)	11 (23.40%)	0.224	0.636
Pore enlargement	5 (10.64%)	6 (12.76%)	0.103	0.748
Preoperative WSRS score	3.21±0.47	3.35±0.51	0.350	0.774

Table 2. Clinical efficacy of patients in the two groups

Variable	Case	Ineffective	Effective	Markedly effective	Overall effective
Observation group	47	4 (8.51%)	15 (31.91%)	28 (59.57%)	43 (91.49%)
Control group	47	6 (12.77%)	27 (57.45%)	14 (29.79%)	41 (87.23%)
χ^2	-	0.448	6.198	8.436	0.448
P	-	0.503	0.013	0.004	0.503

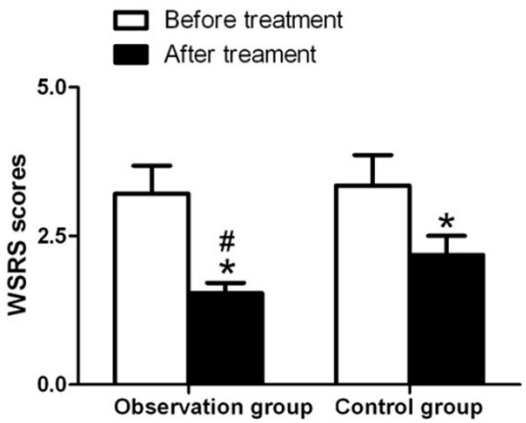

Figure 1. Changes in WSRS scores before and after treatment. *Compared with that before treatment in the same group, the observation group (t=14.152, P<0.001) and control group (t=13.648, P<0.001); #compared with the control group, t=3.155, P=0.016.

ples t-tests were applied for comparisons between the two groups. Count data are described as percentages; Chi-square tests were employed for comparisons between the two groups. P<0.05 was set as significantly different.

Results

Baseline characteristics

Baseline characteristics including age, sex, pigmentation, skin yellowness, and incidence of pore enlargement were basically similar between the observation group and control group (all P>0.05), hence, they were comparable (**Table 1**).

Clinical efficacy

Patients in the observation group showed higher overall effective rate (91.49%) than that (87.23%) of patients in control group but the difference was not statistically significant (χ^2= 0.448, P=0.503). The markedly effective rate (59.57%) of patients in the observation group was substantially higher than that (29.79%) of patients in control group (X^2=8.436, P=0.004; **Table 2**).

WSRS scores of both groups after treatment were remarkably lower than those before treatment (P<0.05); after treatment, WSRS score of the observation group was remarkably lower than that of control group (1.54±0.17 vs 2.18± 0.32; P<0.05; **Figure 1**).

Patient satisfaction in the two groups

Percentages of patients satisfied with treatment immediately after treatment and at 1 month varied insignificantly between the two groups (both P>0.05). However, the percentage (80.85%) in the observation group at 6 months was substantively higher than that (57.45%) in control group (X^2=4.523, P=0.033), as was the percentage at 12 months (63.83% vs 38.29%; X^2=6.131. P=0.023), as seen in **Table 3**.

Duration of effect after treatment

Table 4 shows that duration of effect of patients in respective periods of 2-6 months, 6-12 months, and 12-18 months was remarkably better in the observation group than in control group (93.62% vs 78.72%, X^2=4.374, P=0.036; 68.09% vs 40.43%, X^2=7.244, P=0.007; 44.68% vs 14.89%, X^2=9.969, P=0.002).

Dosage of botulinum toxin type A of patients

The dosage (11.57±4.33 u) of botulinum toxin type A for treating forehead wrinkles of patients in the observation group was remarkably smaller than that (13.28±5.11 u) of control group (t=-

Table 3. Patient satisfaction at diverse time intervals in the two groups

Variable	Case	Satisfaction immediately after treatment	Satisfaction at 1 mon	Satisfaction at 6 mon	Satisfaction at 12 mon
Observation group	47	41 (87.23%)	43 (91.49%)	38 (80.85%)	30 (63.83%)
Control group	47	39 (82.98%)	41 (87.23%)	27 (57.45%)	18 (38.29%)
X^2	-	0.336	0.448	4.523	6.131
P	-	0.562	0.503	0.033	0.023

Table 4. Duration of effect in the two groups after treatment

Variable	Case	2-6 mon	6-12 mon	12-18 mon
Observation group	47	44 (93.62%)	32 (68.09%)	21 (44.68%)
Control group	47	37 (78.72%)	19 (40.43%)	7 (14.89%)
X^2	-	4.374	7.244	9.969
P	-	0.036	0.007	0.002

1.751, P=0.042). This same pattern was also observed in respective dosages for glabellar wrinkles (15.42±2.21 u vs 16.33±2.54 u, t=-1.853, P=0.033), crow's feet (10.52±1.87 u vs 11.53±2.15 u, t=-2.431, P=0.008), and total dosages (46.53±8.37 u vs 51.85±10.33 u, t=-2.743, P=0.003) of botulinum toxin type A between the two groups (**Table 5**).

Adverse events of patients

No significant differences were noted in rate of adverse events (facial congestion, local swelling, dry eye, and headache) between the two groups after treatment (P>0.05, **Table 6**).

Discussion

After birth, the tissues of our skin develop increasingly and their performance gradually becomes mature and active. Skin gradually weakens and degrades as we reach a certain age. Moreover, because of endogenous factors and exposure to sunlight, signs of aging (reduced elasticity, roughness, and pigmentation), gradually appear on our skin. In our daily lives, we often take medicine or wear cosmetics to improve or cover up yellowness and pigmentation of skin arising from overexpose to sunlight. The efficacy of cosmetics and drug use has been poor and of short duration. Many people receive surgical and peel treatments to improve aging skin but these treatments are associated with trauma, adverse events, and long-term recovery [13]. With advances in modern science and technology and in-depth research on minimally invasive aesthetic plastic surgeries, globally, injection treatment has been commonly used in clinical practice. As injection sites are determined by the facial lesions of patients, it can achieve a rapid de-wrinkling effect and is characterized by fewer traumas, quicker recovery, more favorable clinical efficacy, longer duration of effect, and higher patient uptake and adherence, meeting the demands of beauty lovers in modern society. Previously, de-wrinkling was generally performed by injecting botulinum toxin type A alone. Botulinum toxin type A, an exotoxin, has the features of an antagonizing calcium ion, blocking release of acetylcholine, and disturbing contraction of muscle fibers to suppress formation of wrinkles. Nevertheless, this de-wrinkling technique has a short duration and poor effect. In clinical research, researchers in China have found that hyaluronic acid use can repair defects of skin soft tissues and furrows to remove existing wrinkles [14]. Hyaluronic acid, also known as hyaluronic acid, is an acidic polysaccharide. It has the function of significant water-retention. Thus, it is an ideal human moisturizing substance and the best natural moisturizer in nature [15].

At present, very few reports have been concerned with the effect of combination therapy of botulinum toxin type A and hyaluronic acid fillers in facial rejuvenation. Multiple studies have documented that botulinum toxin type A can effectively contract pores of the skin, improve darker skin, and increase skin luster whereas hyaluronic acid acts to significantly enhance water-retention of skin. The combined injection results in more tender skin on the premise of maintenance of the intact skin barrier [16, 17]. Another study revealed that injection of botulinum toxin type A alone has a good effect but it usually lasts for only 3-6 months. Since repeated treatment is necessary, it may adversely affect the physical and mental health of patients [18, 19]. In our present study, the

Table 5. Dosages of botulinum toxin type A of patients in the two groups (u±s)

Variable	Case	Forehead wrinkle (u)	Glabellar wrinkle (u)	Crow's feet (u)	Total dosage (u)
Observation group	47	11.57±4.33	15.42±2.21	10.52±1.87	46.53±8.37
Control group	47	13.28±5.11	16.33±2.54	11.53±2.15	51.85±10.33
t	-	-1.751	-1.853	-2.431	-2.743
P	-	0.042	0.033	0.008	0.003

Table 6. Adverse events of patients in the two groups

Variable	Case	Facial congestion	Local swelling	Eye dry	Headache
Observation group	47	1 (2.13%)	3 (6.38%)	2 (4.26%)	2 (4.26%)
Control group	47	2 (4.26%)	5 (10.64%)	3 (6.38%)	4 (8.51%)
X^2	-	0.344	0.547	0.211	0.712
P	-	0.557	0.459	0.646	0.399

markedly effective rate of patients in the observation group who received a drug injection in combination is higher than that of patients in control group who received a drug injection alone. Patients in the observation group felt more satisfaction than those in control group at 6 months and 12 months, respectively. This might be explained by the fact that hyaluronic acid use can maintain cell wall activity, stabilize cell morphology, prolong the duration of effect, and achieve the same effectiveness but with smaller dosages than botulinum toxin type A, rendering less burden to patients. Duration of effect at different time points in the observation group was remarkably different from those of the control group ($P<0.05$). This may be attributed to the synergy of the two agents in combination therapy. Injection of botulinum toxin type A effectively reduces muscle contraction and significantly decreases the absorption of hyaluronic acid fillers, which contributes to longer duration of effect, reduced dosages of botulinum toxin type A at respective injection sites, reduced total dosage, and minimized side effects [20].

However, this study is not free of limitations. Our sample size was too small. Additional large-scale trials will be necessary for further validation of the effectiveness of this study. Moreover, long-term outcomes warrant longer follow up periods.

In summary, botulinum toxin type A in combination with hyaluronic acid in facial rejuvenation integrates the advantages of two agents. Botulinum toxin type A can effectively eliminate facial wrinkles and large rough pores. It makes the skin more compact and delicate whereas hyaluronic acid can enhance the moisture of skin and make the whole face supple and elastic. Combination therapy is associated with a rejuvenated face, reduced botulinum toxin type A use, and less toxicity. Additionally, the combination medication has longer duration of effect and higher patient satisfaction than single medication. Thus, it is worthy of extensive clinical use. This study provides an orientation and experimental basis for future medications in minimally invasive surgery.

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Disclosure of conflict of interest

None.

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