Original Article

Clinical Efficacy and Safety of Combined Treatment with Hyaluronic Acid and Botulinum Toxin Type A for Reducing Facial Wrinkles and Increases Rejuvenation

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Abstract

Objective: The objective of this study was to evaluate the safety and effectiveness of the concurrent use of botulinum toxin type A and hyaluronic acid (HA) fillers in the context of face rejuvenation. The study examined the synergistic effects of various therapies in achieving a restorative appearance that is both clinically effective and aesthetically pleasing. **Methodology:** In order to investigate the efficacy of botulinum toxin type-A and hyaluronic acid filler in the process of facial rejuvenation, a randomised controlled trial was undertaken from September 22, 2022, to June 28, 2023. The study included a total of 100 participants who were separated into two groups. The control group consisted of 50 patients who had treatment solely with botulinum toxin type A, while the observation group comprised 50 patients who received both botulinum toxin type A and hyaluronic acid filler. The analysis encompassed an evaluation of clinical efficacy, safety, and patient satisfaction in order to provide a comparison between the two groups. **Results:** The findings of the research study revealed that the patients in the experimental group demonstrated a much higher success rate (60.11%) and reported greater satisfaction with their treatment compared to the patients in the control group (25.67%). Furthermore, it was noted that patients who were under surveillance had lower dosages of botulinum toxin type A. However, no significant disparities were found between the groups in terms of adverse effects, such as facial edoema and congestion. However, there were certain time intervals in which the control group exhibited a more favourable duration of effect. Significant statistical differences were seen at both the six-month and nine-month follow-up assessments. **Conclusion**: The efficacy of a combined treatment using botulinum toxin type-A and hyaluronic acid filler has been demonstrated to be a superior choice for face rejuvenation. The administration of this therapeutic intervention leads to prolonged efficacy, diminished dose demands, and heightened patient contentment in contrast to exclusive utilisation of botulinum toxin type A. In conclusion, the use of this integrated therapeutic approach yields enhanced clinical advantages.

Keywords: Clinical efficacy, safety, Botulinum toxin type A, hyaluronic acid, facial rejuvenation.

Introduction

As individuals progress in age, there is a gradual contraction of their muscles, absorption of facial tissues, reduction of subcutaneous fat, and an increase in localised fat deposition. The integumentary system undergoes many alterations, including reduced thickness and moisture levels, diminished elasticity, and heightened pigmentation, which collectively contribute to the development of facial wrinkles as one ages. The objective of facial rejuvenation is to reinstate vitality and youthful appearance in mature faces by a range of procedures, such as the administration of botulinum toxin type A and hyaluronic acid injections.[1,2] The aforementioned strategy has superseded conventional surgical techniques and skin care practises due to its restricted efficacy, physical traumas, and protracted recuperation period. Botulinum toxin type A exerts a transient inhibitory effect on calcium influx in neurons that regulate muscular contractions, hence resulting in the amelioration of facial wrinkles. Hyaluronic acid is utilised to address soft tissue flaws and skin furrows, leading to a reduction in the visibility of wrinkles for a

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limited duration, necessitating subsequent therapy.[1-3]

The comprehensive investigation of the simultaneous application of botulinum toxin type A and hyaluronic acid fillers for face rejuvenation remains incomplete. Individuals who are seeking aesthetic enhancements often have a variety of concerns that necessitate addressing.[3-5] Clinicians frequently adopt a holistic therapy approach, wherein investigations focus on the efficacy of distinct items in targeted facial regions rather than employing a universal method. Nevertheless, the combination of botulinum toxin and dermal filler has demonstrated potential in the context of lower face rejuvenation. The HARMONY study discovered that the incorporation of botulinum toxin A, hyaluronic acid fillers, and bimatoprost into minimally invasive multimodal treatments leads to a notable enhancement in patient satisfaction regarding their physical appearance and the perception of appearing younger within a span of four months.[3-6]

The present study examined the efficacy of a combined treatment regimen comprising botulinum toxin type A and hyaluronic acid fillers for the purpose of face rejuvenation in a sample of 100 individuals. The review encompassed an assessment of clinical outcomes, the duration of results, and patient satisfaction from September 22, 2022, to June 28, 2023.

Materials and Methods

Patients

A total of 100 participants who underwent face rejuvenation procedures at our medical facility between September 22nd, 2022 and June 28th, 2023 were included in the study. Two groups were created through random assignment: the observation group, consisting of 50 participants, and the control group, also consisting of 50 participants. The experimental cohort was administered a combined injection of botulinum toxin type A and hyaluronic acid fillers. Regarding the control group, patients received injections just of botulinum toxin type A.

The study encompassed individuals who sought face rejuvenation and satisfied predetermined criteria. The patients who met the criteria for inclusion in the study had not previously received face rhytidectomy or any other therapeutic interventions. Additionally, they demonstrated normal coagulation levels and adequate cardiopulmonary function, without the presence of severe diseases, injuries, infections, or skin nodules in the specific area of interest. Exclusion criteria encompassed pregnant or breastfeeding individuals, as well as those with botulinum toxin type A antibodies, scars, allergies, or other contraindications. The study received approval from the Hospital Ethics Committee, and all patients who participated in the trial supplied written informed permission.

Treatment methods

Prior to the surgical procedure, medical professionals conducted an assessment of face wrinkles utilising the Wrinkle Severity Rating Scale (WSRS), which encompasses four distinct grades: mild (1 point), moderate (2 points), severe (3 points), and extreme (4 points). A score of zero signifies the absence of wrinkles. The presence of "mild wrinkles" becomes apparent just during facial expressions, whereas "moderate wrinkles" are readily observable during facial movements and become less detectable when the face is in a state of rest. The presence of "severe wrinkles" is observable even in the absence of any facial emotion, but becomes dramatically reduced when the facial muscles are forcefully stretched. Regarding the phenomenon of "extreme severe wrinkles," it is noteworthy that these wrinkles remain visibly prominent even when subjected to substantial pressure exerted on the facial skin.

In order to optimise patient comfort during the course of treatment, a topical anaesthetic containing lidocaine cream was administered subsequent to the disinfection of the skin. The administration of Botulinum toxin type A and hyaluronic acid adhered to established therapeutic recommendations for dosage and injection sites that are tailored to the individual wrinkle region being treated. In the context of treating glabellar wrinkles, it is common for women to be administered a dosage ranging from 20 to 35 units of Botulinum toxin type A, while males often receive a dosage ranging from 25 to 40 units. Botulinum toxin type A was administered to individuals of both genders exhibiting forehead wrinkles, with dosages ranging from 5 to 18 units. The recommended dosage for the treatment of crow's feet varied based on gender. Women typically received a dosage of 20-35 units of Botulinum toxin type A, while men received a dosage of 25-40 units. Additionally, the quantity of hyaluronic acid filler injections administered varied depending on the affected area, with the injected volume ranging from 30 mL to a volume determined by the severity of the condition. The experimental group received therapy through vertical intramuscular injections, with marked sites serving as guides. Suitable concentrations and doses of both Hyaluronic acid filler and Botox were used. The therapy began with administrations of Hyaluronic acid filler, followed by the utilisation of Botox. In contrast, the control group subjects only received a single injection of Botox.

Outcome measures

The objective of the study was to assess the efficacy of botulinum toxin type-A treatment in reducing wrinkles. The main objectives of the study were to assess the alterations in wrinkle severity pre- and post-treatment, as well as to evaluate the therapeutic efficacy in both cohorts. The secondary outcomes encompassed patient satisfaction scores immediately following therapy and at intervals of 1, 6, and 9 months later. The assessment of treatment effectiveness was conducted at intervals of 1-3 months, 3-6 months, and 6-9 months, in addition to the monitoring of the dosage of botulinum toxin type A. The study additionally investigated secondary outcomes pertaining to adverse events, including facial congestion, topical edoema, dry eyes, and headache subsequent to the treatment.

Criteria for efficacy evaluation

The efficacy of the treatment was assessed by conducting a comparative analysis of the WSRS scores prior to and after to the intervention. The efficacy of the intervention

was assessed using a scale that measured the variance in WSRS scores. A discrepancy of at least two grades was classified as highly effective, while a discrepancy of at least one grade was considered effective. If there was no change in results, it was deemed ineffective. The overall efficiency can be determined by dividing the sum of marked and effective cases by the total number of cases.

Statistical analysis

The data was processed using SPSS software version 21.0 and presented as mean values with standard deviation for ease of comparison. Independent samples t-tests were used to comparethe two groups, and Chi-square tests were employed to analyze count data in percentage form. Statistical significance was set at $P<0.05$.

Results

Baseline characteristics

The age, sex, pigmentation, yellow discoloration and incidence of enlarged pores were all similar between the observation and control groups ($P>0.05$), suggesting that they can be compared. (Table 1 and fig 1).

Table 1. Baseline characteristics

Characteristic	Observation group	Control group	Chi square	P value
Age in year	49.8±5.7	48.7±6.5	1.99	0.112
Male/Female	5/45	3/47	0.322	0.589
Level of Pigmentation	38.5%	42.7%	0.177	0.521
Yellow discoloration in skin	29.5%	22.5%	0.119	0.567
Enlargement in Pore	9.5%	13.5%	0.118	0.662
WSRS score	3.16±0.32	3.29±0.90	0.298	0.665

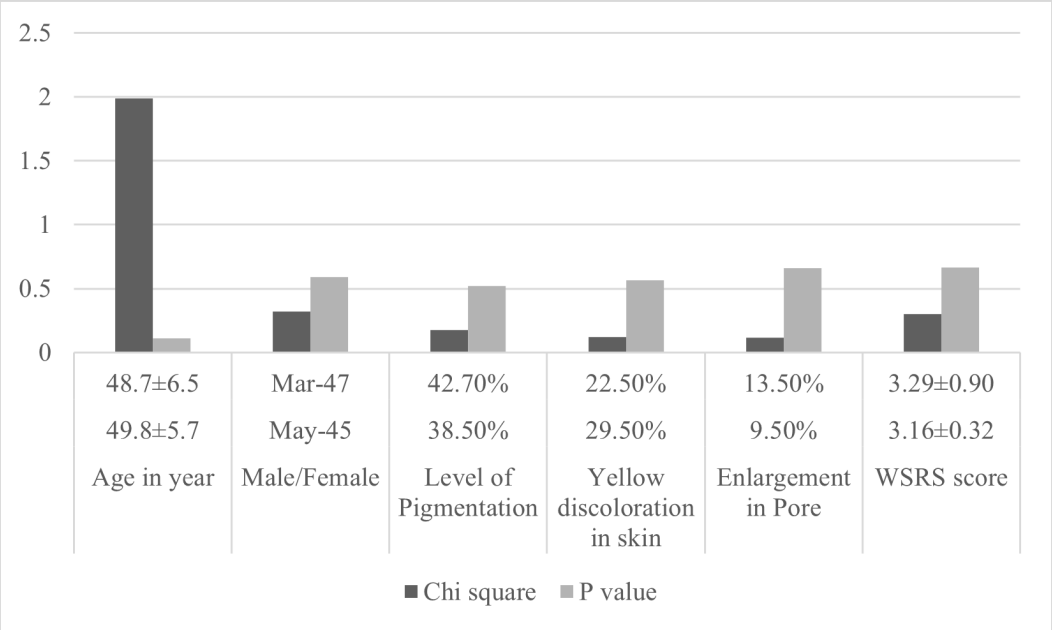

Figure 1. Baseline characteristics

Clinical efficacy

The group of patients under observation had a greater overall effective rate of 92.78% compared to the control group, which had an effective rate of 86.78%. However, it is important to note that this difference did not reach statistical significance, as indicated by a p-value of 0.402. However, the observed rate of effectiveness for the group under observation was 60.11%, which significantly above the rate of effectiveness for the control group at 25.67% ($P>0.05$; refer to Table 2). Following the intervention, both experimental groups exhibited a significant decrease in WSRS scores compared to their pre-treatment scores ($P<0.05$). Furthermore, the observation group had a significantly lower post-treatment WSRS score compared to the control group ($P<0.05$; see Figure 1,2).

Table 2. Clinical efficacy

	Case	Ineffective	Effective	Markedly effective	Overall effective
Observation group	50	7.22%	32.67%	60.11%	92.78%
Control group	50	9.08	65.35%	25.67%	86.78%
Chi square test	-	0.311	5.89	8.90	0.331
P	-	0.401	0.009	0.003	0.402

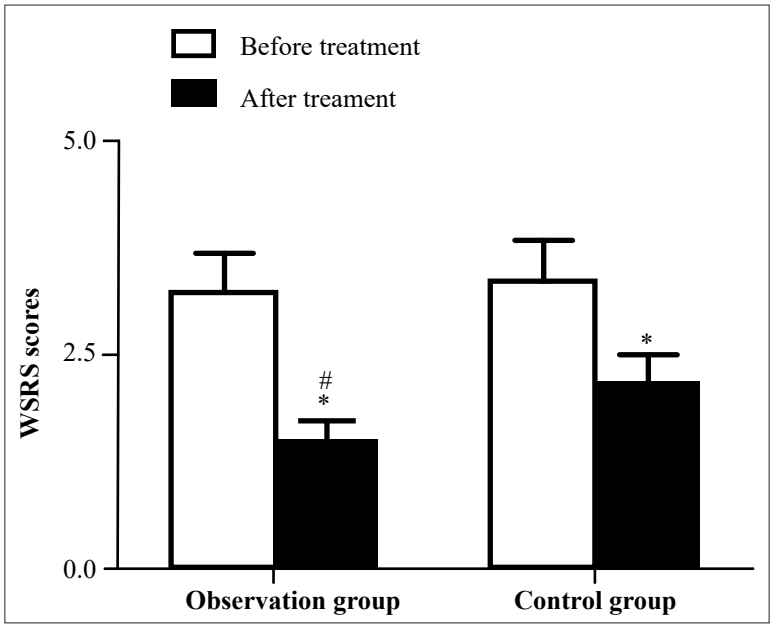

Figure 2. Changes in WSRS scores before and after treatment.

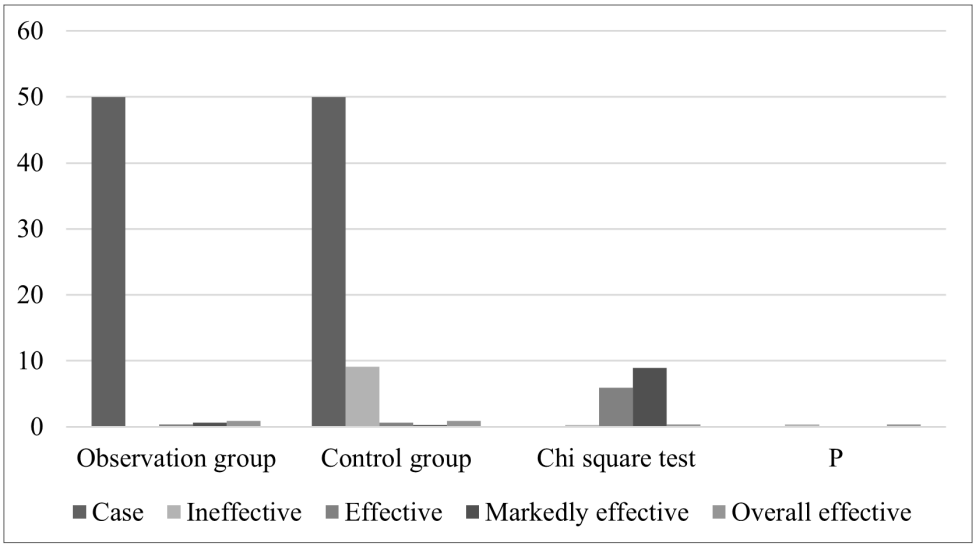

Figure 3. Changes in WSRS scores before and after treatment.

Patient satisfaction in the two groups

The evaluation of patients' satisfaction ratings was conducted at three distinct time intervals: immediately following therapy, at the one-month mark, and at both the six-month and nine-month marks, respectively. The initial findings of the study indicated that there was no statistically significant difference in satisfaction rates between the two groups, as evidenced by both P-values being more than 0.05. However, as the duration elapsed, the observed group exhibited a notably greater rate of success, amounting to 84.15% (P=0.021) at the six-month mark and 66.12% (P=0.012) at the nine-month mark, in contrast to the success rates of 55.12% and 34.11% observed in the control group. The data are presented with enhanced clarity in Table 3 and Figure 4.

Table 3. Level of Satisfaction among groups

	Level of Satisfaction immediately after treatment	After 1month	After 6 months	After 9 months
Observation group	88.79%	92.67%	84.15%	66.12%
Control group	83.78%	86.90%	55.12%	34.11%
X^2	0.445	0.449	5.89	6.78
P	0.590	0.403	0.021	0.012

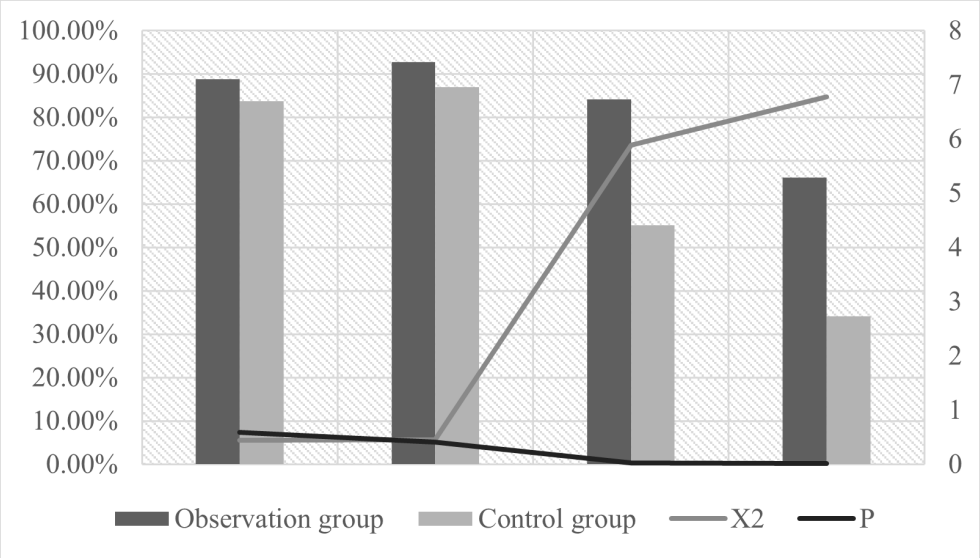

Figure 4. Level of Satisfaction among groups

Duration of effect after treatment

The data displayed in Table 4 and Fig 5 demonstrate that patients who underwent observation experienced superior duration of effects as compared to the control group during different periods. Specifically, these periods included 1-3 months (95.11% vs 75.33%, P=0.021), 3-6 months (69.80% vs 39.12%, P=0.005), and 6-9 months (48.12% vs 13.69)

Table 4. Duration of Effect

	1-3 months	3-6 momths	6-9 months
Observation group	95.11%	69.80%	48.12%
Control group	75.33%	39.12%	13.69%
X^2	3.789	8.670	10.67
P	0.021	0.005	0.001

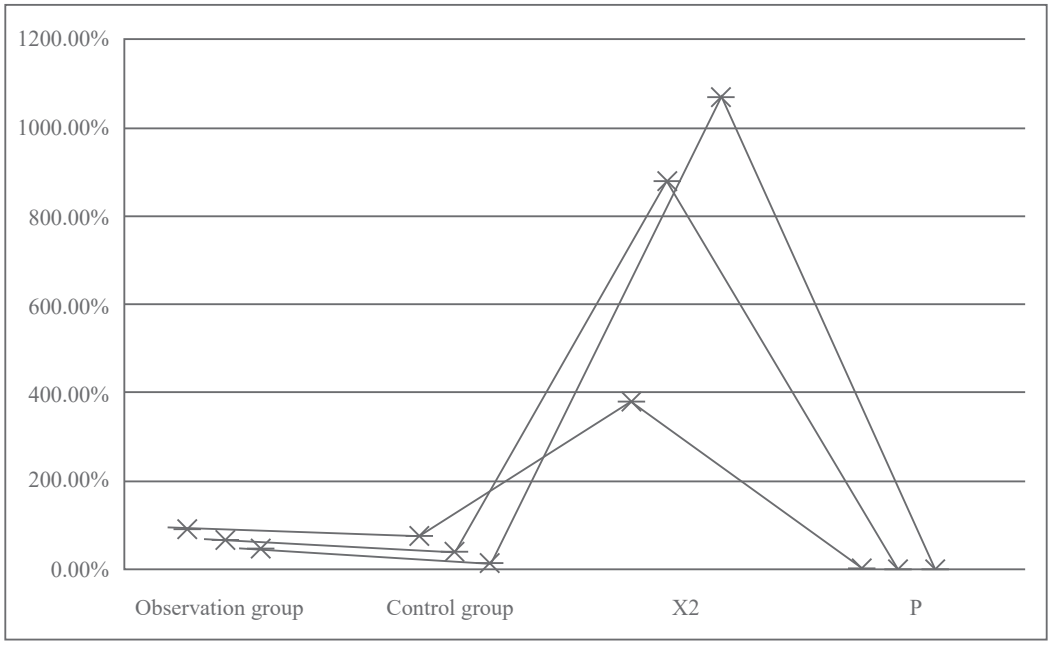

Figure 5. Duration of Effect

Dosage of botulinum toxin type A of patients

The group of individuals observed who received botulinum toxin type A for treating forehead wrinkles required a significantly lower dosage (12.11±3.78 u) compared to the control group's dosage of 15.12±4.90 u (P=0.032). This trend was also visible in doses administered for glabellar wrinkles and the total doses (44.11±7.25 u vs 52.11±9.12 u, t=-2.90, P=0.) given to both groups combined, refer to Table 5 and Fig 6 for details.

Table 5. Site of Effectiveness

	Forehead wrinkle (u)	Glabellar wrinkle (u)	Total dosage (u)
Observation group	12.11±3.78	16.11±3.78	44.11±7.25
Control group	15.12±4.90	17.90±1.22	52.11±9.12
T	-1.345	-1.789	-2.90
P	0.032	0.021	0.002

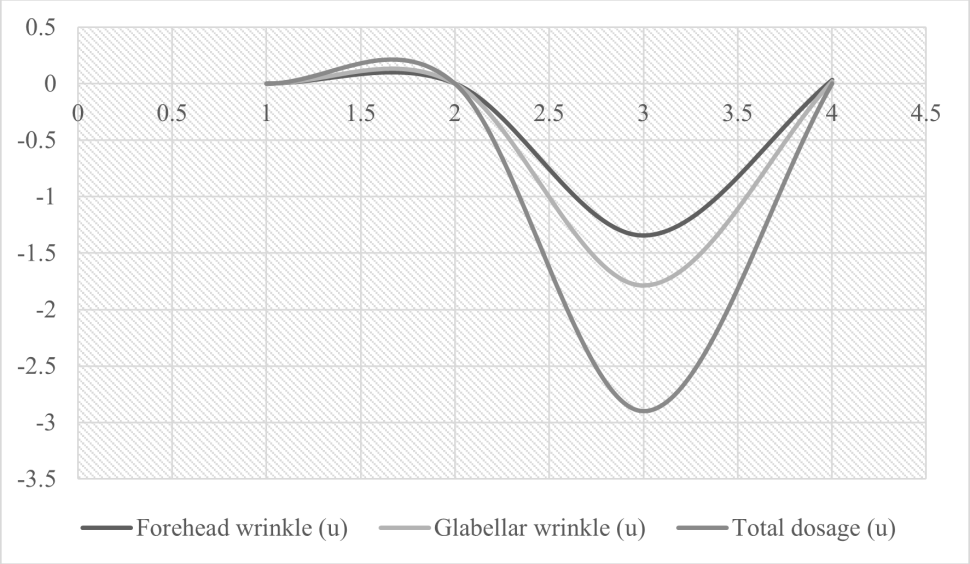

Figure 6. Site of Effectiveness

Adverse events of patients

No significant differences were noted in rate of adverse events between the two groups after treatment (P>0.05, Table 6 and Fig 7)

Table 6. Adverse events

Variable	Congestion	Swelling	Dryness of cornea	Headache/bodyache
Observation group	1.89%	7.78%	3.45%	3.45%
Control group	5.67%	12.78%	7.89%	7.89%
P	0.441	0.390	0.547	0.290

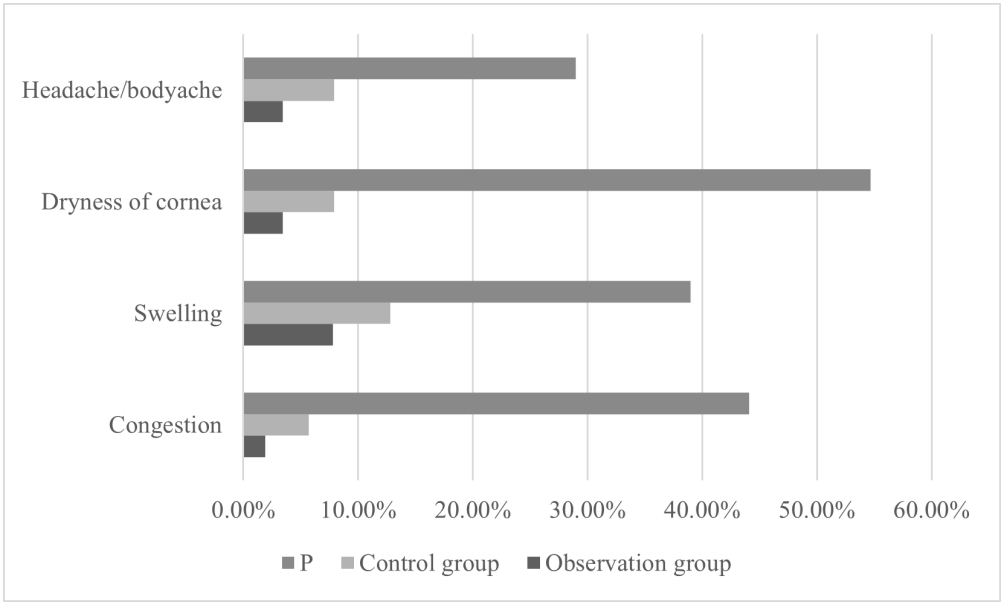

Figure 7. Adverse event

Discussion

Following the process of delivery, the skin tissue undergoes a series of sequential changes that lead to the attainment of an optimal level of functionality and maturity. Nevertheless, as individuals age, the integumentary system undergoes a steady process of deterioration, resulting in a decline in its overall functionality. The manifestation of ageing characteristics, including coarseness, pigmentation, and diminished elasticity, can be attributed to a combination of endogenous causes and chronic solar radiation exposure. A significant number of persons incorporate pharmaceutical or cosmetic medicines into their daily routines with the purpose of concealing discolouration or hyperpigmentation resulting from prolonged exposure to ultraviolet light. The effectiveness and duration of these approaches have been found to be limited in previous studies.[6-11] Surgical operations and chemical peels are alternative methods for improving the appearance of ageing skin. However, it is worth noting that these approaches might result in physical stress and need extended recovery periods. Injection treatments have gained significant popularity on a global scale due to its minimally invasive nature and short recovery period, thanks to advancements in current science and technology.[11-14] The strategic choice of injection sites on the facial region has proven to be an efficient method for minimising wrinkles with minimal tissue damage. This approach has demonstrated superior clinical effectiveness and has gained widespread acceptance among modern individuals who are passionate about beauty.[15]

Historically, conventional methods for wrinkle elimination predominantly centred around the utilisation of botulinum toxin type A, which functions by impeding the release of acetylcholine. This mechanism ultimately leads to diminished muscle fibre contraction, thereby minimising the formation of wrinkles. However, it is worth noting that these traditional procedures have demonstrated restricted effectiveness over prolonged periods. A study conducted by clinical researchers in China has demonstrated the efficacy of hyaluronic acid in treating soft tissue abnormalities that are frequently observed in conjunction with preexisting wrinkles.[15-19] This chemical, known for its ability to retain substantial quantities of water,[20] is widely recognised as one of the most efficacious moisturisers now accessible for human use.

There is a scarcity of research examining the efficacy of concurrent administration of botulinum toxin type A and hyaluronic acid fillers for the purpose of face rejuvenation. Both components exhibit potential advantages in several aspects of skin rejuvenation, including pore reduction, brightness enhancement, and moisture retention.[20-22] Nevertheless, it is worth noting that certain treatments may necessitate multiple sessions as a result of their short period of effectiveness, which might have adverse effects on the overall well-being of patients. The concurrent administration of both components has been demonstrated to be efficacious in enhancing skin texture and mitigating soreness at injection sites, while concurrently minimising adverse effects. The administration of combination treatment has been associated with higher rates of efficacy and greater patient satisfaction in comparison to individuals who get only a single component of treatment. The combination therapy also exhibits an extended duration of efficacy, necessitating lower dosages and so reducing the incidence of adverse effects.[20-23]

Nevertheless, this study has several constraints. The study's sample size was insufficient to establish definitive conclusions. In order to ascertain the efficacy of this investigation, it is imperative to conduct more large-scale experiments. Additionally, it is crucial to include longer follow-up periods in order to assess the enduring impacts.

Conclusion

In summary, the utilisation of a combination therapy including botulinum toxin type A and hyaluronic acid for the purpose of facial rejuvenation amalgamates the advantageous properties of both substances. Botulinum toxin type A has demonstrated efficacy in diminishing wrinkles and enhancing the appearance of coarse pores, whilst specific chemicals have the potential to promote a more refined and delicate skin texture. The utilisation of hyaluronic acid has been found to enhance the levels of skin hydration, as well as increase facial suppleness and elasticity. The utilisation of combination therapy has been observed to effectively renew face features while exhibiting reduced toxicity risks in comparison to the use of individual drugs. Additionally, it demonstrates a prolonged duration of efficacy, resulting in heightened patient satisfaction and reduced utilisation of botulinum toxin type A. Hence, this methodology is deemed appropriate for broad use in the realm of minimally invasive surgery within clinical settings. The present study establishes a theoretical framework and offers empirical evidence that can serve as a basis for future medicinal treatments in this particular domain.

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