META-ANALYSIS

Efficacy of Botulinum Toxin in the Treatment of Facial and Cervical Hypertrophic Scar: A Meta-Analysis

Dong Yin, MM; Mingfan Xi, MM; Lifan Jiang, MM; Mingqiu Du, MM; Jun Qi, MD

ABSTRACT

Objective • Maxillofacial-neck hyperplastic scars have long been a persistent concern among individuals in both Western and Eastern countries. These scars exhibit rapid growth within 3-6 months following wound healing, subsequently receding at a slower pace, leading to skin redness, tension, and potential itching. The lack of comprehensive understanding regarding the formation mechanism and biological attributes of these scars has made them a prominent subject of research both domestically and internationally.

Methods • Research data from 2010 to 2023 was selected, and relevant literature on the efficacy of botulinum toxin in the treatment of facial and neck hypertrophic scars was searched until August 2023. The literature on the incidence of facial-neck hypertrophic scars included in PubMed, the Cochrane Library, EMbase, and Web of Science was searched. Two researchers independently screened and extracted the data according to strict inclusion and exclusion criteria.Risk bias in Review Manager 5.4, provided by the Cochrane Collaboration, was used for methodological quality assessment and meta-analysis of the included literature. In case of any disagreement, the decision shall be made through consultation with the third party. Scar width, patient satisfaction, and visual analogue scale (VAS) were evaluated. Weighted mean difference (WMD), odds ratio (OR), and 95% confidence interval (95%CI) were used for evaluation. Publication bias was intuitively determined by funnel plot, and sensitivity analysis was conducted by removing literatures one by one for risk assessment.

Results • After reading the title, abstract, and full text, a total of 237 patients were included in 7 articles. Scar width was only studied in 6 literatures, and the heterogeneity test of the included studies ($\chi^2 = 148.95$, $P < .001$, $I^2 = 98\%$) showed significant heterogeneity among the studies. Therefore, the random effects model was used to merge the data. Combined effect value WMD =-2.85 [95% CI :(-6.51, 0.81), $P < .001$], the difference between the two groups was statistically significant. The combined OR of the random-effects model was 8.52 [95%CI: (7.96, 9.08), $P < .001$], and the difference between the two groups was statistically significant. Among them, the heterogeneity test ($\chi^2 = 2.69$, $P = .44$, $I^2 = 0\%$) was carried out in two studies, indicating good homogeneity among the studies, so the combined WMD was 0.68 [95%CI: (0.38, 0.99), $P < .001$] by using the fixed-effect model. The median VAS was described in the other two literatures, and the mean scores in the experimental group were 8.9 and 8.25, respectively, while the mean scores in the control group were 7.2 and 6.28, respectively, indicating that local injection of botulinum A toxin at the early stage of wound healing can significantly improve scar quality. Sensitivity analysis suggested that the meta-analysis results were stable and reliable, and publication bias was not analyzed using funnel plots.

Conclusion • Botulinum toxin has a positive effect on preventing hyperplastic scars in the maxillofacial and neck areas, and it can also help fade existing scars. (*Altern Ther Health Med.* 2024;30(12):304-308).

Dong Yin, MM, Resident doctor; **Mingfan Xi,** MM, Resident doctor; **Lifan Jiang,** MM, Resident doctor; **Mingqiu Du,** MM, Resident doctor; **Jun Qi,** MD, Chief physician; Department of Burn and Plastic surgery, Affiliated Hospital of Nantong University, Nantong, China.

Corresponding author: Jun Qi, MD
E-mail: qitdfy@163.com

INTRODUCTION

A hypertrophic scar is the pathological result of tissue fibrosis in the wound healing process. It can cause local tissues to protrude above the surface of the skin, which affects the patient's appearance. It also restricts joint movement in all directions and hampers facial expression muscles, thereby impacting daily communication. Additionally, it may lead to organ dysfunction, seriously affecting both the physical and mental health of patients.[1, 2] Whether in Western or Eastern countries; people have long been troubled by hypertrophic scar. The scar can grow rapidly within 3-6 months after the wound heals slowly retreating, causing red tension in the skin and even itching.[3] The insufficient comprehension of its formation mechanism and biological attributes has made it a subject of extensive research both domestically and internationally. Research has indicated that the pressure exerted in the vicinity of the wound during the wound-healing process is the most crucial factor in developing hypertrophic scars. Consequently, increased pressure surrounding the wound increases the likelihood of hypertrophic scar formation.[4] In vitro experiments have shown that excessive pressure can inhibit fibroblast apoptosis promote cell migration and wound fibrosis.[5] the treatment mainly includes compression therapy, laser therapy, drug therapy, surgical therapy, cryotherapy radiotherapy, etc.[6] Liquid nitrogen cryotherapy has also become popular in recent years. Its principle is that low temperature can shrink blood vessels and induce cell apoptosis of hyperplasia scar tissue, thus achieving the purpose of

inhibiting scar growth.[7] Although people have high aesthetic requirements for early intervention in wound scar repair, there is still no consensus on the treatment of maxillofacial and neck hypertrophic scar, the main reason is that little is known about the mechanism of hypertrophic scar.[8]

Botulinum toxin is a type of neurotoxin secreted by the bacterium Clostridium botulinum. It can induce chemical denervation in muscles, leading to specific neurotoxic symptoms. This potent neurotoxin has been safely utilized for almost 20 years.[9] Besides traditional uses such as eliminating facial wrinkles and treating strabismus, botulinum toxin can also induce the immobilization of fresh wound, improve wound healing and facial beauty.[10] Some scholars have found that botulinum toxin can play a role by inhibiting the release of acetylcholine at neuromuscular junction.[11] A large number of studies have shown that injecting Botox A toxin at the wound edge can temporarily paralyze muscles and reduce wound edge tension.[12] With society's development and modern medical technology's progress, botulinum toxin has been widely used in medicine and dermatology.[13] In recent years, botulinum toxin has been reported to treat hypertrophic scar.[14] Although the molecular mechanism of botulinum toxin in the treatment of hypertrophic scar is not well defined, A large number of experimental results have proved that botulinum toxin can effectively inhibit the proliferation of fibroblasts and promote cell apoptosis.[15] Botulinum A toxin can also reduce the expression of transforming growth factor TGF-β1, and its molecular properties can play a powerful role in the early stage of scar formation by fixing the muscle-pulling force around the wound, thus reducing skin tension. This, in turn, reduces microtrauma and subsequent inflammatory response while maintaining the dynamic balance between fibroblast proliferation and apoptosis. In vitro experiments have shown that fibroblasts play a unique role in the tiny cell cycle, possibly explaining why botulinum toxin can alter the fibroblast cycle to inhibit the development of hypertrophic scars.

Considering that a single study lacks effective statistical power due to small sample size and large clinical heterogeneity. Therefore, we adopted the method of meta-analysis to systematically and comprehensively collect domestic and foreign literature on the prevention of botulinum and maxillofacial and neck hypertrophic scar. The purpose is to conduct quantitative synthesis through strict statistical methods to seek new breakthroughs in clinical treatment and finally arrive at objective and reliable conclusions. To provide more objective evidence-based medical evidence for the treatment and prevention of hypertrophic scar in maxillofacial and neck region.

PATIENTS AND METHODS

Inclusion criteria

The types of studies included were randomized controlled trials. The included literature aims to evaluate the efficacy of Botox in the treatment of maxillofacial and neck hypertrophic scars. The intervention measures were Botox A toxin injection in the experimental group and saline injection in the control group. Botox A toxin and normal saline were injected separately, and neither was doped with other reagents. The final outcome indicators of the study were scar width, patient satisfaction, and visual analogue score (VAS). Experienced observers independently recorded all the observation indicators. After the observation indicators were determined, statistical software was used for statistical processing.

Exclusion Criteria

The relevant literature does not provide sufficient original data and contains duplicate articles. Animal studies are conducted on pregnant or breastfeeding women, as well as individuals with psychiatric disorders. The literature on keloids and scars in burn patients lacks subjects' participation throughout the study. Patients who are allergic to botulinum toxin or experience muscle weakness themselves. Additionally, letters, reviews, and literature of case reports are included.

Literature Search

PubMed, Embase, Web of Science, and Cochrane databases were searched by computer for the incidence of depression in stroke patients. References were strictly screened according to inclusion and exclusion criteria, and references up to August 2023 were strictly screened according to inclusion and exclusion criteria. In order to ensure the recall and accuracy of the references, fuzzy search was carried out for the included references, and literatures of randomized controlled trials and clinical controlled trials meeting the inclusion criteria were comprehensively collected. Keywords: "Botulinum toxin type A", "BTA", "skinscar", "facial wound", "oral and maxillofacial", "neck".

Literature screening and data extraction

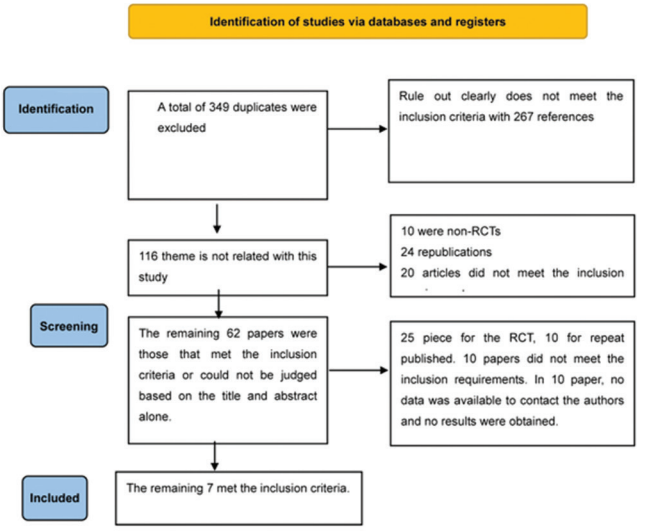
According to the PRISMA process, the required literature can be selected layer by layer. This process can be carried out as follows: two researchers will roughly screen the title and abstract of the retrieved literature, and eliminate the literature that duplicates or does not meet the study's inclusion criteria. The literature obtained after the initial screening was read in full text, and the studies that met the requirements were selected based on the established inclusion and exclusion criteria. Any disputes regarding the included literature will be resolved through negotiation or decided by a third researcher. Two researchers individually extracted the data from the included literature and cross-checked them.The methodological quality of each study was evaluated using Cochrane literature evaluation criteria, which mainly included: Generation of random sequences - describing in detail the methods used to generate randomly assigned sequences to assess inter-group comparability; Allocation hiding - describing in detail the method of hiding random allocation sequences to determine whether the allocation of interventions is predictable; Investigator Participant blinding - describing in detail the method of blinding both the investigator and the subject to prevent them from being aware of the subject's intervention. It provides the intervention

Table 1. Characteristics of eligible studies

Number	Author	Time	Total samples	Scar location	Patient source	T	C	Jadad scale
1	Gassner H G et al[16]	2006	31	frontal part	in hospital	16	15	4
2	Ziade M et al[17]	2013	24	face	outpatient	11	13	5
3	Tollefson T et al[18]	2006	59	face	outpatient	30	29	3
4	Chang CS et al[19]	2014	59	face	in hospital	30	29	5
5	Xiao Z et al[20]	2009	6	face	in hospital	3	3	5
6	Kim YS et al[21]	2022	30	frontal part	in hospital	15	15	5
7	Xiao-Yu W et al [22]	2013	28	face	outpatient	14	14	5

Abbreviations: T, Number of test group; C, Number of control group

Figure 1. Literature screening process and results.



measure to judge whether the blind method is effective. Blinding of measurement results: A method of blinding the evaluators of study results is described in detail to prevent them from being aware of the subjects' interventions. Provide interventions that blind whether the method is effective; Incomplete data: Complete data were reported for each main outcome measure, including lost follow-up and drop-out. Whether loss of follow-up and withdrawal are clearly reported: Selective records should describe information that allows system evaluators to judge the likelihood and circumstances of selective reporting of research results. Based on the provided information, two researchers independently evaluated the included literature one by one, using the categories "low bias," "unclear," and "high bias" for each indicator. In the event of disagreement, an agreement was reached through discussion.

Statistical Analysis

Meta-analysis was performed using the Revman5.4 software provided by the Cochrane Collaboration. The bivariate adoption rate difference (RD) and its 95%CI and the mean difference (WMD) and its 95%CI were used for continuity variables. χ^2 test was used to evaluate the heterogeneity among the trials. The test level α was set at 0.1, and the degree of heterogeneity was expressed. If $P > .10$ and $I^2 < 50\%$, statistical homogeneity existed between the studies, and the fixed-effect model was used to combine the effect size. If $P \leq .10$ and $I^2 \geq 50\%$, there was statistical heterogeneity among the studies, and a random effects model was used for combined analysis. Data from the Juna clinical trials could not be pooled; only descriptive analysis was performed.

RESULTS

Literature screening results and basic characteristics

According to the PRISMA process, 176 articles were initially retrieved after the joint search of all subject words and keywords through electronic search and manual search according to the search strategy. After reading the title and abstract, a preliminary investigation was conducted, and a total of 150 duplicate or irrelevant articles were excluded, and the remaining 26 articles were read in full. Finally, 17 literatures that did not meet the inclusion criteria were excluded. Among them, 3 articles were excluded because they involved animal experimental studies, 6 articles were excluded because of case reports, 3 articles were excluded because they involved systematic reviews, and 7 articles were excluded because they lacked sufficient original data or contained useless data. Finally, a total of 7 literatures were included.[16-22] The basic information and Jadad quality scores of the included literatures are shown in Table 1. The research screening process is shown in Figure 1.

Quality evaluation of included literature

Among the 7 literatures finally included, 7 were randomized controlled trial designs, and the basic characteristics of the included studies were shown in Table 1, which included a total of 237 patients. In terms of ethnic characteristics, 1 study was from Germany, 1 from France, 1 from Egypt, 1 from South Korea, and 3 from China. All groups included in the study had hypertrophic scars in the maxillofacial or neck region. Among them, 3 articles included 6 randomized controlled trials to statistically analyze scar width. The number of cases in the experimental and control groups was 119 and 118, respectively. Two studies were conducted to analyze patient satisfaction. The visual simulation scoring method was statistically analyzed by weighted mean difference in 2 literatures, and the median method was used in the other 2 literatures. All the included literature results data were complete, there was no selective reporting of results, and other sources of bias were uncertain. See Table 2, Figures 2 and 3.

Comparison of scar width results

Scar width was only studied in 6 literatures, because 1 paper studied two points of facial scar width separately, and ultrasound was used to measure scar width. The heterogeneity test of the included studies ($\chi^2 = 148.95$, $P < .001$, $I^2 = 98\%$) showed that there was significant heterogeneity among the studies. Therefore, the random effects model was used to merge the data. Combined effect value WMD =-2.85 [95%CI: (-6.51,0.81), $P < .001$], indicating that the difference between the two groups was statistically significant, suggesting that injection of Botox A toxin around the wound could reduce the width of facial and neck scar. The analysis is shown in Figure 4.

Table 2. Risk-bias evaluation of the included articles

Included literatures	Sequence generation	Baseline characteristics	Concealed grouping	Implementation bias		Measurement bias		Missed visit bias	Selective reporting of results	Other biases
				Random	Blinded method	Randomness of results	Blinded method	Incomplete data reporting		
Gassner H G et al[16]	Yes	Yes	Uncertain	Yes	Uncertain	Uncertain	No	Yes	No	Uncertain
Ziade M et al[17]	Yes	Yes	Uncertain	Yes	Uncertain	Uncertain	No	Yes	No	Uncertain
Tollefson T et al[18]	Yes	Yes	Uncertain	Yes	Uncertain	Uncertain	No	Yes	No	Uncertain
Chang CS et al[19]	Yes	Yes	Uncertain	Yes	Uncertain	Uncertain	No	Yes	No	Uncertain
Xiao Z et al[20]	Yes	Yes	Uncertain	Yes	Uncertain	Uncertain	No	Yes	No	Uncertain
Kim YS et al[21]	Yes	Yes	Uncertain	Yes	Uncertain	Uncertain	No	Yes	No	Uncertain
Xiao-Yu W et al[22]	Yes	Yes	Uncertain	Yes	Uncertain	Uncertain	No	Yes	No	Uncertain

Figure 2. Incorporating Evaluating Literature Quality

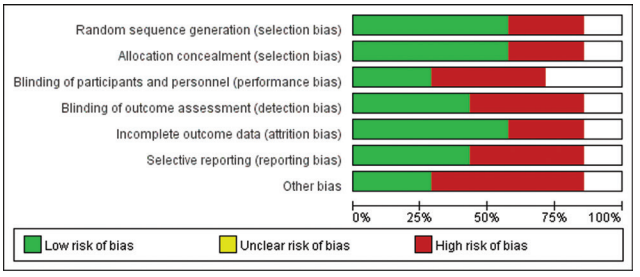


Figure 3. Incorporating Evaluating Literature Quality.

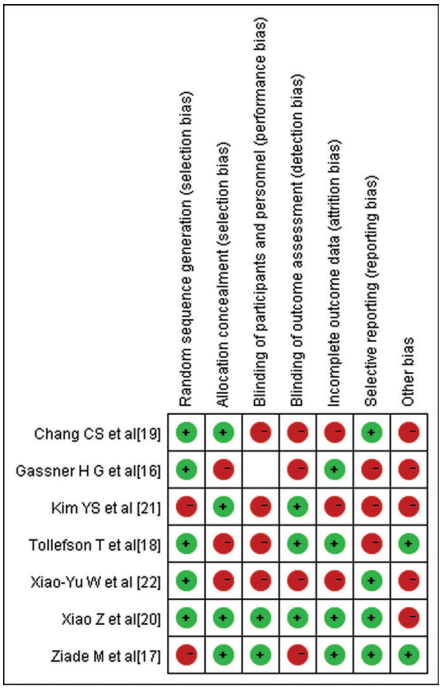


Figure 4. Comparison of scar width results.

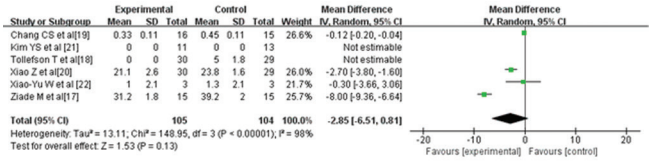


Figure 5. Comparison of patient satisfaction results.

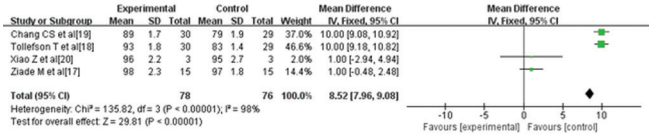
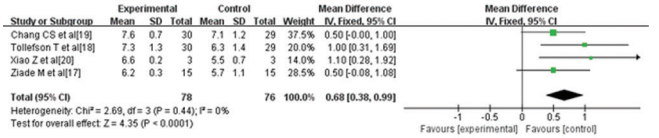


Figure 6. Comparison of scar visual analogue scale (VAS).



Comparison of patient satisfaction results

A total of 4 experiments were included in the statistics. After heterogeneity test, $\chi^2 = 135.82$, $P < .001$, $I^2 = 98\%$, so there was heterogeneity in the included studies. The combined effect value OR was 8.52[95%CI: (7.96, 9.08), $P < .001$] by using the random effects model. The difference between the two groups was statistically significant. The analysis is shown in Figure 5.

Comparison of scar visual analogue scale (VAS)

VAS is a subjective evaluation index and an effective method to explore patient satisfaction. It indirectly reflects the effectiveness of botulinum toxin, with scores ranging from 0 to 10 (0 being the worst scar and 10 being the best scar). VAS was studied in 4 papers, among which 2 were tested for heterogeneity ($\chi^2 = 2.69$, $P = .44$, $I^2 = 0\%$), indicating good inter-study homogeneity. The combined WMD was 0.68 using the fixed effect model [95%CI: (0.38, 0.99), $P < .001$]. The median VAS was described in the other two literatures, and the mean scores in the experimental group were 8.9 and 8.25, respectively, while the mean scores in the control group were 7.2 and 6.28, respectively, indicating that local injection of botulinum A toxin at the early stage of wound healing can significantly improve scar quality. The analysis is shown in Figure 6.

Sensitivity and publication bias analysis

The sensitivity analysis was mainly carried out by the one-by-one exclusion method. The results of the analysis of the three measurement indicators showed that the remaining studies were meta-analyzed again after one review was individually excluded, and no significant changes were found in the combined effect sizes, suggesting that the results of our meta-analysis were stable and reliable. The funnel plot was not used to analyze publication bias due to the small number of articles included between each measure in our study.

DISCUSSION

Meta-analysis is a statistical method for summarizing and combining the results of multiple independent studies in the same study.[23] The prevention and treatment of maxillofacial and neck hypertrophic scars have long been the focus of widespread attention. These scars not only seriously affect the

appearance of the body surface but also cause local dysfunction.[24] Hypertrophic scar usually occurs near the edge of a wound where tension exists. Local movement of the face and neck, such as between the upper and lower lips, cheeks, forehead, and neck, may cause hypertrophic scar.[25] So far, prevention is the main method, that is, some external factors are used to reduce the hyperplasia of scar tissue before wound healing and in the immature stage of wound formation so as to reduce the impact on the body.[26] However, due to insufficient evidence, clinical methods for preventing and treating scar hyperplasia are still not unified. Therefore, this paper aims to lay a foundation for further theoretical basis through the Meta-analysis of the early application of botulinum A toxin to control hypertrophic scars. Compared with the control group, the experimental group using Botox showed higher effectiveness in preventing scar hyperplasia. It has been reported that 90% of patients were highly satisfied with the efficacy of the treatment.[27] However, a few scholars have not found that the width of facial scars in patients has been greatly improved. Xiao et al. injected Botox into a patient's face to evaluate the softness and itching degree of scar and found that hypertrophic scar is better than before injection.[28]

The results of our meta-analysis suggest that botulinum toxin has a good control effect on maxillofacial and neck hypertrophic scar, which is consistent with the results of Gassner's experiment on treating frontal scar in primates like apes.[29] To date, no systematic review or meta-analysis has explored the therapeutic role of botulinum toxin in preventing maxillofacial and neck hypertrophic scar. However, after conducting this analysis, we have identified some flaws in the results. Firstly, we did not consider the variations in the age of the population across different studies. The age range of the patients included in the study was from 3 months to 70 years old. As mentioned earlier, hypertrophic scars predominantly occur during adolescence. Therefore, the degree of scar hyperplasia may vary among different age groups, leading to clinical heterogeneity that cannot be avoided. Secondly, the basic characteristics of patients in different studies are not the same, and the diagnostic criteria and safety evaluation criteria are not uniform, which may have a certain impact on the results. Third, due to the small sample size of each study and the limited amount of evidence included in the literature, the scientific and experimental results need to be further explored and supplemented. Finally, through the quality evaluation of the included literature, some articles may have publication and implementation bias.

In summary, botulinum toxin type A can effectively prevent the occurrence of maxillofacial and neck hypertrophic scars. It not only improves the quality of scars but also meets the aesthetic requirements of patients. However, due to the limited number of included articles, more clinical trials and basic research should be conducted in the near future to better understand the effective control of botulinum toxin on hypertrophic scars.

ETHICAL COMPLIANCE

Not applicable.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

AUTHOR CONTRIBUTIONS

DY and JQ designed the study, MX and LJ collected the data, MX, LJ and MD analyzed the data, DY and JQ prepared the manuscript. All authors read and approved the final manuscript.

FUNDING

This work was supported by the Nantong Burn Clinical Medical Research Center Project (HS2020006); Nantong Basic Science Research Project (JC2021181); Nantong Municipal Guidance Project (MSZ2022085).

REFERENCES

1. Jansky P, Motovska Z, Kroupa J, et al. Impact of admitting department on the management of acute coronary syndrome after an out of hospital cardiac arrest. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2023;167(2):169-176. doi:10.5507/bp.2022.044
2. Kuiper MA, Verlangen R. [Resuscitation among patients with out-of-hospital cardiac arrest; intra-arrest transport, or not?]. *Ned Tijdschr Geneeskd*. 2021;165:D5691.
3. Moderato L, Aschieri D, Lazzeroni D, et al. *Air Pollution and out-of-hospital cardiac arrest risk*. Eur Heart J-Acute Ca; 2023, . doi:10.1101/2023.03.15.23287335
4. Myat A, Song KJ, Rea T. Out-of-hospital cardiac arrest: current concepts. *Lancet*. 2018;391(10124):970-979. doi:10.1016/S0140-6736(18)30472-0
5. Elshahed AR, Elmanzalawy KS, Shehata H, ElSaie ML. Effect of botulinum toxin type A for treating hypertrophic scars: A split-scar, double-blind randomized controlled trial. *J Cosmet Dermatol*. 2020;19(9):2252-2258. doi:10.1111/jocd.13627
6. Park GS, An MK, Yoon JH, et al. Botulinum toxin type A suppresses pro-fibrotic effects via the JNK signaling pathway in hypertrophic scar fibroblasts. *Arch Dermatol Res*. 2019;311(10):807-814. doi:10.1007/s00403-019-01975-0
7. Hua Z, Wei P. Botulinum toxin type a intralesional monotherapy for treating human hypertrophic scar in a dose-dependent manner: in an animal model. *J Plast Reconstr Aesthet Surg*. 2021;74(11):3196-3211. doi:10.1016/j.bjps.2021.05.067
8. Zhou N, Li D, Luo Y, Li J, Wang Y. Effects of Botulinum Toxin Type A on Microvessels in Hypertrophic Scar Models on Rabbit Ears. *BioMed Res Int*. 2020;2020:2170750. doi:10.1155/2020/2170750
9. Li Y, Shan X, Mao Q, Xiang R, Cai Z. Botulinum toxin type a intralesional monotherapy for treating human hypertrophic scar in a dose-dependent manner: in an animal model. *J Plast Reconstr Aesthet Surg*. 2021;74(11):3186-3195. doi:10.1016/j.bjps.2021.03.062
10. Yang Z, Lv Y, Yang Z, Cao L, Cao D. Concentration-Dependent Inhibition of Hypertrophic Scar Formation by Botulinum Toxin Type A in a Rabbit Ear Model. *Aesthetic Plast Surg*. 2022;46(6):3072-3079. doi:10.1007/s00266-022-03008-0
11. Zhang S, Li K, Yu Z, et al. Dramatic Effect of Botulinum Toxin Type A on Hypertrophic Scar: A Promising Therapeutic Drug and Its Mechanism Through the SP-NK1R Pathway in Cutaneous Neurogenic Inflammation. *Front Med (Lausanne)*. 2022;9:820817. doi:10.3389/fmed.2022.820817
12. Li YH, Yang J, Zheng Z, Hu DH, Wang ZD. Botulinum toxin type A attenuates hypertrophic scar formation via the inhibition of TGF-β1/Smad and ERK pathways. *J Cosmet Dermatol*. 2021;20(5):1374-1380. doi:10.1111/jocd.13842
13. Liu XG, Zhang D. Evaluation of Efficacy of Corticosteroid and Corticosteroid Combined with Botulinum Toxin Type A in the Treatment of Keloid and Hypertrophic Scars: A Meta-Analysis. *Aesthetic Plast Surg*. 2021;45(6):3037-3044. doi:10.1007/s00266-021-02426-w
14. Kasyanju Carrero LM, Ma WW, Liu HF, Yin XF, Zhou BR. Botulinum toxin type A for the treatment and prevention of hypertrophic scars and keloids: updated review. *J Cosmet Dermatol*. 2019;18(1):10-15. doi:10.1111/jocd.12828
15. Bi M, Sun P, Li D, Dong Z, Chen Z. Intralesional Injection of Botulinum Toxin Type A Compared with Intralesional Injection of Corticosteroid for the Treatment of Hypertrophic Scar and Keloid: A Systematic Review and Meta-Analysis. *Med Sci Monit*. 2019;25:2950-2958. doi:10.12659/MSM.916305
16. Gassner HG, Brissett AE, Otley CC, et al. Botulinum toxin to improve facial wound healing: A prospective, blinded, placebo-controlled study. *Mayo Clin Proc*. 2006;81(8):1023-1028. doi:10.4065/81.8.1023
17. Ziade M, Domergue S, Batifol D, et al. Use of botulinum toxin type A to improve treatment of facial wounds: a prospective randomised study. *J Plast Reconstr Aesthet Surg*. 2013;66(2):209-214. doi:10.1016/j.bjps.2012.09.012
18. Tollefson TT, Senders CM, Sykes JM, Byorth PJ. Botulinum toxin to improve results in cleft lip repair. *Arch Facial Plast Surg*. 2006;8(3):221-222. doi:10.1001/archfaci.8.3.221
19. Chang CS, Wallace CG, Hsiao YC, Chang CJ, Chen PK. Botulinum toxin to improve results in cleft lip repair: a double-blinded, randomized, vehicle-controlled clinical trial. *PLoS One*. 2014;9(12):e115690. doi:10.1371/journal.pone.0115690
20. Xiao Z, Zhang F, Cui Z. Treatment of hypertrophic scars with intralesional botulinum toxin type A injections: a preliminary report. *Aesthetic Plast Surg*. 2009;33(3):409-412. doi:10.1007/s00266-009-9334-z
21. Kim YS, Lee HJ, Cho SH, Lee JD, Kim HS. Early postoperative treatment of thyroidectomy scars using botulinum toxin: a split-scar, double-blind randomized controlled trial. *Wound Repair Regen*. 2014;22(5):605-612. doi:10.1111/wrr.12204
22. Tirico MCCP, Jensen D, Green C, Ross EV. Short pulse intense pulsed light versus pulsed dye laser for the treatment of facial redness. *J Cosmet Laser Ther*. 2020;22(2):60-64. doi:10.1080/14764172.2020.1717540
23. Fu Y, Xue G. Meta-Analysis of Atezolizumab vs Docetaxel in Non-Small Cell Lung Cancer Treatment Outcomes. *Altern Ther Health Med*. 2023;29(6):128-133.
24. Li YH, Yang J, Liu JQ, et al. A Randomized, Placebo-Controlled, Double-Blind, Prospective Clinical Trial of Botulinum Toxin Type A in Prevention of Hypertrophic Scar Development in Median Sternotomy Wound. *Aesthetic Plast Surg*. 2018;42(5):1364-1369. doi:10.1007/s00266-018-1187-x
25. Huang YL, Wallace CG, Hsiao YC, et al. Botulinum Toxin to Improve Lower Blepharoplasty Scar: A Double-Blinded, Randomized, Vehicle-Controlled Clinical Trial. *Aesthet Surg J*. 2021;41(9):1003-1010. doi:10.1093/asj/sjab024
26. Khatery BHM, Hussein HA, Abd-El-Raheem TA, El Hanbuli HM, Yassen NN. Assessment of intralesional injection of botulinum toxin type A in hypertrophic scars and keloids: clinical and pathological study. *Dermatol Ther*. 2022;35(10):e15748. doi:10.1111/dth.15748
27. Samarth A, Budamakuntla L, Shilpa K. The Use of Botulinum Toxin-A as an Adjunctive Treatment for Facial Atrophic and Hypertrophic Scars After Surgical Correction. *J Cutan Aesthet Surg*. 2022;15(2):131-134. doi:10.4103/JCAS.JCAS_8_21
28. Austin E, Koo E, Jagdeo J. The Cellular Response of Keloids and Hypertrophic Scars to Botulinum Toxin A: A Comprehensive Literature Review. *Dermatol Surg*. 2018;44(2):149-157. doi:10.1097/DSS.0000000000001360
29. Çalıskan E, Gamsızkan M, Açıkgöz G, et al. Intralesional treatments for hypertrophic scars: comparison among corticosteroid, 5-fluorouracil and botulinum toxin in rabbit ear hypertrophic scar model. *Eur Rev Med Pharmacol Sci*. 2016;20(8):1603-1608.