INTRODUCTION

The Coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), wreaked havoc on the entire globe. A new hope to overcome the pandemic has arisen following the approval of messenger RNA (mRNA) vaccines against SARS-CoV-2. The two authorized mRNA COVID-19 vaccines, BNT162b2 and mRNA-1273, are chemically modified vaccines expressing the perfusion spike glycoprotein of SARS-CoV-2 packaged in lipid.

Botulinum toxin type A (BTA) is a neurotoxin that is produced by Clostridium botulinum. It induces reversible muscle paralysis by inhibiting nanoparticles. With more than 90% of individuals achieving a satisfactory humoral response, mRNA COVID-19 vaccines displayed promising immunogenicity and efficacy results among immunocompetent subjects. BTA is used widely for facial cosmetic and therapeutic purposes such as blepharospasm, chronic migraine, and strabismus. Due to the favorable efficacy and predictable adverse events of BTA, its use continued during the COVID-19 pandemic.
Two cases of subacute hypersensitivity reaction to BTA following COVID-19 vaccination were recently reported. This observation might suggest that an immune response targeting BTA might ensue after COVID-19 vaccination. While it is tempting to assume that such an immune response might interfere with the effectiveness of BTA, the influence of COVID-19 vaccination on the outcomes of BTA remains to be determined.

The aim of this retrospective study was to assess the influence of BNT162b2 mRNA vaccine on the efficacy of BTA injections performed for aesthetic indications. This influence is assumed to be reflected by the latency between BTA injections before and after vaccination. To the best of our knowledge, this is the first study in the literature aiming to investigate this question. In addition, we sought to evaluate the safety of BTA following BNT162b2 vaccine.

2 | MATERIALS AND METHODS

A retrospective cohort study was conducted to follow patients undergoing BTA treatment who completed two doses of BNT162b2 mRNA vaccine (Comirnaty, Pfizer-BioNTech). mRNA vaccines were included in this study as they are the only vaccines that are available in the country. The current study was conducted in a primary oculoplastic clinic, adhering to the principles of the Declaration of Helsinki.

Patients were eligible for inclusion if the following criteria were fulfilled: (i) undergoing at least two BTA treatments before and two BTA treatments after COVID-19 vaccination, (ii) BTA injections are exclusively indicated by aesthetic purposes, (iii) completing two doses of BNT162b2 vaccine at least 30 days prior to BTA injection, (iv) attending the clinic at least four times between January 1, 2020, to January 31, 2022. Patients who suffered from COVID-19 disease were excluded from this study.

All eligible patients were injected with BTA in the frontalis muscle, glabella, and lateral periorbital bilaterally to correct forehead and crow’s feet wrinkles by the same physician (SHA). The same units were injected for the same area before and after the vaccine. Injections were conducted under sterile conditions and without local anesthetics. BTA mixture was injected after mixing it with 2.5 ml of 0.9% sodium chloride and 500 U BTA (Dysport, Ipsen Biopharm Ltd, United Kingdom). The exclusive indication for additional BTA injections was the reappearance of wrinkles and dissatisfaction with previous BTA injection outcomes.

The medical files of eligible patients were retrospectively screened. The following variables were retrieved: age, sex, past medical history, dates of COVID-19 vaccine, number of BTA injections prior to and following COVID-19 vaccine, the average interval between BTA injections pre- and post-COVID-19 vaccine, and the need for correction following BTA injection. Average interval between BTA injections represents longevity of the treatment and was selected as an indicator of its effectiveness. If a patient received more than two BTA injections, the average interval between all injections was calculated. In addition, a telephone questionnaire was conducted to all included patients whether a socioeconomic factor affected their clinical visits and whether a time lag occurred between the disappearance of the BTA and their clinical visits.

Categorical variables were described using frequencies and percentages, whereas continuous variables were described using means and standard deviations (SD). Comparison between different subgroups was performed using the chi-square test and t-test for categorical and continuous variables, respectively.

3 | RESULTS

Forty-five healthy participants were included in the current study. The mean (SD) age was 48.3 (8.9) years (range 36–72 years), and 40 (88.9%) patients were females.

Figure 1 illustrates the distribution of the mean intervals between BTA injections before and after getting vaccinated against COVID-19. The mean (SD) interval between BTA injections before completing COVID-19 vaccination was estimated at 118.64 (22.73) days (range, 90–200 days), whereas the same interval after getting vaccinated was 95.95 (12.24) days (range, 75–120 days). The average interval between BTA injections was significantly shorter after getting vaccinated as compared to the interval prior to the beginning of the vaccination campaign (p < 0.001). Moreover, the intervals between BTA injections in the medical records were the same as the intervals from the patient-based questionnaire.

The injection procedure was eventless in all study participants. None of the injected patients developed swelling, erythema, or...
The current study attested that BNT162b2 vaccine is associated with shortening the interval between BTA injections. This observation probably mirrors a decreased effectiveness of BTA injection after being exposed to COVID-19 mRNA vaccine.

Botulinum toxin type A is typified by a favorable efficacy and predictable adverse events rendering it one of the most commonly used treatments for cosmetic procedures. A systematic review of the literature investigated hypersensitivity reactions triggered by cosmetic injections prior to COVID-19 pandemic. Hypersensitivity reactions were reported merely in three patients after BTA injection and were considered as type I immediate hypersensitivity reactions. The longevity and response of BTA injection after these immunological responses were not longitudinally evaluated.

In 2021, two cases of subacute hypersensitivity reaction against BTA following COVID-19 vaccination were reported by Guo et al. Both patients were previously BTA injected prior to the pandemic without adverse effects. They were treated with corticosteroids and antihistamines and recovered without any sequela. A case of severe hyperalgesia during BTA injection in a patient 1 week following COVID-19 infection was recently published. The presumed mechanism was increased pro-inflammatory cytokine levels secondary to COVID-19 infection, including IL-6, which may cause allodynia or thermal hyperalgesia. Both publications recommended postponing BTA injection at least 1 to 2 months after COVID-19 vaccination or infection.

Our study demonstrated a significant shortening of the interval between BTA injections after getting vaccinated against COVID-19. Since patients undergoing BTA treatment for aesthetic considerations perform recurrent and periodic injections in accordance with the clinical response, it is conceivable to assume that shortening the latency between BTA injections mirrors a reduction in the effectiveness of BTA. This assumption is further substantiated by the fact that the same clinician evaluated the entire study population and made the clinical decisions, thus arguing against the existence of selection bias.

The precise pathomechanism underlying this observation is yet to be investigated. Extracutaneous therapeutic features of BTA were discussed to be utilized in the treatment of SARS-CoV-2 infection. These include increasing platelet counts and enhancing antigen presentation and macrophages-mediated phagocytosis, which contribute to the elimination of virulent factors. It remains to be determined whether these systemic properties exert a role in the reduced efficacy of BTA after COVID-19 vaccine. The rapid accumulation of two case reports of BTA-associated hypersensitivity reactions after COVID-19 vaccine opposes the extremely rare nature of this phenomenon, as shown by a systematic review screening the literature before the pandemic. This implies that the COVID-19 vaccine might possess an immunogenic nature that facilitates mounting an immune response against BTA. Such an immunological reaction might alter the therapeutic function of BTA and decreases its effectiveness, thus necessitating more frequent injections. Further immunoserological studies are warranted to investigate neutralizing antibodies targeting BTA.

The current study sheds light on a timely and clinically relevant question that has not been addressed yet. Owing to the uniformity of injection technique and clinical decision-making by the same plastic surgeon, the probability of selection and ascertainment biases is very low. Loss to follow-up was negligible, which corroborates the validity of our findings. Our study, however, is limited by its relatively small sample size. Larger study populations are necessary to reproduce our findings. In addition, it may be of interests to evaluate the influence of COVID-19 disease on the efficacy of BTA, and to compare it to the BNT162b2 vaccine group in the future.

The current study provides a novel insight into the fact that BNT162b2 vaccine might confer reduced effectiveness of BTA. This conclusion was drawn by the significantly shorter interval between BTA injections required to maintain the clinical response. In light of the severe and ongoing COVID-19-associated morbidity and mortality, vaccination should not be discouraged. On the contrary, physicians and patients should be aware that there might be a diminished efficacy of BTA injections after COVID-19 vaccination. Further research is warranted to delineate the mechanism accounting for our observation. Studies originating from other ethnic populations are critical to reproduce our findings.

**AUTHOR CONTRIBUTIONS**

S.H.A and A.M. designed the research study. S.H.A, A.M., M.H., and K.K. performed the research and read and approved the final manuscript. S.H.A, M.H., and K.K. analyzed the data. S.H.A and K.K. wrote the paper.

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None.

**CONFLICT OF INTEREST**

None of the other authors have any conflicts of interest to declare.

**DATA AVAILABILITY STATEMENT**

Data is available in the medical records of the patient.

**ETHICAL APPROVAL**

This study adhered to the principles of the Declaration of Helsinki.

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