The Effect of Climate on the Dose Requirements of Botulinum Toxin A in Cosmetic Interventions

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Background: Botulinum toxin A to the glabella is a popular cosmetic intervention. Functional musculature differences may arise from chronic behavioral adjustment to high sun exposure levels, requiring greater doses. This could affect clinical practice globally. This study investigated the effect of climate on real-world doses.

Methods: The authors conducted a comparative cohort study using data from a registry from a single provider practicing across two centers: the United Kingdom and Malta. They classified one center as low sun exposure (United Kingdom winter month treatment) and the other as high sun exposure (Malta summer months). Patients were followed up once every 3 weeks and received top-up doses until full clinical paralysis was achieved. To standardize the comparison, the study included only women aged 35 to 60 years undergoing glabellar botulinum toxin treatment by experienced clinicians following standard procedures from 2012 to 2019. Smokers, those not seeking maximal paralysis, those documented as not compliant with posttreatment advice, those with colds or fevers, and those with broken cold supply chains were excluded. Univariable and multivariable analyses were undertaken.

Results: A total of 523 patients were included: 292 "high-sun" patients and 231 "low-sun" patients. Mean total doses were significantly higher in the high-sun group (29.2 units versus 27.3 units; $P = 0.0031$). When correcting for age in multivariable analysis, the low-sun group still had lower total dose requirements ($P = 0.00574$).

Conclusion: Patients injected with glabellar botulinum toxin in high-sun climates may have significantly increased dose requirements to achieve maximal paralysis. *(Plast. Reconstr. Surg.* 154: 57e, 2024.)

CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, III.

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THERAPEUTIC

Botulinum toxin intramuscular injection is a well-established treatment in cosmetic practice, with proven efficacy and safety.[1–3] There are eight distinct serotypes (botulinum toxin A through G), but only botulinum toxin serotype A (BoNT-A) and botulinum toxin serotype B are generally used in clinical practice, and only BoNT-A is approved for cosmetic use.[2,4] There is a range of BoNT-A products on the market. Robust, randomized, doubled-blinded trials with large patient cohorts do not support the superiority of one product over the other.[5–8] Nevertheless, clinicians anecdotally noted differences in efficacy, and other studies tried to explain these, evaluating differences in diffusion profiles, protein load, reconstitution solutions, injection volumes, and postinjection protocols. In two large reviews critically evaluating the available literature on these parameters, most differences in efficacy could ultimately be traced back to differences in dosing.[2,9] Adjusting doses when different products are used is complicated by the fact that unit and volume doses are not directly interchangeable between different products. This seems to have led to a string

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of falsely presumed correlations between the characteristics of a product and its efficacy that was ultimately caused by differences in dosing, with a higher dose proving to be more effective.[10]

The only other published parameters that consistently have a significant effect are muscle mass,[11–13] sex,[14–17] age,[18,19] and ethnicity.[20,21] Higher muscle mass requires higher doses to achieve the same results. Differences in effectiveness by sex, age, and ethnicity are also at least partially mediated by muscle mass. Men have on average more muscle mass, muscle mass declines with age, and there are differences in muscle mass between ethnicities.[2] All of this must be taken into consideration when choosing the correct dose for a patient. Anecdotally, even in very homogenous patient groups, there seem to be differences in the required doses, suggesting that other parameters, not yet identified in the literature, influence the efficacy of BoNT-A.

The glabella was chosen for the purposes of this study, as it remains the most common area to be treated in Aesthetic Virtue clinics, with little anatomical variation between patients. The muscles injected include procerus (responsible for the horizontal movement and rhytides) and depressor and corrugator supercilii. Furthermore, it was the first area approved for cosmetic facial injections, and at the time of the start of data collection, it was the only facial area approved.

We hypothesized that functional musculature differences may arise from chronic behavioral adjustment to high sun exposure levels, leading to greater dose requirements, and that sunlight itself could affect the efficacy of the toxin. This study investigates the effect of climate on real-world doses of BoNT-A used to achieve glabellar paralysis.

PATIENTS AND METHODS

This two-center, single-provider, comparative cohort study involved secondary use of anonymized prospectively collected data from patients injected into the glabellar complex from 2012 to 2019. One center was classified as low sun exposure (United Kingdom winter months treatment) and the other as high sun exposure (Malta summer months). To avoid muscle mass bias, only female patients were included. In addition, to obtain homogenous patient cohorts and minimize the potential for confounders, only nonsmokers between the ages of 30 and 60 years with Glogau grade 2 rhytides[22] and full animation of the glabella complex at the start of the treatment (Medical Research Council muscle strength grade 5) were included. Exclusion criteria were patients with a cold or fever or who developed a cold or fever within 2 weeks after injection, men, smokers, patients who did not want maximal paralysis as a final result, patients who admitted to not adhering to the posttreatment instructions, or whether the cold supply chain of the used toxin was broken. This study met the definition of service evaluation, which does not require ethical approval in the United Kingdom.[23]

Intervention

All injections were performed by experienced clinicians who had been injecting BoNT-A for years before the start of this study. For initial injections, 20 units of BoNT-A (Allergan) were injected into five sites in the glabellar complex.[24] Bacteriostatic saline (2 mL per 100 units) was used for reconstitution. Only toxins with a documented, unbroken cold supply chain were used. Full paralysis of the glabellar complex was checked at 3 weeks after injection, as part of routine clinical practice. If full paralysis was not achieved, top-ups with varying units (5 to 20 units) were performed depending on the degree of paralysis between the muscles. Routinely, patients were then seen again at 3 weeks or sent photographs with a maximal attempt to frown, based on their convenience. Top-ups and 3-weekly evaluations were repeated until full clinical paralysis was achieved.

Outcome and Statistics

Primary outcomes are the required top-up doses and the total dose to achieve full paralysis. The secondary outcome was the number of treatments to achieve full paralysis. The t test for continuous variables, Mann-Whitney U test for the categorical variable "number of treatments needed to achieve full results," and univariable and multivariable analyses were undertaken to assess differences between the two groups (high sun versus low sun). Values of $P < 0.05$ were considered significant. All statistical analyses were performed using R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 523 patients were included, with 292 patients in the high-sun group and 231 in the low-sun group. Table 1 summarizes the key findings for both groups. In both groups, more than half of the patients needed a top-up dose to achieve full paralysis (68.5% in the high-sun group and 61.5%

Table 1. Key Findings for Both Cohorts with *P* Values for Differences between the Two Groups

	High Sun (%)	Low Sun (%)	P[a]
No.	292	231	
Mean age ± SD, yr	46 ± 7	48 ± 7	0.0039[b]
No. of treatments needed			0.1032
1	81 (27.74)	83 (35.93)	
2	200 (68.49)	142 (61.47)	
>3	11 (3.77)	6 (2.60)	
Mean top-up dose ± SD, units	9.30 ± 7.95	7.06 ± 7.36	0.0009[b]
Mean total dose ± SD, units	29.23 ± 7.85	27.25 ± 7.32	0.0031[b]

[a]The difference in the number of required sessions to achieve full results was tested with Mann-Whitney *U* test; all other parameters were tested with *t* tests.
[b]Statistically significant.

in the low-sun group), although this difference was not significant ($W = 36032$; $P = 0.1032$). All patients achieved full paralysis with the treatment protocol used. Both mean top-up and total doses were significantly larger in the high-sun group ($P = 0.0009$ and $P = 0.0031$, respectively). The distribution of the total doses for maximal paralysis across the two groups is displayed in Figure 1.

The two groups differed in age, with the low-sun group being older ($P = 0.0039$). However, in univariable linear regression, age did not significantly affect top-up dose and total dose requirements ($P = 0.087$ and $P = 0.121$, respectively).

The average top-up dose in the low-sun group was 2.24 units less than in the high-sun group ($P = 0.001$), and the total dose was 1.98 units less ($P = 0.0033$). When correcting for age on multivariable analysis, the low-sun group still had significantly smaller top-up and total dose requirements. Average top-up or overall doses throughout the years did not vary significantly (Table 2).

DISCUSSION

This study supports there being a difference in the doses of BoNT-A needed for glabellar paralysis among patients with different levels of sun exposure. Patients subject to less sun exposure require a lower dose than patients with high sun exposure, and this was present and persisted when controlling for potential confounders. Although robustly demonstrated, the difference in doses seen here was small, and so may not directly impact at a health economic level, as the difference would not necessarily change the number of vials used. However, it may be of relevance to training and protocolization of treatments. Rigid protocols about doses and distributions may lead to undertreatment if applied in sunnier climates. This might be more of an issue than waste from overtreatment from applying protocols to less sunny climates.

Commonly discussed relationships between dose and efficacy revolve around different products, their diffusion profiles, protein load, reconstitution solutions, injection volumes, and postinjection protocols. Even though none of these were consistently found to have a significant

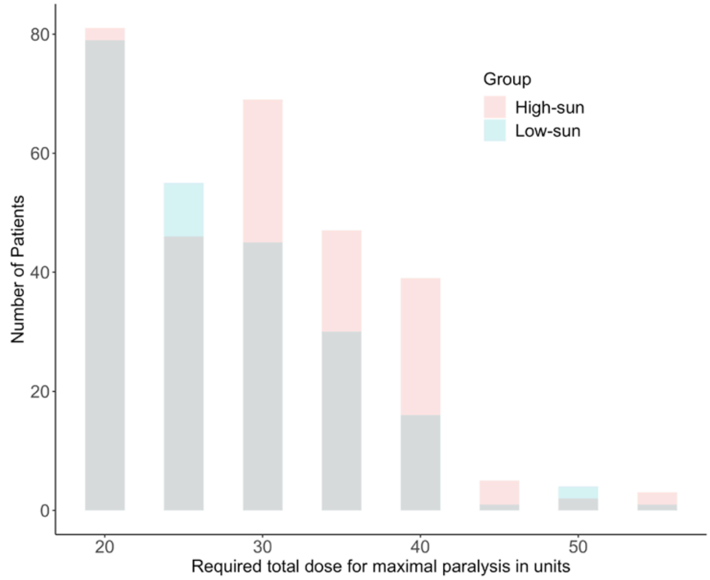

Fig. 1. Required total dose in units of BoNT-A to achieve maximal paralysis by group (high sun versus low sun).

Table 2. Univariable and Multivariable Analysis for Age as a Continuous Variable and Group (High Sun versus Low Sun) for Required Top-Up Dose and Total Dose to Achieve Maximal Results and Univariable Analysis to Investigate the Influence of Injection Techniques over Time on Dose Requirements

	Univariable Analysis			Multivariable Analysis		
	β	*P*	R^2	β	*P*	R^2
Top-up dose						
Age	0.08	0.087	0.0037	−0.06	0.1864	0.0201
Group (low sun vs. high sun)	−2.24	0.001[a]	0.0187	−2.13	0.0019[a]	
Year	−0.11	0.139	0.0023			
Total dose						
Age	−0.07	0.121	0.0027	−0.06	0.2304	0.0153
Group (low sun vs. high sun)	−1.98	0.0033[a]	0.0145	1.88	0.0057[a]	
Year	−0.11	0.161	0.0019			

[a]Statistically significant.

impact in robust clinical trials,[2,9] we took steps to eliminate them as potential confounders in this study. All patients received the same product, reconstituted in the same manner with equal doses and volumes to predefined injection sites. They were all instructed in the same manner after injection, and patients who were noncompliant with the instructions were excluded, although it could be said that compliance was self-reported by the patient, and there was no objective control mechanism.

Some studies suggest an influence of injection technique on the efficacy.[25] All injections in our patient cohort were performed by experienced clinicians, all injecting with a highly consistent technique by the time we started this study. This is further supported by the fact that neither average total dose nor average top-up dose changed significantly across either patient cohort when looking at each year individually.

Other parameters found to influence the dose are age, sex, muscle mass, and ethnicity. To reduce muscle mass bias, only female patients were included. Although age ranged from 35 to 60 years and showed different distributions in both groups, it was not significant on univariable analysis, and the two groups still showed significant differences in average required doses when controlled for age in multivariable analysis.

It could be argued that the two patient cohorts have acquired differences that may explain the findings. Malta has a much higher sun exposure all year round than the United Kingdom, and the glabellar complex is the primary muscle group involved in squinting. Chronic behavioral adjustment to high sun exposure levels such as squinting may lead to functional musculature differences, which could explain the higher dose requirements in this group. Although there is no study directly evaluating facial muscle mass in relation to sun exposure, there are studies highlighting the importance of vitamin D in muscle growth and strength.[26,27] Furthermore, studies identified that different contracture patterns of the glabellar complex results in different BoNT-A requirements.[28,29] In addition to this, we hypothesized that increased sun exposure and the ongoing attempt to recruit the paralyzed muscles might interfere with the efficacy of the toxin. To the best of our knowledge, only one study has investigated this hypothesis. Wei et al. evaluated the purposeful activation of the masseter muscle after injection with BoNT-A. However, their study found that increased activation after injection can improve the efficacy.[30]

Several studies have shown that diffusion of the toxin is inversely proportional to the density of receptors at the injection site, which can vary from patient to patient.[31,32] Although there is no practical way to control for this, the toxin not only binds to receptors in muscles but also to receptors on sweat glands. Sweat gland hypertrophy can result from health acclimation.[33] Patients living in Malta are exposed to much higher average temperatures year-round than the people in the United Kingdom, and hypertrophic sweat glands and the resulting higher receptor density could influence the required doses of the toxin to achieve maximal paralysis. Furthermore, higher temperatures can result in increased vasodilation and tissue perfusion rates. It could also be argued that, consequently, the diffusion potential or even systemic uptake rather than targeted, localized effects could reduce the efficacy of the toxin. A clear relationship between temperatures and increased diffusion of the toxin could not be found in the literature. There are studies showing that the toxin uptake into neurons takes much longer at 20°C.[34,35] However, this temperature is not achieved naturally and would only result from external cooling, which the patients were not instructed to do after injection and would therefore not explain the observed differences.

Sunlight might also directly interfere with the toxin. To our knowledge, only one study to date has investigated this. Sycha et al. evaluated the effects of ultraviolet light type B (UVB) exposure postinjection on dermal BoNT-A.[36] Their study found a significant and stable decrease of the effect of intradermal BoNT-A on local sudomotor activity of the sweat glands. Their results suggested that UVB only affects the intercellular BoNT-A excess before absorption into the neurons but not the intracellular portion of the toxin. Based on these findings, they recommended limiting sun exposure after injection, especially during the first 2 weeks until most of the toxin is internalized into the neurons.[36] There are several limitations to this study that limit the generalizability of their findings. The patient cohort for the study was very small ($n = 6$), which does not allow for the detection or correction of confounders. They also used abobotulinum toxin (Dysport) and injected the toxin exclusively intradermally. A significant amount of UVB gets absorbed in the epidermis and dermis, and does not penetrate deeper. Therefore, it is still unknown what effects it would have on the toxin injected into deeper layers.[36] Nevertheless, this is the first and only study investigating the degradation of the toxin in situ caused by UV radiation and seems to support our findings. Future studies should try to replicate these findings with larger cohorts, evaluate the intramuscular applications, and research the effects of UVA radiation.

Finally, a few studies have described that patients who had previous injections can have longer lasting effects, therefore lengthening the intervals or decreasing doses required in-between sessions.[8,25] Although we included only patients with Glogau grade 2 rhytides in our study who had full animation of the glabellar complex at the start of the treatment (Medical Research Council muscle strength grade 5), we did not fully control for this potential confounder and did not exclude patients with previous treatments.

Our study has limitations. A potential bias is the unblinded design, with the same person assessing the success of the initial injection and all top-up injections; and the subsequently required doses to achieve maximal paralysis were also defined by this person. Ethnicity was not evaluated or controlled for. The population of Malta is very homogenous, mainly made up of Maltese with less than 5% foreigners.[37] In contrast, the demographics of the United Kingdom and especially London, where the injections were performed, are much more diverse. According to the 2011 census, London has the smallest percentage of White people across England and Wales, and 40.2% of its residents identified as Asian, Black, mixed, or other ethnic groups.[38] Furthermore, London patients may have traveled from other residential locations, including abroad, for treatment. Thus, their main sun exposure might be higher or lower than London's climate. The specific cohorts were available based on the nature of our team's practice. It provides an exploration of a potential effect, which could be verified in future studies. Lastly, R^2 was low for univariate and multivariate regression. However, this does not necessarily suggest poor fit of the models, as there can be other reasons for a low R^2 despite good model fit. R^2 can get arbitrarily driven close to 0 depending on how certain parameters within the regression analysis are set and therefore needs to be interpreted cautiously.[39]

CONCLUSIONS

Patients living in regions with high sun exposure and temperatures have significantly higher average top-up dose and total dose requirements for glabellar BoNT-A treatment to achieve maximal paralysis. Treatment protocols may need to account for the climate in which treatments are being undertaken to achieve more predictable results.

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DISCLOSURE

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