Brazilian Dental Journal (2021) 32(4): 31-44
http://dx.doi.org/10.1590/0103-6440202104127

ISSN 0103-6440

Efficacy and safety of Botulinum toxinA for improving esthetics in facial complex: A systematic review

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Aim: To evaluate efficacy and safety of Botulinum toxinA for improving esthetics in the facial complex and correlating them to the dosage and side effects through a systematic review. Methods: A literature search was performed using PubMed, Medline, Web of Sciences, and Scopus databases. Quality of studies was appraised through the GRADE system. This review follows the 'Preferred reporting items for systematic review and meta-analysis protocols' (PRISMA-P) 2015 statement. Efficacy was analyzed through improvement rate and effect sizes. Graphical comparison of efficacy and ocular adverse effects (adverse effects around the eye) at various anatomical locations was made by calculating the average improvement rate and adverse events. Results: Twenty-five studies were included in this systematic review after application of the inclusion criteria. Moderate to severe cases in glabellar, lateral canthal, and forehead regions showed higher improvement rates between 20U to 50U, with an effect lasting up to 120 days. Gender and age seemed to have a direct effect on efficacy. Headaches were the most common adverse effect, followed by injection site bruising; all adverse effects resolved within 3-4 days. Conclusions: Treatment with Botulinum toxinA to enhance esthetics of facial complex is efficient and safe at all recommended dosages. Presence of complexing proteins influenced the efficacy of BoNT-A. undesirable muscular adverse effects around the eyes were more predominant when treating the glabellar region. There was no correlation found between the BoNT-A dosage and side effects, however, an increase in dosage did not always lead to an increase in efficacy.

Key Words: Botulinum toxinA, esthetics, facial, efficacy, adverse effects

Introduction

The face being a critical feature of communication and appearance is profoundly affected by self-perception and self-esteem(1). A couple of the common esthetic complaints encountered in the facial region are facial wrinkles and a gummy smile(2). Hyperfunctional muscles in the facial region is one of the prominent causes of these functional and esthetic concerns(3). Surgical approaches to resolve these can be invasive, irreversible and may not be ideal for all patients. Over the years, more techniques that are conservative have emerged for resolving these esthetic concerns(4). One such technique involves the use of a neurotoxic protein called Botulinum toxin A (BoNT-A)(5). This toxin inhibits the docking of acetylcholine vesicles on the inner surface of the cellular membrane, which prevents the release of acetylcholine into the neuromuscular junction. This mechanism prevents the activation of muscle fibers, and resulting in reduction of tone in the injected muscle(5,6).

The Food and Drug Administration (FDA) of the United States of America approved BoNT-A for cosmetic use in the facial region in 2002 (Submission tracking no.: BL 103000/5000). Following this approval, BoNT-A gained popularity amongst medical and dental practitioners for facial cosmetic use. As with any exogenous compound injected into the human body, BoNT-A has shown to manifest adverse effects. Some of the adverse effects seen in past studies using BoNT-A are headaches, pain at injection site, and mild bruising(7). Undesirable muscular adverse effects are esthetically compromising and can impact the phycological well-being of the patient. It also can prolong the treatment recovery time(1,2). Hence, a detailed understanding of the causative factors might aid in producing safer experiences for patients undergoing BoNT-A treatment. The current review focuses on the adverse effects of BoNT-A along with their possible causes.

BoNT-A as a cosmetic treatment modality has been widely discussed in literature reviews (2,8). However, the co-relation between dosage and efficacy is unclear. Dastoor et al. (2007) study discussed

a controversial correlation between dosage and efficacy. They identified that a higher dosage sometimes resulted in higher efficacy and conversely it sometimes resulted in a lower efficacy(8). Hence, their study could not establish the pattern of dosage curve. Another, review by Gadhia and Walmsley (2009), looked into the efficacy and safety profiles in the region of facial complex. Their study also showed a high variance in dosage recommendations making the correlation between the effect and dosage nuclear (7). Parameters such as muscle type, muscle volume, age, gender, and the presence of complexing proteins within the BoNT-A compound might have the potential to influence the efficacy of BoNT-A(6,10,11). This puts forth the need to validate these parameters when considering efficacy. Therefore, this review addresses these concerns by including the parameters that influence efficacy and it aims to assess the efficacy and safety profile of BoNT-A for improving esthetics of the facial complex.

Materials and methods

The current systematic review was conducted in accordance with the protocols underlined in the Preferred reporting items for systematic review and meta-analysis protocols' (PRISMA-P) 2015 statement(12). The population, intervention, comparison, and outcomes for this systematic review were as follows: Population - Patient requesting esthetic treatment in facial complex; Intervention- BoNT-A; Control – Placebo; Outcome – Improved esthetics of facial complex.

The databases of Medline (1996 to 2017), Scopus, PubMed and Web of Sciences were used to conduct a literature search. The search syntax was as follows:
((“botulinum toxinA” OR “botulinum toxin*” OR “acetylcholine release inhibitors*”) AND (“esthetic, dental” OR “facial muscle*” OR “hyperactive facial muscle” OR smiling OR skin OR “gummy smile” OR “excessive gingival display” OR chin OR “chin projection”) AND (efficacy OR efficiency) AND (“treatment outcome” OR “adverse effects” OR “side effects” OR safety))

Reference lists of trials and BoNT-A review studies were also hand searched. The initial search resulted in a total of 1531 articles. Removal of duplicates and application of inclusion criteria reduced the number of studies to 530 unique studies. Primary screening of titles, abstracts, and exclusion criteria further reduced the number of studies to 54. Upon full text review 33 studies were excluded due to inconsistency in data collection and result expression, resulting in 25 studies that were included in this study. Full text studies were screened by 2 reviewers (RG and VB) to evaluate the quality of the studies. They appraised the included studies by applying the GRADE system published by the British Medical Journal Clinical (13). The score was determined by a sum of the individual scores in the following category: type of study, quality, consistency, directness, and effect size. Quality of studies were graded as high (at least 4 points overall), moderate (3 points), low (2 points), and very low (1 point or less).

The studies included in this systematic review have only used BoNT-A as a treatment option for improving esthetics in the facial region. Included studies are from 1996 to 2017 which involve adults (18 years or above) and which compared the efficiency of BoNT-A with placebos in the Glabellar, lateral canthal, and forehead regions. Studies that lacked a placebo control group but had a moderate/high GRADE score (13), were included as there was a lack of placebo-controlled studies for gummy smile and chin projection groups. Case reports having a sample size of 5 or below, and non-English studies were excluded. Studies that did not provide either improvement rate or pre-treatment and post-treatment mean values were also excluded. Results of the search and final sample size derivation is explained through a PRISMA flowchart (Figure 1).

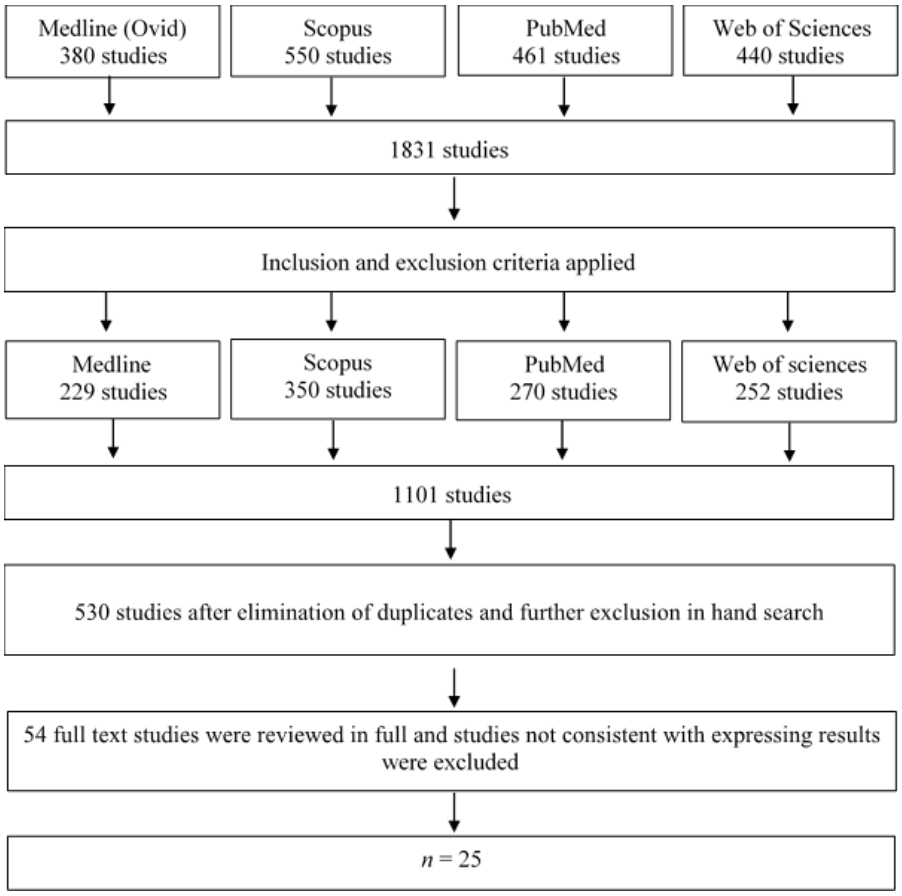

Figure 1: PRISMA Data flow of literature search

Results

Studies recorded efficacy data on various scales, hence only the improvement rate at maximum frown expressed in terms of percentage improvement were considered for graphical comparison. In 17(14-30) out of 25 studies across fixed time intervals: 7 days (1 week), 30 days (4 weeks) and 112-120 days (16 weeks). Seven (31-37) studies provided pre-treatment and post-treatment data. One(38) study provided mean percentage improvement. The studies that provided pre- and post-treatment data were useful in calculating the net improvement through Cohen's effect size. Cohen suggested that ≤ 0.2 be considered a 'small' effect size, 0.5 represents a 'medium' effect size and ≥ 0.8 a 'large' effect size(39).

Twenty(14-32,34) placebo-controlled studies and 5(33,35-37,38) prospective studies were included in this review paper. These studies used Abobotulinum toxin/BonTA (Dysport, Ipsen:France), OnaBotulinum toxinA (Botox, Allergan Inc:U.S.A), DaxiBotulinum toxinA and IncoBotulinum toxinA (Xeomin, Merz Pharmaceuticals GmbH:Germany) for the following facial muscles: Glabellar lines (corrugator supercilii, procerus, depressor supercilii)(*n*=12), lateral canthal lines (orbicularis oculi) (*n*=3), glabellar lines and forehead lines (*n*=3), lateral canthal lines and forehead lines (corrugator supercilii, procerus, depressor supercilii and frontalis) (*n*=1), gummy smile (upper lip elevator muscles) (*n*=4), chin projection (mentalis muscle) (*n*=2) (Tables 1 & 2).

Table 1: GRADE score of the reviewed studies

Authors	Type of study	Quality	Degree of consistency	Directness	Effect size	Score	Grade
Ascher et al., 2004[14]	4	0	1	0	N.A	5	High
Brandt et al., 2009[15]	4	0	1	0	N.A	5	High
Carruthers et al., 2014[16]	4	0	1	0	N.A	5	High
Carruthers et al., 2013[17]	4	0	1	0	N.A	5	High
Carruthers et al., 2002[18]	4	0	1	0	N.A	5	High
Carruthers et al., 2003[19]	4	0	1	0	N.A	5	High
Carruthers et al., 2017[20]	4	0	1	0	N.A	5	High
Fagien et al., 2007[21]	4	0	1	0	2	7	High
Harii and Kawashima,	4	0	1	0	N.A	5	High
Kane et al., 2009[23]	4	0	1	0	N.A	5	High
Kerscher et al., 2015[24]	4	0	1	0	N.A	5	High
Lowe et al., 2002[25]	4	0	1	0	N.A	5	High
Lowe et al., 2005[26]	4	0	1	0	N.A	5	High
Rzany et al., 2006[27]	4	0	1	0	N.A	5	High
Solish et al., 2016[28]	4	0	1	0	N.A	5	High
Wu et al., 2009[29]	4	0	1	0	N.A	5	High
Keen et al., 1994[30]	4	0	1	0	N.A	5	High
Beer et al., 2005[31]	2	0	1	0	N.A	3	Moderate
Feng et al., 2015[32]	4	0	1	0	N.A	5	High
Hsu and Frankel, 2017[33]	2	0	1	0	0	3	Moderate
Lowe et al., 1996[34]	4	0	1	0	1	6	High
Polo, 2008[35]	2	0	1	0	1	4	High
Suber et al., 2014[36]	2	0	1	0	N.A	3	Moderate
Sucupira and Abramovitz et	2	0	1	0	0	3	Moderate
Mazzuco and Hexsel, 2010[38]	2	0	1	0	N.A	3	Moderate

The quality of reporting of the studies by using the GRADE system in this review are noted in Table 1. The studies reviewed were analyzed in 2 different categories. The first group of studies, which expressed the efficacy of BoNT-A through percentages of improvement rate, are represented in Table 2. Twenty(14-16,18,19,20,22-23,25-29,31-37) studies used BoNT-A with complexing proteins and 3(17,20,24) studies used BoNT-A free of complexing proteins. Feng et al. (2015) used Hengli Botulinum toxinA (HBTX-A, China), in which the complexing protein presence was not specified(21). In 2 papers, the BoNT-A manufacturer used was not specified(30,38). The remaining studies are represented in Table 3 and they expressed efficacy of BoNT-A through means and standard deviations recorded by observers. Effect sizes were calculated in these studies based on the means and standard deviations provided. Sixteen studies(14-29) were used to calculate average improvement rate at 30 days in the glabellar, lateral canthal and forehead region at different doses and the values were plotted on the graphs (Figures 2 to 4) for easier correlation. The placebo commonly used was either sterile preservative-free normal saline or all constituents present in the active group without the active ingredient Botulinum toxin. Efficacy of BoNT-A with complexing proteins (AboBotulinum toxinA and OnaBotulinum toxinA) was compared with that of BoNT-A free of complexing proteins (Daxibotulinum toxinA, IncoBotulinum toxinA) at various doses whenever possible. Correlation of anatomical and ocular adverse effects (adverse effects around the eye) were also assessed by calculating the percentage of reported ocular adverse effects across the studies.

Table 2: Improvement rates adverse effect incidence expressed in percentage

Authors Year	Number of subjects	Subjects Mean age (years)	Dosage	Efficacy - outcome Improvement rate (%)							Rank
				Day 7 - 8		Day 30		Day 112-120		AE	
				a	b	a	b	a	b	(%)	
[G] Ascher et al., 2004[14]	*n*=119	48.6	25U			72.4	51.7			14.7	High
		50.9	50U			93.1	75.9			8.8	
		48.8	75U			75.9	75.9			0	
		48.3	Placebo			13.3	6.7			5.8	
[G] Brandt et al., 2009[15]	*n*=158	43.1	50U			89.3	75.7	24.2	20.2	47.0	High
		42.7	Placebo			3.9	9.8	4.1	6.1	40.0	
[L] Carruthers et al., 2014[16]	*n*= 445	46.7	24U	≈76	≈52	≈89	≈78	≈58	≈43	39.1	High
		46.2	Placebo	≈9	≈9	≈12	≈13	≈15	≈28	33.0	
[G] Carruthers et al., 2013[17]	*n*=276	46.6	20U*			87.5	71.2			7.1	High
		46.4	Placebo			9.8	10.9			2.2	
[G] Carruthers et al., 2002[18]	*n*=264	44.7	20U	82.3	69.1	83.7	79.4	26.2	67.6	28.1	High
		44.3	Placebo	4.9	29.4	1.6	23.5	0	35.0	33.3	
[G] Carruthers et al., 2003[19]	*n*=273	47.7	20U	≈65.0	≈78.	76.7	69.9	24.4	52.7	26.9	High
		46.4	Placebo	≈7.0	≈22	≈5.0	≈18	2.9	≈35	37.2	
[G] Carruthers et al., 2017[20]	*n*=268	49.0	20U*			100	100	88.2	82.4	24.3	High
		50.0	40U*			100	100	97.4	89.7	26.4	
		47.0	60U*			100	100	85.4	87.8	32.2	
		50.0	20U			97.6	95.2	80.5	70.7	29.8	
		50.0	Placebo - 52			0	2.9	0	2.9	13.0	
[G] Feng et al., 2015[21]	*n*=488	44.2	10U-183	71.5		73.7		30.6		28.3	High
		42.8	20U-183	85.7		87.4		60.6		26.7	
		44.3	Placebo			2.4				5.7	
[G] Harii & Kawashima, 2008[22]	*n*=135	45.7	10U	81.8	84.1	86.4	84.1	23.8	35.7	67.4	High
			20U	88.6	81.8	88.6	93.2	31.8	45.5	75.0	
			Placebo	0	0	0	2.1	0	0	59.2	
[G] Kane et al., 2009[23]	*n*=816	49.2	50U			96.0	96.0			31.0	High
			60U			90.0	89.0				
			70U			81.0	85.0				
			80U			61.0	76.0				
		48.7	Placebo			0-9	9-0			28.0	
[G,F,L] Kerscher et al., 2015[24]	*n*=156	47.4	20U*(G)	98.1		95.1		41.7		61.9	High
			10-20U*(F)	93.3		91.3		41.7			
			12U*(L)	92.3		93.2		30.1			
		47.5	Placebo (G)	5.9		6.3		2.2		54.9	
			Placebo (F)	9.8		4.2		6.5			
			Placebo (L)	17.6		14.6		15.2			
[L] Lowe et al., 2002[25]	*n*= 60	46.9	6U			≥89.0				11-25	High
		49.5	12U			≥95.0					
		46.3	18U			≥95.0					
		N.S	Placebo			N.S					
[L] Lowe et al., 2005[26]	*n*=162	47.0	3U	36.4	40.0	45.5	42.4	27.3	19.4	17.0	High
			6U	51.5	37.5	51.5	48.4	33.3	40.6	17.0	
			12U	64.5	55.2	87.1	73.3	41.9	40.0	15.0	
			18U	60.6	45.2	84.8	51.6	39.4	25.8	16.0	
			Placebo	12.5	16.7	15.6	14.8	9.4	6.3	18.0	
[F] Rzany et al., 2006[27]	*n*=110 for 3	46.6	10U			86.1				4.1	High
			Placebo			18.9				5.4	
	n=111 for 5	46.4	10U			86.3				13.8	
			Placebo			7.90				10.5	
[F] Solish et al., 2016[28]	*n*=175	46.8	30U			84.7	89.8			33.9	High
			40U			92.9	91.2			35.1	
			Placebo - 59			13.6	15.3			25.4	
[G] Wu et al., 2009[29]	*n*=227	41.7	20U	91.7	91.1	94.1	95.2	52.9	52.9	32.3	High
		44.1	Placebo	3.5	1.7	3.5	0	1.7	0	19.3	
[F,L] Keen et al., 1994[30]	*n*=11	42.8	16U (F)			100	90.9			27.2	High
			Placebo-			N.S	N.S				
[g] Mazzuco and	*n*=16	N.S	5-15U			75.1				6.2	Moderate

Values expressed as % unless otherwise indicated

F =- Forehead region, G = Glabellar region, L = Lateral canthal region, g = Gingival region

*AE= adverse effects (% incidence rate), ≈ = approximate value, * Bont-A free of complexing protein, N.S=not specified, U= Units, , a= at maximum frown; b= at rest*

Table 3: Improvement rate expressed in terms of effect sizes and adverse effect incidence expressed in percentage

Author/s Year	Assessment used	Number of subjects	Mean age (years)	Dosage	Baseline		Week 1		Week 4		Week 12		Effect size	AE (%)	Rank
					a	b	a	b	a	b	a	b			
[C] Beer et al., 2005[31]	Change from baseline	*n*=20	N.S	5U			-0.8 ± 1.2		-1.3 ± 1.2		-0.8 ± 0.9		1.1	N.R	Moderate
				Placebo			-0.2 ± 1.2		-0.2 ± 1.1		-0.1 ± 0.8		0.1		
[G] Fagien et al., 2007[32]	i) Maximum contraction ii) Rest	*n*=70	44.0	20U	2.8 ± 0.9	1.7 ± 0.8			0.7 ± 0.8	0.5 ± 0.8	1.2 ± 0.6	0.4 ± 0.5	i) 5.5 ii) 2.7	1.5	High
				Placebo	2.8 ± 0.4	1.7 ± 0.9			2.8 ± 0.6	1.7 ± 0.9			i) 0 ii) 0		
[C] Hsu and Frankel, 2017[33]	i) Vertical position of pogonion ii) Horizontal position of pogonion	*n*=11	46.3	12-15U	1.4 ± 0.2	0.1 ± 0.1			1.4 ± 0.18	0.1 ± 0.1			i) 0.2 ii) 0.4	N.R	Moderate
[G] Lowe et al., 1996[34]	i) Glabellar line length ii) Depth at maximum frown	*n*=30	N.S	10U	54.2 ± 10	7.5 ± 2.1			30.8 ± 23.6	2.03 ± 2.3	37.9 ± 11.9	3.0 ± 1.7	i) 2.3 ii) 2.7	20	High
				Placebo	62.7 ± 15.1	8.1 ± 3.02			63.7 ± 15.9	8.6 ± 3.0	64.9 ± 16.6	8.1 ± 3.2	i)0.1 ii)0.0		
[g] Polo, 2008[35]	Gingival display	*n*=30	24.4	2.5U	5.2 ± 1.4		0.1 ± 1.1						3.6	10	Moderate
[g] Suber et al., 2014[36]	Gingival display	*n*=14	34.0	4-6U	4.8 ± 0.9		0.7 ± 1.3						3.5	N.R	Moderate
[g] Sucupira and Abramovitz, 2012[37]	Gingival display	*n*=52	N.S	1.95U	3.6		0.6						0.7	N.R	Moderate

- Indicates improvement of mean from baseline
N.S = not specified
N.R = not recorded
C = Chin region
g = Gingival region
G = Glabellar region

Efficacy

Efficacy was assessed through improvement rate at maximum frown and rest for facial lines and at maximum smile for excessive gingival display, by both the investigator and the patient. BoNT-A showed a higher improvement rate compared to placebo at all given doses and the effect reached its peak at 30 days (Table 2). The average calculated from the improvement rate at maximum frown for the 3 regions (Glabellar, lateral canthal and forehead region) at 30 days are plotted on Figure 2. Improvement rate for the glabellar region increased from 20U to 50U, but beyond that they showed a decline. In the lateral canthal region an increase in the improvement rate was observed for injections of 3U to 12U. The improvement rate curve remained relatively flat up to 15U and then showed a slight decline (Figure 3). Highest improvement rate (92.9%) was found in the forehead region and was seen for 40U of BoNT-A with complexing proteins. However, BoNT-A free of complexing proteins showed a similar improvement rate of 91.3% for a dose of 10U to 20U (Figure 4). To standardize the results Cohen's effect size was calculated for all the available pre- and post- study measurements (Table 3). BoNT-A resulted in a large magnitude of effect, while placebo showed zero/very small effect (Table 3). The mean ages of patients included in this review ranged from 41 to 50 years and they ranked moderate (grade 2) to severe (grade 3) on the facial wrinkle scale. Carruthers et al. (2013) compared efficacy of BoNT-A in patients below 50 years of age and above 51 years of age and they found a statistically significant difference ($p > 0.05$)(19).

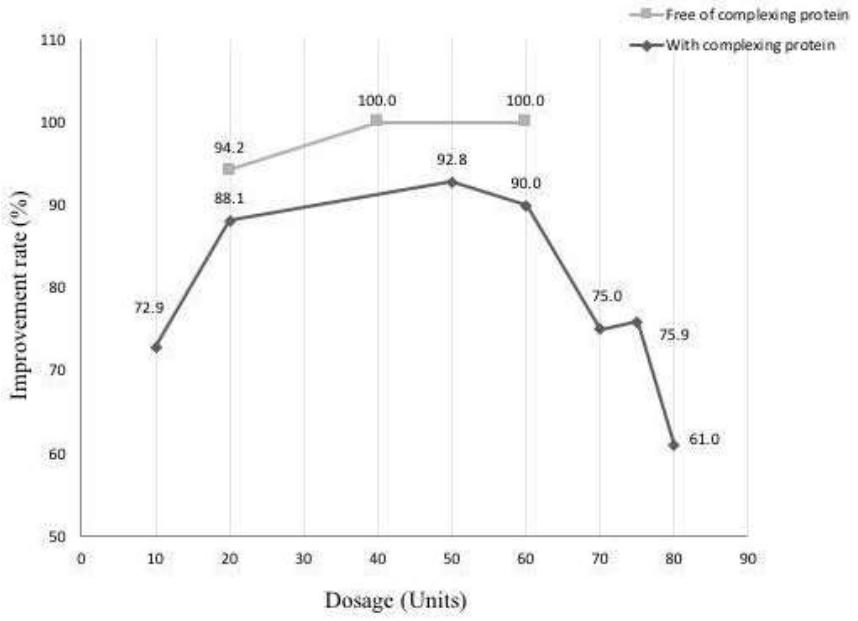

Figure 2: Summary of average improvement rate of complexing protein free and complexing protein rich BoNT-A at 30 days in the glabellar region

Adverse effects

The most frequently reported adverse effects in the glabellar and lateral canthal regions were headache, nasopharyngitis, and abnormal sensation in the eye. None of these were statistically different when comparing the BoNT-A group and the placebo group ($p > 0.05$)(18,29). Most headaches lasted only a few hours and all resolved successfully(18,21,23,32,34). The calculated percentages of general adverse effects (minor and major effects) across all the studies are represented in Table 2 and 3.While treating glabellar region, undesirable muscular adverse effects were only seen around the eyes, such as eyelid ptosis/blepharoptosis and drooping of the eyebrow. Reported adverse effects in the region of the forehead were painful injection site, eyebrow dropping, change in shape of eyebrow, and a heavy forehead(30). The average values of the undesirable muscular adverse effects around the eyes from the 20 studies are graphically represented in Figure 5. There were no cases of blepharoptosis or eyelid ptosis in the lateral canthal region for both BoNT-A and the placebo(16,25,26). Amongst 4(35-38) studies on gummy smile, 1 study reported 1 case of asymmetric smile and 1 case of difficulty in smiling while treating posterior gummy smile(38). Polo (2008)(35) reported greater pain at the injection sites and twitching by 4 subjects, while 1 subject reported headache and dizziness after the injection session. Both

were transient and lasted for only a few hours(35). Studies in the region of the chin did not record any significant adverse effects, with all the observed effects being mild in severity and short lived(31,33).

Discussion

Efficacy of BoNT-A in improving esthetics has been proven in individual studies, however evaluating efficacy at different doses is not well defined. A limitation of this review is that long-term efficacy and safety could not be concluded due to irregular and short follow-up periods in the available studies. In addition, there was an absence of comparative trials in the region of chin and gingiva. Similarly, adverse effects and efficacy of the BoNT-A free of complexing protein could not be concluded due to shortage of studies.

Studies included in the current review treated patients with moderate to severe cases of facial wrinkles and BoNT-A was efficacious at all treated ages(14-32,34). However, there are various factors that affect the efficacy of BoNT-A therapy. One of these factors is the viscoelasticity of human skin, which varies with anatomical region and age(10). Carruthers et al. (2003) found that the magnitude of wrinkle improvement with BoNT-A was consistently less for patients above 51 years of age, compared with those under 50 years of age(19). One possible reason for this is the slow degeneration of elastin and collagen networks as the dermis thins with age(10). It is also important to consider the fact that muscle content decreases with age, which might make the action of BoNT-A less effective(40). Additionally, with increase in age the skin's ability to recover from stress decreases(10). This might enhance wrinkles after the effect of BoNT-A fades. This fact was not evaluated in this review, as all the included studies involved a first-time BoNT-A intervention. It would be interesting to evaluate the change in efficacy on further intervention.

Another factor affecting efficacy is the gender of the subject. Fagien et al. (2007) study showed the highest effect size (5.5 at maximum smile) (Table 3). When looking at the demographics of the population, this study included only female subjects(32). Muscle morphology and fiber content vary between genders, as women have more of Type I muscle fibers, which are slower in contraction(41). These muscle fibers might show a better treatment effect with BoNT-A as it further relaxes the muscle(41,42). This could be one parameter for the clinician to consider while evaluating outcomes.

A factor influencing efficacy that is also worth noting is the presence of complexing proteins in the BoNT-A compound. In the glabellar region, BoNT-A free of complexing proteins showed a higher improvement rate than BoNT-A which contained complexing proteins at all doses (20, 40, 50U) (Figure 2). The improvement rate showed a decline for doses of 60U to 80U, establishing a negative correlation at higher doses(14-20,22,29)(Figure 2). This data could not be analyzed for lateral canthal lines (Figure 3) and excessive gingival display as complexing protein free BoNT-A was not used in these studies(16,25,26,35-38). However, for the studies that looked at the forehead region, the average improvement rate (Figure 4) showed that complexing protein free BoNT-A resulted in higher values for efficacy for a comparatively lower dosage than the BoNT-A with complexing proteins. The complexing protein free solutions of 10U – 20U studied by Kerscher et al. (2015) displayed higher improvement rate to 30U (84.7%) complexing protein containing BoNT-A studied by Solish et al. (2016)(24,28). Correlation between the complexing protein content in the BoNT-A and efficacy could not be firmly established due to insufficient data(24,27,28). This interesting correlation can be an area of interest for further research.

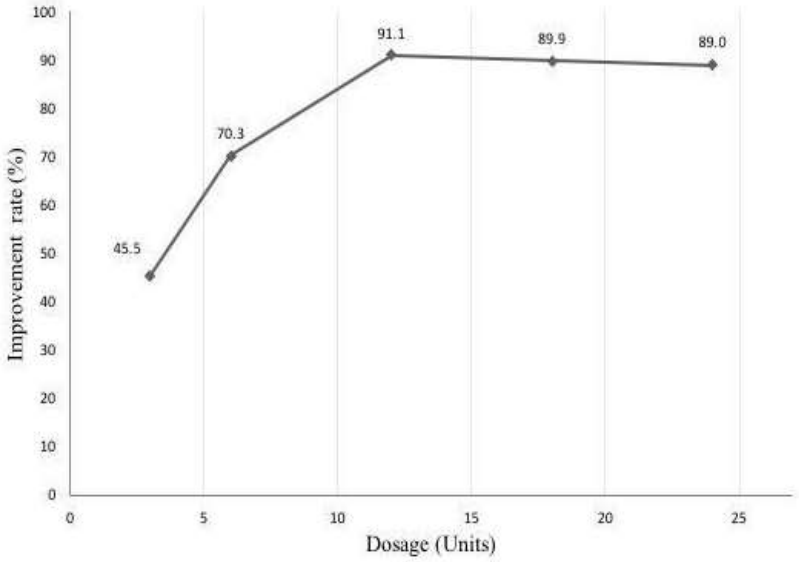

Figure 3: Summary of average improvement rte of complexing protein rich BoNT-A at 30 days in the lateral canthal region

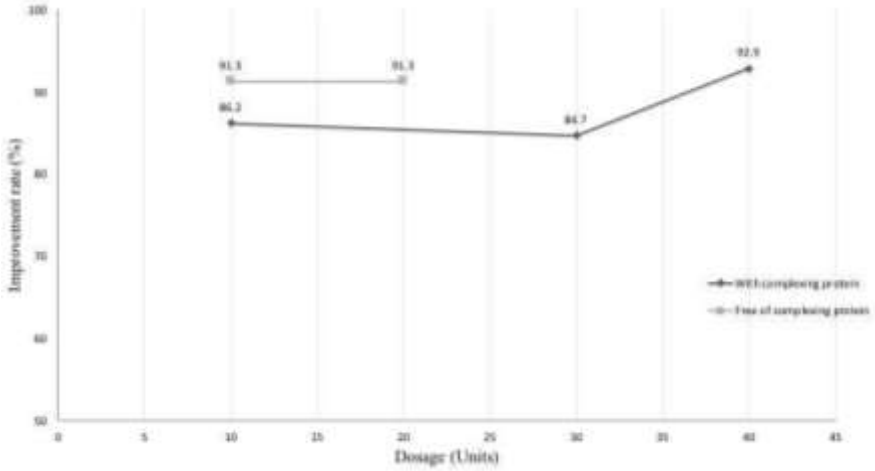

Figure 4: Summary of average improvement rate of complexing protein free and complexing protein rich BoNT-A at 30 days in the forehead region

The studies reported that the effect of BoNT-A appeared to be higher than the placebo, with statistical superiority achieved at several time points, up to day 120(14,20,22,28,29) (Table 2). Reduction in glabellar, lateral canthal, and forehead lines at maximum frown and rest occurred within 1-week post-injection. The glabellar line severity showed greater improvement during maximum contraction than at rest. However, the results were sustained longer at rest(14,17-19). The studies also show a good agreement between investigator's ratings and participant's rating(15,20,22,28,29). Average improvement rate calculated at maximum frown in glabellar region at 30 days showed the highest improvement rate (92.8%) for 50U protein containing BoNT-A (Figure 2). Studies in the region of lateral canthal lines used lower doses of BoNT-A when compared to glabellar region. The highest improvement rate was observed for 12U (91.05%) (26) (Figure 3). In the region of the forehead, 10U five-injection pattern (3 glabellar injection points with 2 additional forehead points) showed similar results when compared with a 3-injection pattern (3 glabellar injection points)(27). In contrast, Kerscher

et al. (2015) supported the view of treating the glabellar region along with the forehead to increase efficacy(24).

Another use of BoNT-A is in the treatment of excessive gingival display, which is also referred to as 'gummy smile'. Mazzuco & Hexsel (2010) believed that gummy smile is mainly caused due to extensive contraction of 2 group of muscle fibers namely - levator labii superioris alaeque nasi muscle (anterior gummy smile) and zygomatic muscles (posterior gummy smile)(38). Follow-up period for BoNT-A treatment in the included studies ranged from 2 weeks(36,37) to 24 weeks(35). Effect sizes of improvement calculated from results gathered before and after BoNT-A treatment for Polo (2008), Suber et al., (2014) and Sucupira & Abramovitz (2012) were 3.64, 3.45 and 0.65 respectively (Table 3). The study by Mazzuco & Hexsel (2010) did not provide improvement rates for patients before BoNT-A injection. The authors represented their results via improvement percentages that ranged from 15.8% to 100%(38) (Table 2). Gingival display gradually reverted from 2 weeks post-injection through 24 weeks(35). This wide range of results makes us question the underlying etiology; as skeletal based etiology cannot be masked with BoNT-A treatment(5,36). Dose recommendations for gummy smile is dependent on the type and extent of gingival display. Further investigations into the action of BoNT-A on excessive gingival display is required to consider treatment with BoNT-A as an independent treatment modality.

Only 2 studies observed the effects of BoNT-A on chin projection(31,33). The effects of BoNT-A were observed to be more prominent than the placebo in both studies(31,33). Projection of the chin showed peak response at 4 weeks(31) (Table 3). Chin contour and the position of the pogonion improved in all mild cases selected when toxin was applied to the mentalis muscle (33). Further investigations into the action of BoNT-A on chin projection is required to consider treatment with BoNT-A as an independent treatment modality.

Although the rate of occurrence of adverse effects was high across the included studies, they were considered to be mild and reversible. The incidence of adverse effects was recorded in both the BoNT-A and placebo groups. Of the 25 studies included in this review, 4 studies recorded no adverse effects caused by the BoNT-A or the placebo intervention(31,33,36,37). BoNT-A showed higher incidence of adverse effects than placebo in 11 studies(14-17,20-24,27-29). Seven studies reviewed multiple doses of BoNT-A and found no statistical difference in the incidence of adverse effects among the different doses of BoNT-A(14,20,21,23,25,28). Headaches were the most common adverse effect followed by injection site bruising, which resolved within 3-4 days(14-20,23,28,29). Three studies assessing the effect of BoNT-A in glabellar lines reported undesirable muscular effects around the eyes. The adverse effects were resolved within an average duration of 20 to 40 days without medication(18,19,27). Average incidence of undesirable muscular effects around the eyes were calculated for each intervened region (Figure 5). Lateral canthal region had no adverse effects around the eyes for both BoNT-A and placebo (16,25,26). The glabellar region had the highest incidence (8.5%), followed by the forehead region (4.9%). However, it is difficult to isolate the adverse effects to the forehead region, as 3 out of the 4 studies treated the forehead region along with the glabellar region and they showed high adverse effects incidence rates around the eyes (Table 2)(24,27,28). Keen et al. (1994) treated the forehead region with the lateral canthal region and showed the least abnormality around the eyes (0.9%) (30)(Figure 5). Adverse effects like bruising and headache did not vary based on the anatomical site treated, whereas, undesirable muscular abnormalities were specific to the glabellar region. Lateral canthal line injections showed no such adverse effects despite the proximity to the ocular region. It was also interesting to note that BoNT-A showed higher incidence rates of adverse effects than placebo for both the glabellar and forehead regions (Figure 5). Hence, anatomical location and the depositing solution (BoNT-A or placebo) are potential risk factors for overall adverse effects with undesirable muscular abnormalities especially around the eyes.

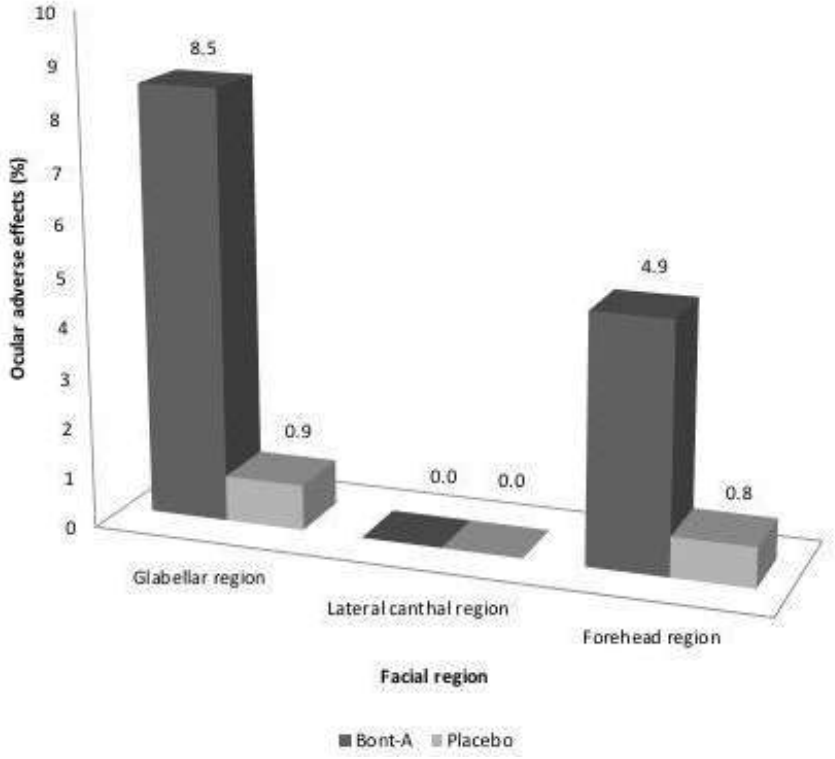

Figure 5: Summary of average ocular adverse effects with BoNT-A and placebo

It appears that case selection plays a major role in the efficacy outcome of the treatment with BoNT-A. It is also important to understand that an increase in dosage does not always lead to an increase in efficacy. For excessive gingival display and chin projection the treatment with BoNT-A could not be concluded as an independent treatment modality due to lack of studies. Further studies on the adverse effects of BoNT-A in different regions of the face would be beneficial in understanding their cause. This systematic review has identified a possible correlation between the efficacy outcome of the treatment with the age of the patient. However, more studies evaluating this concept are required to confirm this correlation. BoNT-A free of complexing protein showed higher efficacy at all given doses. However, more studies evaluating this would be helpful in knowing the magnitude of improvement in efficacy. Knowing the factors influencing the improvement rate will help the clinician in case selection and communication with the patient of the potential adverse effects associated with BoNT-A treatment. The clinician should be aware and cautious about the possibility of undesirable muscular effects around the eyes when treating the glabellar and forehead regions.

Conclusions

Within the limitations of this systematic review the following conclusions can be made:

- BoNT-A was found to be effective in improving esthetics in the facial complex involving glabellar, lateral canthal and forehead regions.
- Treatment with BoNT-A was observed to be safe in all the facial complex areas.
- Presence of complexing proteins influenced the efficacy of BoNT-A. Undesirable muscular adverse effects around the eyes were more predominant when treating the glabellar region.
- There was no correlation found between the BoNT-A dosage and side effects.
- An increase in BoNT-A dosage did not always lead to an increase in efficacy.

Resumo

Objetivo: Avaliar a eficácia e segurança da toxina botulínica-A para melhorar a estética no complexo facial e correlacioná-la com a dosagem e os efeitos secundários através de uma revisão sistemática. Métodos: Foi realizada uma pesquisa bibliográfica utilizando bases de dados PubMed, Medline, Web of Sciences, e Scopus. A qualidade dos estudos foi avaliada através do sistema GRADE. Esta revisão segue a declaração "Preferred reporting items for systematic review and meta-analysis

protocols" (PRISMA-P) 2015. A eficácia foi analisada através da taxa de melhoria e da dimensão dos efeitos.A comparação gráfica da eficácia e dos efeitos adversos oftalmológicos (efeitos adversos em torno do olho) em vários locais anatômicos foi feita através do cálculo da taxa média de melhoria e dos eventos adversos. Resultados: Vinte e cinco estudos foram incluídos nesta revisão sistemática após a aplicação dos critérios de inclusão. Casos moderados a graves em regiões glabelares, canais laterais e testa mostraram taxas de melhoria mais elevadas entre 20U a 50U, com um efeito que durou até 120 dias. O sexo e a idade mostraram ter efeito direto na eficácia. As dores de cabeça foram o efeito adverso mais comum, seguido de hematomas no local da injecção; todos os efeitos adversos foram resolvidos em 3-4 dias. Conclusões: O tratamento com toxina botulínica-A para melhorar a estética do complexo facial é eficiente e seguro em todas as dosagens recomendadas. A presença de proteínas complexas influenciou a eficácia do BoNT-A. Os efeitos adversos musculares indesejáveis à volta dos olhos foram mais predominantes no tratamento da região glabelar. Não foi encontrada qualquer correlação entre a dosagem de BoNT-A e os efeitos secundários, contudo, um aumento da dosagem nem sempre levou a um aumento da eficácia.

References

1. Castle DJ, Honigman RJ, Phillips KA. Does cosmetic surgery improve psychosocial wellbeing? Med J Aust 2002;176:601-603.

2. Nayyar P, Kumar P, Nayyar PV, Singh A. Botox: broadening the horizon of dentistry. J Clin Diagn Res 2014;8:25-29.

3. Binder WJ, Blitzer A, Brin MF. Treatment of hyperfunctional lines of the face with Botulinum toxin. Dermatol Surg 1998;24:1198-1205.

4. Chang C-S, Kang GC-W. Achieving ideal lower face esthetic contours: combination of tridimensional fat grafting to the chin with masseter Botulinum toxinA injection. Aesthet Surg J 2016;36:1093-1100.

5. Aoki KR. Evidence for antinociceptive activity of Botulinum toxinA in pain management. Headache 2003;43:9-15.

6. Blasi J, Chapman ER, Link E, Binz T, Yamasaki S, De Camilli P, Sudhof TC, Niemann H, Jahn R. Botulinum neurotoxin A selectively cleaves the synaptic protein SNAP-25. Nature 1993;365:160-163.

7. Gadhia. K and Walmsley A. D. Facial aesthetics: is botulinum toxin treatment effective and safe? A systematic review of randomised controlled trials. Br. Dent. J. 2009;207:E9.

8. Dastoor SF, Misch CE, Wang H-L. Botulinum toxin (Botox) to enhance facial macroesthetics: a literature review. J Oral Implantol 2007;33:164-171.

9. https://www.fda.gov - FDA approved drug products; Approval letters 2002, 2013, 2017

10. Takema Y, Yorimoto Y, Kawai M, Imokawa G. Age-related changes in the elastic properties and thickness of human facial skin. Br J Dermatol 1994;131:641-648.

11. Roepstorff C, Donsmark M, Thiele M, Vistisen B, Stewart G, Vissing K, et al. Sex differences in hormone-sensitive lipase expression, activity, and phosphorylation in skeletal muscle at rest and during exercise. Am J Physiol Endocrinol Metab 2006;291:1106-1114.

12. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew, M., & Stewart, L. A. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1-7.

13. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924

14. Ascher B, Zakine B, Kestemont P. A multicenter, randomized, double-blind, placebo controlled study of efficacy and safety of 3 doses of Botulinum toxinA in the treatment of Glabellar lines. J Am Acad Dermatol 2004;51:223-233.

15. Brandt F, Swanson N, Baumann L, Huber B. Randomized, placebo-controlled study of a new botulinum toxin type a for treatment of Glabellar lines: efficacy and safety. Dermatol Surg 2009;35:1893-1901.

16. Carruthers A, Bruce S, Coninck A, Connolly S, Paula G. Davis, Campo A, Somogyi C, Beddingfield F. Efficacy and safety of OnabotulinumtoxinA for the treatment of crows feet lines: A multicenter, randomized, controlled trial. Dermatol Surg 2014;40:1181-1190.

17. Carruthers A, Carruthers J, Coleman W, Donofrio L, Flynn T, Gold M, et al. Multicenter, randomized, phase III study of a single dose of IncobotulinumtoxinA, free from complexing proteins, in the treatment of Glabellar frown lines. Dermatol Surg 2013;39:551-558.

18. Carruthers J A, Lowe N J, Menter M A. A multicenter, double-blind, randomized, placebo-controlled study of the efficacy and safety of Botulinum toxinA in the treatment of Glabellar lines. J Am Acad Dermatol 2002;46:840-849.

19. Carruthers J D, Lowe N J, Menter M A. Double-blind, placebo controlled study of the safety and efficacy of Botulinum toxinA for patients with Glabellar lines. Plast Reconstr Surg 2003;112: 1089-1098.

20. Carruthers J, Solish N, Humphrey S, Rosen N, Muhn C, Bertucci V, Swift A, Carruthers A. Injectable daxibotulinumtoxinA for the treatment of Glabellar lines: A phase 2, randomized, dose-ranging, double-Blind, multicenter comparison with onabotulinumtoxinA and placebo. Dermatol Surg 2017;43:1321-1331.

21. Feng Z, Sun Q, He L,Wu Y, Xie H, Zhao G, Xu J, Yao C, Li H. Optimal Dosage of Botulinum toxin A for Treatment of Glabellar Frown Lines: Efficacy and Safety in a Clinical Trial. Dermatol Surg 2015;41:56-63.

22. Harii K, Kawashima M. A double-blind, randomized, placebo- controlled, two-dose comparative study of Botulinum toxinA for treating Glabellar lines in Japanese subjects. Aesthet Plast Surg 2008;32:724-730.

23. Kane MAC, Brandt F, Rohrich RJ. Evaluation of variable-dose treatment with a new US Botulinum toxinA (Dysport) for correction of moderate to severe Glabellar lines: results from a phase 3, randomized, double-blind, placebo-controlled study. Plast Reconstr Surg 2009;124:1619-1629.

24. Kerscher M, Rzany B, Prager W, Turnbull C, Trevidic P, Inglefield C, Efficacy and safety of IncobotulinumtoxinA in the treatment of upper facial lines: Results from a randomized, double-Blind, placebo-controlled, phase III study. Dermatol Surg 2015;41:1149-1157.

25. Lowe N J, Lask G, Yamauchi P, Moore D. Bilateral, double-blind, randomized, comparison of 3 doses of Botulinum toxinA and placebo in patients with crow's feet. J Am Acad Dermatol 2002; 47:834-840.

26. Lowe NJ, Ascher B, Heckmann M, Kumar C, Fraczek S, Eadie N. Double-blind, randomized, placebo-controlled, dose-response study of the safety and efficacy of Botulinum toxinA in subjects with crow's feet. Dermatol Surg 2005;31:257-62.

27. Rzany B, Ascher B, Fratila A, Monheit G, Talarico S, Sterry W. Efficacy and safety of 3- and 5-injec- tion patterns (30 and 50U) of Botulinum toxinA (Dysport) for the treatment of wrinkles in the glabella and the central Forehead region. Arch Dermatol 2006;142:320-326.

28. Solish N, Rivers J, Humphrey S, Muhn, Bhogal M, Caulkins C. Efficacy and safety of onabotulinumtoxinA treatment of forehead lines: A multicenter, randomized, dose-ranging controlled trial. Dermatol Surg 2016;42:410-419.

29. Wu Y, Zhao G, Li Y, Zhong S, Feng Z, Yang Q, Zhu X, Botulinum toxinA for the Treatment of Glabellar lines in Chinese: A Double-Blind, Randomized, Placebo-Controlled Study. Dermatol Surg 2009;36:102-108.

30. Keen M, Blitzer A, Aviv J. Botulinum toxinA for hyperkinetic facial lines: results of a double blind, placebo controlled study. Plast Reconstr Surg 1994;94:94-99.

31. Beer K, Yohn M, Closter J. A double-blinded, placebo-controlled study of Botox for the treatment of subjects with chin rhytids. J Drugs Dermatol 2005;4:417-422.

32. Fagien S, Cox S E, Finn J C, Werschler P, Kowalski J W. Patient reported outcomes with Botulinum toxinA treatment of Glabellar rhytids. A double blind, randomised, placebo-controlled study. Dermatol Surg 2007;33:2-9.

33. Hsu AK, Frankel AS. Modification of chin projection and esthetics with onabotulinumtoxinA injection. JAMA Facial Plast Surg 2017;19:522-527.

34. Lowe N J, Maxwell A, Harper H. Botulinum A exotoxin for Glabellar folds: A double-blind, placebo-controlled study with an electromyographic injection technique. J Am Acad Dermatol 1996; 35:569-572.

35. Polo M. Botulinum toxinA (Botox) for the neuro- muscular correction of excessive gingival display on smiling (gummy smile). Am J Orthod Dentofac Orthop 2008;133:195-203

36. Suber JS, Dinh TP, Prince MD, Smith PD. OnabotulinumtoxinA for the treatment of a "gummy smile". Aesthet Surg J 2014;34:432-437.

37. Sucupira E, Abramovitz A. A simplified method for smile enhancement: Botulinum toxinA injection for gummy smile. Plast Reconstr Surg 2012;130:726-728.

38. Mazzuco R, Hexsel D. Gummy smile and botulinum toxin: a new approach based on the gingival exposure area. J Am Acad Dermatol 2010;63:1042-1051.

39. Cohen, J. Statistical power analysis for the behavioral sciences. Hillsdale: Erlbaum Associates; 1988. 32-35p.

40. Grimby G, Saltin B. The aging muscle-Mini review. Clin Physiol 1983; 3:209-218.

41. Steffensen CH, Roepstorff C, Madsen M, Kiens B. Myocellular triacylglycerol breakdown in females but not in males during exercise. Am J Physiol Endocrinol Metab 2002;282:634-642.

42. Gollnick, P.D., R. B. Armstrong, C. W. Saubert IV, K. Piehl, and B. Saltin. Enzyme activity and fiber composition in skeletal muscles of untrained and trained men. J Appl Physiol 1972; 33:312-319.

Received: 22/11/2020
Accepted: 17/03/2021