

Article Original

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The present study was carried out at the Dermatology Ambulatory, Dermatology Clinic, Santa Casa de Belo Horizonte—Belo Horizonte (MG), Brazil.

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Conflict of interest: None

Double-blind randomized study performed with 4% lidocaine cream and vehicle in the application of type A botulinum toxin: analysis of the pain during the procedure and of the interference with the efficacy and duration of the effect

Estudo duplo-cego randomizado com lidocaína creme 4% e veículo na aplicação de toxina botulínica tipo A: análise da dor durante o procedimento e interferência na eficácia e duração do efeito

ABSTRACT

Introduction: For some patients, pain during the injection of botulinum toxin can represent a limitation for performing the procedure. There are doubts about whether the use of topical anesthetic decreases pain or interferes with the treatment's efficacy and duration of effect.

Objectives: To study the effect of 4% lidocaine cream in controlling pain during BoNT-A – Speywood Unit botulinum toxin application, comparing it to the vehicle. In addition, the study was aimed at verifying whether the cream influences the treatment's outcome and duration.

Methods: An experimental, prospective, double-blind, randomized study was carried out. The pain was assessed through a compartmentalized numerical rating scale (CNRS). The effect was assessed through a four-point contraction qualitative scale.

Results: After evaluating the pain scale, higher values were observed in the placebo group when compared to the group that used anesthetic, with statistical significance. Furthermore, there was no statistical difference in the efficacy and duration of effect over weeks 4, 8, 12, and 16.

Conclusions: BoNT-A – Speywood Unit toxin was effective and safe for the treatment of glabellar and frontal wrinkles. The use of topical anesthetics (4% lidocaine cream) reduced the pain during the procedure. In addition, there was no interference in the toxin's efficacy and effect duration.

Keywords: botulinum toxin type A; lidocaine; pain; therapy.

RESUMO

Introdução: A dor durante a injeção da toxina botulínica pode representar, para alguns pacientes, uma limitação à realização do procedimento. Há dúvidas se o uso de anestésico tópico diminui a dor ou interfere no efeito e duração do tratamento.

Objetivos: Objetiva-se estudar o efeito da lidocaína 4% creme no controle da dor durante aplicação da toxina botulínica BoNT-A – Speywood Unit, comparando-a ao veículo. Ademais, deseja-se verificar se o referido creme influencia o resultado e a duração do tratamento.

Métodos: Estudo experimental, prospectivo, duplo-cego e randomizado. A dor foi avaliada por escala de graduação numérica compartimentada (EGNC), e o efeito, pela escala qualitativa de contração de quatro pontos. Resultados: avaliando-se a escala de dor observaram-se valores maiores no grupo placebo quando comparado ao grupo que usou anestésico, com diferença estatisticamente significativa. Além disso, não houve diferença estatística na eficácia e na duração do efeito ao longo das semanas 4, 8, 12 e 16.

Conclusões: A toxina BoNT-A – Speywood Unit mostrou-se eficaz e segura para tratamento de rugas glabulares e frontais. A aplicação de anestésico tópico (lidocaína 4% creme) reduziu a dor durante o procedimento sem interferir na eficácia e duração do efeito da referida toxina.

Palavras-chave: toxinas botulínicas tipo A; lidocaína; dor; terapêutica.

INTRODUCTION

In 1817, Justinus Kerner first described the symptoms of a highly lethal, progressive paralysis associated with the ingestion of sausages, later known as botulism (from the Latin *botulus*, meaning sausage).¹ In 1895, Emile van Ermengen described the bacterial agent responsible for the disease and the agent's mechanism of toxic action.¹

Botulinum toxin is one of the most potent bacterial toxins known to date. It is produced by the *Clostridium botulinum*, a gram-positive anaerobic bacteria in the form of a spore, commonly found in the soil and in marine environments. Eight immunologically distinct serotypes have been identified, of which seven (A, B, C1, D, E, F, and G) are neurotoxins. Although all neurotoxins are able to reduce the release of acetylcholine by the motor plate, they vary in size, cellular biosynthesis, and mechanism of action. Serotype A has the greatest neuromuscular blocking potency, with rare systemic effects, and has been used for several years with various therapeutic objectives, and is the first to be manufactured for clinical use.² In 1980, the serotype described was introduced in medical practice for the treatment of strabismus.³

In 1982, after a multicentric study on the use of botulinum toxin type A for correcting strabismus and other facial muscle problems, one patient reported a reduction of glabellar wrinkles. This was the landmark case for the treatment of glabellar wrinkles with this product, with its results being published in 1988.⁴ Since then, botulinum toxin has seen increasing use, in isolation or associated with other facial rejuvenation techniques, and is currently one of the main procedures performed in dermatology practices.²

Several botulinum toxins are available in the market for clinical use: abobotulinumtoxinA (Dysport®, Ipsen Biopharm Limited—UK), onabotulinumtoxinA (Botox®, Allergan, Inc., Irvine, CA—USA), incobotulinumtoxinA (Xeomin® Merz Pharma, Frankfurt—Germany),⁵ Lanzhou type A—LBTXA (Prosigne, Cristália, China), among others.⁶ Botulinum toxin is manufactured from different strains of bacteria, undergoing various purification and stabilization processes, resulting in different chemical and biological properties.⁷ Abobotulinumtoxina (Dysport—Ipsen Biopharm Limited—UK), a derivative of botulinum toxin A, has been used in Europe for the correction or mitigation of facial wrinkles for over two decades, and in April 2009 its use was approved by the U.S. FDA. It is measured in Speywood Units (s.U.), and collectively referred to as BoNT-A (Speywood Unit).⁸ The product is sold in 300 s.U. and 500 s.U. vials.^{8,9}

Neuromuscular diseases, the use of aminoglycosides and anticholinergic drugs, pregnancy and lactation, and allergy to cow's milk are reported as contraindications. Unrealistic expectations are a relative contraindication and must be thoroughly evaluated by the physician.¹⁰

Some adverse effects associated with the use of botulinum toxin type A in the treatment of dynamic wrinkles in the upper third of the face have been reported: headache, facial edema, sensation of facial swelling, palpebral ptosis, eyebrow

ptosis, local pain and bruising, mild pruritus, and nausea.⁶ Local pain during the procedure is one of the most important and limiting side effects of the technique.^{6,10}

For some patients, pain during the injection of the toxin may represent a limitation for undergoing the procedure. Topical anesthetic in the form of a dermatological cream offers a non-invasive and relatively safe analgesia in various dermatologic procedures, such as cutaneous fillings, curettage, electrocauterization, laser, and botulinum toxin application, among others.^{11,12} The standard drug used is 4% lidocaine cream.¹²

The present study is aimed at determining whether the use of 4% lidocaine cream modifies pain during the application of botulinum toxin. In addition, it is intended to study whether the cream described affects the outcome and duration of treatment. The scarcity of scientific reports on the influence of the use of anesthetic cream and the effect of treatment justifies the study.

METHODS

An experimental, prospective, double-blind, randomized study was conducted at the Cosmetic Dermatology Ambulatory of the Dermatology Clinic of the Santa Casa de Belo Horizonte, Minas Gerais—Brazil, in ambulatorial patients bearing glabellar and frontal hyperfunctional facial lines, from April 20–August 24, 2012.

Fifteen patients were included in the study, which was submitted to the Ethics Committee in Research, and all participants signed a Free and Informed Term of Consent.

The patients were randomized: half the glabellar and frontal region received topical anesthetic cream (4% lidocaine cream) applied to the injection points, and the other half received a pure cream vehicle (Figure 1).

Each vial containing 500s.U. of abobotulinumtoxinA (Dysport® Ipsen Biopharm Limited—UK) was diluted in 2 ml of 0.9% saline solution without preservatives, resulting in a concentration of 250 s.U./ml. The syringe used in the dilution process was the BD ultrafine II 100UI, with all vials used being from the same batch (D31307 exp. date 05/2013). The application was performed immediately after dilution.

Each patient received 100 s.U. of BoNT-A treatment, as



FIGURA 1: Aplicação de lidocaína creme 4% (lado direito) e placebo (lado esquerdo)

follows: eight points in the frontal muscle, each with 5 s.U. (0.02 ml of the dilution), totaling 40 s.U., and five glabellar points, totaling 60 s.U. (one point in the procerus muscle—20 s.U., 0.08 ml of the dilution and four points in the corrugator muscles—10 s.U., 0.04 ml each point). BD ultrafine II 30 UI syringes were used for injection.

The study was double-blind and the applications of the topical anesthetic and the vehicle were carried out by a research assistant. The injection of botulinum toxin was performed by the main investigator physician, who was also responsible for assessing the effectiveness and duration of effect of the botulinum toxin, and was unaware of which area was treated with topical anesthetic or placebo.

The patients were assessed immediately after the procedure for the verification of pain, through the compartmentalized numerical grading scale (EGNC) 13 and in weeks 4, 8, 12, and 16, for the verification of efficacy and duration of treatment effect through photographic analysis and qualitative scale of four-point contraction.^{14,15}

The photographic analysis was carried out at each visit, with patients being photographed at rest and at maximal contraction of muscles. All photographs were taken with the same digital camera respecting parameters regarding body site, background, and distance.

The following inclusion criteria were observed: women with hyperfunctional glabellar and frontal lines, age over 18, and signature on a Free and Informed Term of Consent.

The following exclusion criteria were observed: pregnant and lactating women, patients with infection in the application site, patients with a known hypersensitivity to one of the contents of the anesthetic cream or botulinum toxin, patients with psychological instability and unrealistic desires regarding the treatment, patients who rely on facial mimicry for their work, patients bearing neuromuscular diseases such as myasthenia gravis or Eaton-Lambert syndrome, patients taking drugs such as aminoglycosides, penicillamine, kinins, or calcium channel inhibitors.

The studied variables—pain and degree of paralysis—were analyzed according to the presence or absence of anesthetic. Initially, a characterization of the sample by means of frequency distribution tables, and central tendency and variability measures, was performed. To check for differences between groups—control (placebo) and experimental (anesthetic)—the Pearson's Chi-square test or Fisher's exact test were employed for comparing proportions. To compare continuous variables, the nonparametric test of Mann-Whitney, suitable for comparing two groups, was used. The intraclass correlation coefficient was used to assess the correlation between the physician's and the patient's assessments. In all analyses a 5% significance level was adopted. The software SPSS 15.0 was used.

RESULTS

Fifteen patients 26- to 52-years-old (mean = 37-years-old) (Table 1) were evaluated. All were originally from urban regions (information not shown in the table). Most had photo-

TABLE 1: Descriptive statistics of evaluated patients' characteristics.

Phototype	N	%
II	3	20
III	7	46,7
IV	4	26,7
V	1	6,7
Phototype		
Ex-smoker	3	20
Smoker	1	6,7
Has never smoked	11	73,3
Previous skin disease		
Yes	3	20
No	12	80
Active skin disease		
No	4	26,7
Yes	11	73,3
Systemic disease		
No	5	33,3
Yes	10	66,7
Use of medicaments		
Yes	10	66,7
No	5	33,3
Previous toxin		
No	4	26,7
Yes	11	73,3
Adverse reaction to toxin application		
Yes	1	6,7
No	14	93,3
Age		
Mean	37,1	
Standard-deviation	9,3	
Maximum	26	
Maximum	52	
Percentile 25	29	
Median	35	
Percentile 75	47	

type III (46.7%) and 73.3% had never smoked. The prevalence of prior skin disease was 20% (73.3% of active disease and 66.7% of systemic disease). It is worth noting that the prior skin disease reported was acne, and the active disease was melasma. Arterial hypertension, asthma, lupus syndrome NEM-2 A were informed as systemic diseases. Pharmaceutical use was reported in 66.7% of cases, with contraceptives being the most frequently declared. The majority of respondents reported previous use of botulinum toxin (73.3%), and only one patient (6.7%) mentioned adverse reaction.

According to the results presented in Table 2, the values for the anesthesia duration were similar in both groups, with an average of 42 minutes (min = 30' and max = 54'). On the pain scale, higher mean and median values were observed in the placebo group when compared to the anesthetic group, with a sta-

TABLE 2: Comparison of anesthesia duration (in minutes) and pain scale between anesthesia and placebo groups.

	Anesthesia	Placebo	p-value
Duration of anesthesia			
Mean	42	42	1,000***
Standard-deviation	6.9	6.9	
Minimum	30	30	
Maximum	54	54	
Percentile 25	36	36	
Median	42	42	
Percentile 75	47	47	
Pain scale			
Mean	2.8	6.7	<0,001***
Standard-deviation	1.9	2.7	
Minimum	1	2	
Maximum	6	10	
Percentile 25	1	4	
Median	2	7	
Percentile 75	5	9	

*** Man-Whitney test

tistically significant difference (p-value < 0.05).

According to the results shown in Table 3, the physician's assessment in week 4 attributed a score of 4 to both the anesthetic and the placebo group. In that same week, according to the patients' evaluation, 80% of the anesthetic group and 86.7% of the placebo group received a score of 4. In week 8, in the physician assessment, both groups had a score of 4. In the evaluation of patients, 60% of the anesthetic group and 46.7% in the placebo group received that score. In weeks 12 and 16 an identical percentage was observed in the comparison between the two groups. The prevalence of a score of 4 was 13.3% in both weeks, both in the physician's and the patients' evaluations. There were no significant differences between groups in any of the evaluations (p-values > 0.05).

Table 4 shows the correlation between the assessments carried out by the physician and the patient. Due to the fact that it is a case of correlation between two ordinal variables (physician's assessment x patient's assessment) the intraclass correlation coefficient was used. For weeks 4 and 8 it was not possible to carry out an estimate due to the lack of variability in the physician's assessment (which attributed a score of 4 for all patients).

As for week 12, the correlation between the two assessments can be classified as moderate (0.517) and in week 16, the correlation was good (0.764).

DISCUSSION

The mean age of the treated group was 37 years (range = 26-52 years). This finding reinforces the use of botulinum toxin for the correction of hyperfunctional wrinkles of the facial muscles, which was more frequent in that age group. Only one patient (6.7%) reported adverse reaction to the treatment: local pain for three days in the points of application and a sensation

TABLE 3: Comparison of results between anesthesia and placebo groups.

	Anesthesia	Placebo	p-value
Week 4 (physician)	15	15	-
4	100%	100%	
Week 4 (patient)			
3	3	2	1.000*
	20%	13.3%	
4	12	13	
	80%	86.7%	
Week 8 (physician)			
4	15	15	-
	50%	50%	
Week 8 (patient)			
2	1	-	0.462*
	6.7%	-	
3	5	8	
	33.3%	53.3%	
4	9	7	
	60%	46.7%	
Week 12 (physician)			
3	13	13	1.000*
	86.7%	86.7%	
4	2	2	
	13.3%	13.3%	
Week 12 (patient)			
2	2	2	1.000*
	13.3%	13.3%	
3	11	11	
	73.3%	73.3%	
4	2	2	
	13.3%	13.3%	
Week 16 (physician)			
2	5	5	1.000*
	33.3%	33.3%	
3	8	8	
	53.3%	53.3%	
4	2	2	
	13.3%	13.3%	
Week 16 (patient)			
1	2	2	1.000*
	13.3%	13.3%	
2	5	5	
	33.3%	33.3%	
3	6	6	
	40%	40%	
4	2	2	
	13.3%	13.3%	

* Fisher's exact test

that the eyebrow had "sunk", a fact that was not confirmed by the dermatological clinical examination.

The visual analogue scale (VAS) and the compartmentalized numeric graded scale (EGNC) are commonly used to evaluate

TABLE 4: Assessment of the correlation between the physician's and the patients' evaluation per week.

Physician's evaluation	Patients' evaluation				CCI	
	1	2	3	4		
Week 4						
4			5	25	-	
			16.7%	83.3%		
Week 8						
4		1	13	16	-	
		3.3%	43.3%	53.3%		
Week 12						
3			4	20	2	0.517
		15.4%	76.9%	7.7%		
4		-	2	2		
		-	50%	50%		
Week 16						
2	4	4	2	-	0.764	
	40%	40%	20%	-		
3	-	6	8	2		
	-	37.5%	50%	12.5%		
4	-	-	2	2		
	-	-	50%	50%		

ICC = intraclass correlation coefficient

luate the intensity and severity of pain. Its use is justified by the reproducibility, and can be used both clinically and in research. The VAS consists of a straight, not numbered, ten-centimeter line, presented on a blank sheet, where the left end means an absence of pain and the right end, the greatest level of pain perceived by the patient. It is one of the most-used scales for measuring pathological pain for scientific purposes, since it allows for the minimizing of the subjective factor. Another variation of this type of scale would be the EGNC, which is numbered from 0 to 10, in ascending order, from the left to right within a frame. The minimum value measured means absence of pain, and the maximum value, a greater intensity of pain; the patient chooses the number that best represents his or her perception of pain.¹³

In developing countries, the best option is the EGNC scale, which presents greater ease of interpretation and makes it therefore more accessible to patients with a low level of education. In EGNC pain is expressed in numbers and patients tend to prefer it to quantify their pain; 13 in this study, it was the chosen scale for the assessment of pain.

There was a significant reduction in pain in the group treated with a topical anesthetic versus the one treated with the placebo: in the first, the average pain was 2.8 and in the second 6.7 ($p < 0.001$ %). The placebo group felt 2.4 times more pain than the anesthetic group. Anesthesia time ranged from 30 to 54 minutes (mean = 42 minutes).

Some studies tested the efficacy and safety of using topical lidocaine in botulinum toxin application. In 2010, Baumann et al. evaluated 26 patients regarding pain during botulinum toxin application, concluding that there is a statistically significant reduction in pain, with proven efficacy when applying 4%

lidocaine before the procedure.¹² In 2005, Carruthers A. et al. also found similar effectiveness in a randomized double-blind study involving 24 patients.¹⁶ These observations were confirmed by the present study.

In addition, it aimed at studying the interference of the use of a topical anesthetic in the effectiveness and duration of the effect of the treatment with BoNT-A (Speywood Unit). There is anatomical variability of the muscles in the frontal and glabellar regions, a fact that has generated interest and stimulated the realization of recent studies describing different patterns of contraction in these areas. These studies have reinforced the need for individualization of the points of application of botulinum toxin, based on those anatomical variations.^{17,18} For standardization, conventional doses and points of application for the treatment of glabellar and frontal regions were used, following the literature data.^{1,8} In a recent study about the international consensus for the use of botulinum toxin type A (BoNT-A, Speywood Unit), the recommended dose for the frontal region ranged from 20 to 60 s.U., and for the glabellar region the recommendation was 50 s.U.⁸ In the present study, we used doses of 40 s.U. for the frontal region and 60 s.U. for the glabellar region.

The muscular mobility was evaluated both by the physician and the patient at each visit using a qualitative four-point scale (1 = unaltered, 2 = slightly reduced, 3 = moderately reduced, 4 = considerably reduced).^{14,15} The physician assessed the patients directly, and the volunteers observed themselves in mirrors.

There was no statistical difference in efficacy and duration of effect when the anesthetic and placebo groups were compared, over weeks 4, 8, 12, and 16, as can be seen in Table 3.

The same table provides important information about the duration of the muscle paralysis throughout the study. It is possible to observe that in week 16, 66.6% of patients had moderately reduced muscle contraction (value = 3) or considerably reduced (value = 4), regardless of the side (anesthetic or pure vehicle), according to the physician's evaluation. In the patients' assessment, that ratio stood at 53.3%.

In week 16, the correlation between the observations relating to decreased muscle contraction assessed by the physician and the patients was good (intraclass correlation coefficient = 0.764). This demonstrates that at the end of four months there were no significant differences between doctor and patient in the evaluation of the BoNT-A, Speywood Unit's effect.

CONCLUSIONS

The BoNT-A, Speywood Unit toxin was effective and safe for the treatment of glabellar and frontal wrinkles. The application of topical anesthetic (4% lidocaine cream) reduced pain during the procedure. Furthermore, there was no interference in the efficacy and duration of the toxin's effect. ●

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