

# EMLA® Cream Application without Occlusive Dressing before Upper Facial Botulinum Toxin Injection A Randomized, Double-Blind, Placebo-Controlled Trial

Mohsen Bahmani-Kashkouli, MD,<sup>1</sup> Shabnam Salimi, MD<sup>2</sup>  
Pejman Bakhtiari, MD,<sup>3</sup> Mostafa Soltan-Sanjari, MD<sup>3</sup>

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## Abstract

**Purpose:** To assess the effect of EMLA® cream application without occlusive dressing on pain on needling (PN) and pain on injection (PI) felt during multiple botulinum toxin type A (BTA) injections for correction of hyperkinetic upper facial lines

**Methods:** A Prospective, randomized, double-blind, placebo-controlled clinical trial was conducted on 44 subjects seeking upper facial wrinkles correction. Either EMLA® or placebo cream without occlusive dressing was applied on each side of the upper face at least for 60 minutes prior to injections of BTA. PN and PI scores were measured with Visual Analog Scale (VAS).

**Results:** Patients age ranged from 27 to 57 (mean=40.95) years. Mean PN score (3.46) was less than PI score (3.61) (non significant); the two scores were highly correlated ( $r: 0.63, P=0.000$ ). While both PN and PI scores were less in the EMLA® (3.02 and 3.34, respectively) than those of placebo group (3.90 and 3.89, respectively), the difference was statistically significant only for PN score ( $P=0.000$  for PN and  $P=0.06$  for PI). Male subjects had less PN and PI scores than females which was not statistically significant ( $P=0.66$  for PN and  $0.63$  for PI). Time intervals between the cream application and BTA injections (60 to 110 minutes; mean=73.02, SD=10.15) did not have significant effect on the pain scores.

**Conclusion:** EMLA® cream application without occlusive dressing significantly reduces PN associated with multiple BTA injections. Reduction of PI was not significant. Longer duration of EMLA® cream application (up to 110 minutes) did not show lower pain score in either type of the pain.

**Keywords:** EMLA cream, botulinum toxin, facial lines, pain, pain control

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1. Associate Prof. of Ophthalmology, Oculoplastic Service, Eye Research Center, Rassoul Akram Hospital, Iran University of Medical Sciences
  2. Researcher, Eye Research Center, Rassoul Akram Hospital, Iran University of Medical Sciences
  3. Assistant Prof. of Ophthalmology, Eye Research Center, Rassoul Akram Hospital, Iran University of Medical Sciences

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Correspondence to:  
Mohsen Bahmani-Kashkouli, MD  
Eye Research Center  
Rassoul Akram Hospital  
Tel: 66509162  
Email: bahmanik@yahoo.com

## Introduction

Botulinum toxin type A (BTA) is produced by *Clostridium botulinum* and causes a reversible, selective muscle relaxation that leads to a temporary flattening of the mechanical component of the wrinkling without the stigmata of invasive surgery. It is now widely used to correct hyperkinetic facial lines especially in the upper third of the face around the eyes and eyebrows such as frown lines, forehead creases, and crow's feet. The injections need to be repeated because the effect lasts only for a few months. The most common adverse effects are pain and hematoma.<sup>1</sup> The pain felt by the patients during multiple BTA injections may be at times become so distressing that lead to occasional interruption during a treatment or deter some patients from seeking further treatment. This problem is further intensified in patients who have needle phobia. This pain could be due to skin puncturing with a needle (pain on needling, PN) or skin stretching related to the injection of BTA (pain on injection, PI).

There are some methods developed to reduce the pain during BTA injection such as using preservative-containing saline solutions that contain benzyl alcohol<sup>2</sup> and skin cooling<sup>3,4</sup> before injection. Lidocaine tape<sup>5</sup> and EMLA® cream<sup>6</sup> have also been used with a significant effect to reduce the pain due to the BTA injection in patients with facial dyskinesia. EMLA® cream has been shown to reduce the pain associated with skin puncturing and other superficial skin procedures in both children and adults.<sup>7-9</sup> It is applied under an occlusive dressing.<sup>6-9</sup> Based on our previous experience with EMLA® cream application in subjects who were seeking facial cosmetic BTA injections, there are three problems complained by these subjects: the first was that not all of the subjects felt the same about its pain reducing effect, the second problem was the longevity of its application before BTA injections which was time consuming, and the third was that almost all of them were unhappy with the occlusive dressing.

This study aimed to investigate the effects of EMLA® cream application without occlusive dressing on both PN and PI felt during multiple BTA injections for correction of hyperkinetic upper facial lines and assess the correlation between PN and PI. A new technique of separate needle injection is also

introduced to possibly increase ease of multiple skin needling. To the best of our knowledge, this is the first clinical trial assessing the effect of EMLA® cream application on different pains felt during multiple BTA injections for correction of hyperkinetic facial lines and also the first study assessing its effect without occlusive dressing.

## Methods

A prospective, randomized, double-blind, placebo-controlled clinical trial was performed. Our institutional ethics committee approved the study and informed consent was obtained from 44 consecutive subjects who were seeking for correction of hyperkinetic facial wrinkles on the upper face including the forehead, lateral orbital, and glabellar regions. All the BTA injections were performed in a private practice setting by an oculoplastic surgeon (MBK) from July to December 2005.

Difference between the scores of the two groups estimated as 1.5,  $\sigma$  as 1.9, and a 5%  $\alpha$  error, two sided required sample size was 44 with 80% power.<sup>10</sup>

Subjects with systemic conditions requiring the regular use of analgesics or anxiolytics, those with a known sensitivity to local anesthetics, those with previous facial surgery or trauma, subjects with medical, psychological, or social conditions predisposing to a different perception of pain, and subjects who needed different number and amount of BTA injections on two sides of the face were excluded.

### Cream application

Subjects were randomly (table of random digits) allocated to have EMLA® cream (eutectic mixture of 2.5% lidocaine and 2.5% prilocaine, *Tehran Chemie Ltd, Tehran, Iran*) application on either the right or left side of the upper face. They were coded and secured by a trained staff. A thick layer of EMLA® cream was placed on one half of the face and Vaseline cream (*Tolidarou Ltd, Tehran, Iran*), as placebo, was placed on the other half of the upper face. It was applied by a trained staff at least 60 minutes before BTA injection. The creams were kept out of the periorbital area by applying them no closer than the bony orbital rims. Demographics data were

recorded and the Visual analog scale (VAS) was explained to the subjects while they were waiting. They were asked if they had previous BTA injection at the same facial area, too. The creams were gently wiped off with 4x4 gauzes at time intervals after 60 minutes just before sending the subjects for the injections. Staff who applied the creams also randomly (table of random digits) determined which side of the face was to be injected first.

### **BTA injection**

The skin was sterilized with alcohol in the injection room. BTA, Dysport (500 units, Ipsen Ltd, *Berkshire, UK*) was used in this study. It was diluted with normal saline totally in 2.5 ml, leading to 20 units BTA per 0.1 ml. The injections were administered by a 1-ml, 27-gauge, 13-mm-long disposable needle syringe (*Supa, Tehran, Iran*). Regarding the injections either with EMLA® or placebo, the same-volume and equal dose of BTA was given to each side of the face in each subject. A larger volume and more injections were given in males. Ten to twenty units of BTA per site (0.05- 0.1 ml) was injected, distributed over 2-3 injection points at the area of crow's feet, 2-3 at the forehead creases, and 2 at the glabellar area in each side of the face.

Intensity of the pain on puncturing the skin and during injections were assessed immediately after the injection at each side using a VAS (0= no pain, 10= maximal pain).

Subjects were asked to put a cross on the 0-10 VAS both for PN and PI after finishing each side. They were also asked to compare the overall pain felt during the injections at each side with the previous injections. These data were recorded in a special form.

A new needle was used at each side of the face. The nasal bridge point of injection for procerus muscle was given after completion of injections and marking the VAS on both sides.

Completed forms and data regarding subject's codes were separately given to the statisticians. Data was analysed using the software SPSS MS Window Release 11.0, *Chicago*. Pearson correlation test was used to assess the correlation of PN and PI with age and duration of cream application. It was also used to assess the correlation between PN and PI. Sample K-S test was used to find the type of distribution of the pain among

responders. Independent sample t test was used to compare the PN and PI scores between males and females. Paired samples t test was used to compare pain scores between case and control groups as well as the effect of starting side of injection on the pain scores.

### **Results**

Forty-four subjects, of which 5 (11.40%) were males, were studied. Age ranged from 27 to 57 years (mean=40.95 SD=7.65). There was at least one previous injection of BTA without using any pain reducing method in 16 (36.40%) patients. Time intervals between the cream application and BTA injections were 60 to 110 minutes (mean=73.02, SD=10.15).

Male subjects had less PN (mean=2.82, SD=2.30) and PI (mean=2.92, SD=1.60) scores than female (mean=3.24, SD=2.02 for PN and mean=3.38, SD=2.12 for PI). This difference was however not statistically significant ( $P=0.66$  for PN and  $0.63$  for PI scores).

Mean PN score ( $3.46 \pm 2.11$ , 0.1 to 8.5) was less than PI score ( $3.61 \pm 2.34$ , 0 to 9.1). However, there was a significant correlation and no difference between PN and PI scores (Table 1). Age and duration of EMLA® cream application (range, 60-110 minutes) did not demonstrate a statistically significant correlation with PN and PI scores (Table 1).

One-sample K-S test showed a normal distribution for both PN and PI scores.

While both PN and PI scores were less in the EMLA® than placebo group, the difference was only statistically significant for PN score (Table 2).

Starting the injection from the EMLA® cream side or placebo side did not have any significant impact on the pain scores (PN and PI) ( $0.22 < P < 0.86$ ).

Sixteen subjects compared their overall pain with their previous experiences with BTA injections for upper facial wrinkles (Table 3).

No significant local side effects of EMLA® cream such as erythema, scaling, edema, and conjunctival congestion were noted. There was one subject who developed a minimal unilateral ptosis which was disappeared in 2 weeks time.

**Table 1.** Correlation of pain scores, age, and duration of EMLA® cream application in 44 subjects undergoing multiple botulinum toxin type A injections for upper facial wrinkles. Scores are based on Visual Analog Scale measured from 1 to 10.

	Pain on needling score 3.46±2.11	Pain on injection score 3.61±2.34
Pain on needling score 3.46±2.11	N/A	r: 0.63 P=0.000
Age (27-57 years)	r: 0.04 P=0.77	r: 0.08 P=0.60
Duration of EMLA® cream application (60-110 min)	r: 0.01 P=0.89	r: 0.05 P=0.58

**Table 2.** Mean pain scores felt by subjects undergoing multiple botulinum toxin type A injections for upper facial wrinkles. Scores are based on Visual Analog Scale measured from 1 to 10.

	EMLA® cream side	Placebo side	Paired-Sample t test
Mean pain on needling score	3.02 (SD=2.12)	3.90 (SD=2.02)	P=0.000 95% CI; -1.35 to -0.41
Mean pain on injection score	3.34 (SD=2.25)	3.89 (SD=2.43)	P=0.06 95% CI; -1.12 to 3.38

**Table 3.** Comparison of pain on each side of the face to pain on previous injections of botulinum toxin type A for the correction of upper facial wrinkles in 16 subjects

	Equal pain	More pain	Less pain
EMLA® cream group	5 (31.25%)	2 (12.5%)	9 (56.25%)
Placebo group	10 (62.5%)	2 (12.5%)	4 (25%)

## Discussion

The pain problem and accompanying “distressing period” are still a significant problem that needs to be overcome both by doctor and patient. In patients who have needle phobia, distressing processes are further intensified.

Multiple BTA injections can be associated with significant pain due to both needle insertion and stretching related to the toxin injection. *Kristan* and *Stasior*<sup>11</sup> reported an incidence of 100% pain associated with BTA injection for patients with blepharospasm.

*Van Laborde et al*<sup>2</sup> proposed diluting the BTA with benzyl alcohol containing preservative saline and found a 32% reduction of pain. They also noted that diluting toxin with lidocaine and epinephrine did not reduce the effectiveness of the drug and caused less pain during injection.<sup>12,13</sup>

Ice application can significantly reduce the pain associated with BTA injection.<sup>3,4</sup>

EMLA® (eutectic mixture of local anesthetics) cream is an oil-water emulsion of lidocaine and prilocaine. The mixture is termed eutectic, because the crystalline bases mix to create lower melting points than what would be achieved individually, creating ideal circumstances for skin penetration.<sup>9</sup> Analgesia of the skin is achieved by the release of lidocaine and prilocaine from the cream into the cutaneous and subcutaneous nociceptors and free nerve endings.<sup>14</sup> EMLA® has been shown to reduce the pain associated with skin puncturing and other superficial skin procedures in both children and adults.<sup>7-9</sup>

*Kuwahara* and *Skinner*<sup>15</sup> compared ice and EMLA® prior to injection of a 30-gauge needle containing a painful stimulus and stated that although both decrease the discomfort, EMLA® performed significantly better in pain control than ice. *Soylev* and associates<sup>6</sup> used EMLA® cream for 17 patients with facial

dyskinesia and concluded that it is significantly effective method to decrease the pain. Gotsis et al<sup>8</sup> used EMLA® cream to anesthetize the eyelid for some eyelid skin surgeries and found excellent results in 76.3% (29/38) of cases. All of the investigators used EMLA cream under an occlusive dressing.

We achieved a significant reduction of PN with at least a 60-minute application of a thick layer of EMLA® cream without occlusive dressing before multiple BTA injections over the upper face area. Whereas, pain on injection was not reduced to a statistically significant degree.

*Bjerring and Arendt-Nielsen*<sup>16</sup> studied the depth and duration of analgesia during needle insertion after the application of EMLA® cream on the forearm. They found several factors influenced the depth and duration of analgesia including cutaneous blood flow, epidermal thickness, history of atopic dermatitis, and diffusion after the cream has been removed. There has been no study assessing the PI score alone after EMLA® cream application for BTA injections. *Tatsuya et al.*<sup>5</sup> however used lidocaine tape on the eyelid skin before BTA injection for patients with Meige syndrome and found significantly less PN and PI in the case than control group. We applied EMLA® cream without occlusive dressing on the upper face skin excluding eyelid. Although results showed less PI in the EMLA® group, it was not statistically significant. Thicker skin in the upper face comparing to the eyelid and/or absence of an occlusive dressing might account for the ineffectiveness of the EMLA® cream on PI. A comparative trial of EMLA® cream application with and without the occlusive dressing before multiple BTA injections would clarify if occlusive dressing has a better effect on PI. *Kuvaki et al*<sup>17</sup> used EMLA® cream to assess the pain of retrobulbar injection and reported no difference between EMLA® and control group. They stated that ineffectiveness of EMLA® cream should be considered for deep injections.<sup>17</sup>

Our results showed that a longer duration of EMLA® cream application (up to 110 minutes) did not reduce the pain score in either type of the pain (Table 1).

There was a high correlation and no significant difference between the PN and PI (Table 1). While mean score of PI was more than PN in both EMLA® and placebo group

(Table 2); this difference did not reach significance.

We assumed that starting the injections on the EMLA® or placebo side might result in a different feeling of the pain. Some subjects might experience more pain on the second side due to lower threshold after repeated injections on the first side. On the other hand, it could be reverse. Expectedness of the pain on the second side injections might reduce feeling of the pain. Therefore, the side of first injections was randomly determined by our staff. The pain scores (PN and PI) were analyzed in these two groups and found to be no different.

EMLA® cream is highly alkaline and can be particularly toxic to the eye.<sup>18</sup> While it frequently causes blanching of the skin,<sup>19</sup> skin hyperpigmentation<sup>20</sup> has also been reported. However, no significant local side effects of EMLA® cream such as erythema, scaling, edema, hypo- or hyperpigmentation, and conjunctival congestion were noted in this series.

Multiple skin puncturing with one needle may gradually increase the pain on needling on the second side of the face because of dulling of the needle. Thus, we routinely use two needles for two sides of the face and feel the skin puncturing is much easier. It however is not clear whether in practice it benefits the patients as well.

Subjects compared their pain during the recent BTA injections with the same injections they had previously without any pain reducing application. Almost one-third (5/16) of the responders felt the same pain as previous injections in the EMLA® group. One-fourth of the responders felt less pain than previous injections in the placebo group (Table 3). Parallel to our previous experiences, results show that EMLA® cream is useful for some but not all subjects seeking multiple BTA injections for hyperkinetic facial lines. Measuring "fear of injection" scores preoperatively would help to assess which group of patients might benefit most from any measure of reducing pain associated with multiple BTA injections. We did not measure a "fear of injection" score preoperatively which could be a subject for future research.

## Conclusion

Simple use and particularly minimization of patient discomfort makes EMLA® cream application without occlusive dressing a recommendable option in multiple BTA injections. This is especially worthwhile when multiple injections are given to subjects who have needle phobia and psychological

distress because of injections. These subjects could be educated how to apply the cream at home to save time.

Using separate needle for each side of the face may increase the ease of skin puncturing and reduce pain on needling as well.

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