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Botulinum toxin injection pain relief using a topical anesthetic skin refrigerant

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KEYWORDS

Botox;
Pain relief;
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Summary Background: This study was performed to determine if pretreatment application of a topical anesthetic skin refrigerant reduced discomfort during botulinum toxin injection.

Methods: Twenty patients were assigned to four groups determined by side of the face pretreated with skin refrigerant and side receiving the first injection. On a Visual Analog Scale of 0–10 patients rated discomfort levels after injections in the glabellar complex with and without pretreatment.

Results: Mean discomfort rating for the pretreated side was 3.1, while the mean discomfort rating for the non-pretreated side was 4.5. Discomfort was not affected by the side sprayed ($p = 0.33$) nor by administering the injection to the sprayed side first ($p = 0.37$). The paired t-test revealed a significant difference between discomfort levels on the pretreated and non-pretreated sides ($p = 0.038$) yielding a 95% confidence interval of $(-2.71, -0.09)$.

Conclusions: Topical anesthetic skin refrigerant significantly reduces discomfort in a cost-effective manner for reported by patients undergoing botulinum injections.

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Botulinum toxin A injections for facial rhytides has become the most common cosmetic procedure with nearly 3,000,000 injections performed in 2006 in the United States alone.¹ While clearly effective, the pain and associated anxiety can be significant for some patients. Such pain can be a significant deterrent to subsequent treatments.^{2,3}

Various techniques have been described to reduce injection discomfort including topical refrigerants, nerve blocks and topical anesthetic creams.^{4–18} Although these

modalities may be effective, they have a variety of disadvantages among them including cost, time to onset, skin irritation and allergic skin reactions.^{19–22}

The purpose of this study was to determine if the use of a topical anesthetic skin refrigerant (Pain Ease, Gebauer Company, Cleveland, OH) can decrease the pain associated with injection of botulinum toxin and, therefore, improve the overall experience for the patient and physician.

Patients and methods

Pain Ease (Gebauer Company, Cleveland, OH) is a topical anesthetic skin refrigerant with the key ingredients 1,1,1,3,3-

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Pentafluoropropane and 1,1,1,2-Tetrafluoroethane. It is a vapocoolant intended for topical application to skin, intact mucosa and minor open wounds.²³

Patients were randomised into one of four groups, determined by which side of the face was pretreated with the refrigerant prior to the injection and whether the pretreated or non-pretreated side received the first injection of botulinum toxin A (Botox, Allergan, Inc., Irvine, CA) (Table 1). Each of the twenty patients served as his/her own control with either the left or right corrugator muscle receiving the pretreatment refrigerant and the opposite corrugator receiving no pretreatment. All patients received two injections of 5 units of botulinum toxin in each corrugator for a total of 20 units.

Botox was reconstituted with 2.0 ml of 0.9% non-preserved saline to a final concentration of 5.0 U/0.1 ml as described in the package insert.²⁴ A single tuberculin syringe with a 30-gauge needle was used for injections into both corrugator muscles.

Prior to spraying the test area, each patient's hand was sprayed to acquaint him/her with the refrigerant sensation. The treatment area was sprayed with the refrigerant continuously for 5 s at a distance of 8 to 18 cm. The injection of botulinum toxin immediately followed using standard techniques. The side of the face not pretreated with the refrigerant was injected with botulinum toxin only.

Upon completion of their injections, patients were asked to rate their level of discomfort in the two areas. Discomfort was also rated prior to the procedure, but patients uniformly rated pre-procedure discomfort as 0. Ratings were made on a Visual Analog Scale (0 to 10) with greater numbers representing higher levels of discomfort.²⁵ Patients were permitted to report their discomfort as non-integer numbers (i.e., 4.5).

Statistical analysis

Post-procedure discomfort levels for pretreated and non-pretreated sides were compared using a Student's paired *t*-test. Differences between groups were evaluated using regression analysis. Results were considered significant if *p*-values were less than 0.05.

Results

Of the 20 patients who participated in this study, 19 were female and 1 was male. The mean age of the participant was 52.15-year-old. The mean and standard deviation of

the discomfort ratings reported for the pretreated side, non-pretreated side and the difference between these groups are presented in Table 2. Of the 20 patients, 13 felt they had less pain on the treated side, 3 had less pain on the nontreated side and 4 felt they had similar pain on both sides. The overall mean discomfort rating for the pretreated side was 3.1, (± 2.54) while the overall mean discomfort rating for the non-pretreated side was 4.5 (± 2.35). The difference in overall means was 1.4 (± 2.81), indicating that the mean discomfort rating was lower for the pretreated side than for the non-pretreated side ($p = 0.038$).

Table 3 presents the results of the regression analysis. The analysis was performed over the two variables used to define the groups: if the patient was treated on the left or right side and if the patient received the botulinum injection on the pretreated side first or second. Discomfort was not affected by the side sprayed ($p = 0.33$), nor was it affected by giving the injection to the sprayed side first ($p = 0.37$). Age was not related to the reported difference in discomfort ($p = 0.63$). The Student's paired *t*-test showed a statistically significant difference between discomfort levels on the pretreated and non-pretreated sides ($p = 0.038$) and yielded a 95% confidence interval of (-2.71, -0.09). Since both regression analysis and Student's paired *t*-tests were used, one can reasonably attribute the decrease in discomfort to the use of the refrigerant and not to other factors. This indicates that discomfort levels were significantly reduced by the pretreatment with the refrigerant.

With regard to the likelihood of patients who returned for retreatment, the numbers are too small on which to comment definitively. Of the patients who received topical refrigerant, the average return for Botox was 1.9 (range 0–5) compared to 1.6 for the group that did not prefer the spray (range 0–3).

Discussion

While botulinum toxin A injections are well tolerated by most, the occasional patient finds these injections both painful and anxiety provoking. Alleviating these deterrents to treatment may therefore be an attractive option.

A number of authors have demonstrated significant pain relief from botulinum toxin A injections using topical anesthetic creams such as EMLA.^{6,7,9,10,14} The efficacy of pain relief associated with EMLA application is directly related to time of application. That is, EMLA is most effective if 45 min have elapsed from time of application until injection.^{19–22} This is somewhat of a drawback with regard to efficiency in the office setting. Patients either have to apply EMLA in the office and wait 30–45 min until its effect is achieved, or apply it prior to arriving at the office. The cost of the product is also a significant issue. While applying an occlusive dressing over EMLA once it is applied to the face is recommended, a recent study has demonstrated that a dressing is not necessary for pain reduction. This study also differentiated needle puncture pain from injection pain. These authors found that EMLA cream significantly reduced the pain experienced during needle insertion but not the pain on injection.¹⁸

Table 1 Randomisation of patients into treatment groups. Patients were randomized into one of four groups (A-D) depending upon which corrugator muscle was treated first and which side received the first injection (left or right).

Group	Side Treated with Pain Ease	Side Receiving First Injection
A	Left	Left
B	Left	Right
C	Right	Right
D	Right	Left

Table 2 Mean and Standard deviation of the discomfort ratings reported for the pretreated side, non-pretreated side, and the difference between these groups. Discomfort levels were reported on a Visual Analog Scale of 0 to 10.

Factor	Overall		Group A		Group B		Group C		Group D	
	N	Mean(SD)	N	Mean(SD)	N	Mean(SD)	N	Mean(SD)	N	Mean(SD)
Discomfort on Treated Side	20	3.1(2.54)	5	2.7(1)	5	2.9(1.41)	5	1.8(2)	5	5.1(1.73)
Discomfort on Non-treated Side	20	4.5(2.35)	5	4.5(1)	5	5.1(1.41)	5	3.9(2)	5	4.6(1.73)
Difference of Treated and Non-Treated Side	20	-1.4(2.81)	5	-1.8(1)	5	-2.2(1.41)	5	-2.1(2)	5	0.5(1.73)

The use of ice and other means of cooling to decrease the pain associated with botulinum toxin injections have also been reported by numerous authors.^{5,6,9,11,13,15} Cold temperature reduces discomfort by decreasing the nerve conduction velocity of pain fibers (C-fibers and A-delta fibers) and interrupting nociceptive inputs to the spinal cord.²⁶ Several studies have compared the use of EMLA cream to ice in reducing the pain from botulinum toxin injections in a prospective manner.^{6,9,11,13} These studies demonstrate significant pain reduction after five minutes of cooling. Further, skin cooling appears to be as effective as EMLA cream while being significantly less costly.

The use of a cryoanalgesic spray for pain relief has been reported for the treatment of hyperhidrosis.²⁶ A distinct advantage of this method over the previously discussed methods of analgesia is its quick onset and short duration of action. The anesthetic properties last approximately 60 s.

Our current prospective study also demonstrated a significant reduction in pain from botulinum toxin A injections when a skin refrigerant was used. However, the amount of reduction was less than that seen in several of the studies noted above. Although the patient acted as his/her own control both in our and in the studies cited, the site of the injections was different. In our study the corrugator muscle was used while the previous half-face studies used the periocular area. It is our experience that botulinum toxin A injections in the corrugator area are significantly more painful than in the periocular area. This may explain the differences noted.

In practice, patients' desires vary with regard to pretreatment analgesia. While many patients undergoing repeat botulinum toxin injections requested the refrigerant, others objected to the sudden burst of refrigerant spray and/or found it headache provoking. Some preferred

pretreatment with ice and others preferred no pretreatment at all. It is our practice to offer the patient their choice of pretreatment.

Limitations of this study should be recognised. While the study was prospective and the patient acted as his/her own control, it was not blinded. Therefore, the possibility of a placebo effect cannot be discounted. While we realise that needle insertion pain and pain on injection may represent two different entities, we were unable to differentiate between the two.¹⁸

The small sample size is also a limit of our study and additional studies with more patients may be more helpful to determine the benefit of the refrigerant. An additional study comparing the topical skin refrigerant to ice and/or EMLA could provide more insight into the most effective method of pretreatment for botulinum toxin injections.

Pain data was not compiled by objective measurements but rather by subjective patient-reported scores. Since pain thresholds from patient to patient are often variable, so too can the pain scores vary. To minimise this potential variability the patients acted as his/her own control and a Visual Analog Scale 0–10 score was used to grade pain.²⁵

With regard to cost, the refrigerant spray is significantly less costly than EMLA but more expensive than ice. The cost to the physician for the refrigerant spray is approximately 80 cents if two areas are treated. Each can supplies 50 applications based on a 5 s spray time. Given the current physician cost of \$20, this computes to a cost of 40 cents per injection. Since two areas are treated per patient, total cost is estimated at 80 cents per patient.

Unlike other types of skin refrigerants such as ethyl chloride, refrigerant used in this study is nonflammable. Therefore, the risk of fire is reduced if electrocautery is used.²⁷ Since refrigerant only affects the skin surface, no interaction or reduction in efficacy with botulinum toxin should occur. However, this was not proven in our study. Finally, the aerosolization can be non-ozone depleting and environmentally safe.

Pretreatment using a topical anesthetic skin refrigerant significantly reduced the discomfort associated with the injection of botulinum toxin A when, with the patient acting as his/her own control, one corrugator mass was sprayed with the topical refrigerant and the opposite side was not treated. This technique provides a rapid, inexpensive and consistent means of pain relief for most patients.

Disclosure

The authors have no financial interest in any product or device mentioned in this article.

Table 3 Regression analysis performed over two variables: the side the patient was pretreated with Pain Ease and if the botox injection was performed on the side pretreated with Pain Ease first. Discomfort was not affected by side sprayed ($p = 0.33$), nor was it affected by giving the injection to the sprayed side first ($p = 0.37$).

Factor	Beta	95% Confidence Interval	P value
Sprayed Left Side	-1.34	(-4.16, 1.48)	0.33
Sprayed Side Received Injection			
First	-1.21	(-4, 1.58)	0.37
Age	-0.04	(-0.19, 0.12)	0.63

Conflict of interest

None.

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References

1. *Cosmetic surgery national data bank statistics*. The American Society for Aesthetic Plastic Surgery. Available at: <http://www.surgery.org/download/2007stats.pdf>; 2007.
2. Dutton JJ. Botulinum-A toxin in the treatment of craniocervical muscle spasms: short- and long-term, local and systemic effects. *Surv Ophthalmol* 1996;41:51–65.
3. Grandas F, Elston J, Quinn N, et al. Blepharospasm: a review of 264 patients. *J Neurol Neurosurg Psychiatr* 1988;51:767–72.
4. Alam M, Dover JS, Arndt KA. Pain associated with injection of botulinum A exotoxin reconstituted using isotonic sodium chloride with and without preservative: a double-blind, randomized controlled trial. *Arch Dermatol* 2002;138:510–4.
5. Baumann L, Frankel S, Welsh E, et al. Cryoanalgesia with dichlorotetrafluoroethane lessens the pain of botulinum toxin injections for the treatment of palmar hyperhidrosis. *Dermatol Surg* 2003;29:1057–9. discussion 1060.
6. Elibol O, Ozkan B, Hekimhan PK, et al. Efficacy of skin cooling and EMLA cream application for pain relief of periocular botulinum toxin injection. *Ophthalm Plast Reconstr Surg* 2007;23:130–3.
7. Gambart G, Mette F, Pellot AS, et al. [Evaluation of analgesic protocol with nitrous oxide and EMLA cream during botulinum toxin injections in children]. *Ann Readapt Med Phys* 2007;50:275–9.
8. Gassner HG, Sherris DA. Addition of an anesthetic agent to enhance the predictability of the effects of botulinum toxin type A injections: a randomized controlled study. *Mayo Clin Proc* 2000;75:701–4.
9. Kuwahara RT, Skinner RB. Emla versus ice as a topical anesthetic. *Dermatol Surg* 2001;27:495–6.
10. Lander J, Hodgins M, Nazarali S, et al. Determinants of success and failure of EMLA. *Pain* 1996;64:89–97.
11. Linder JS, Edmonson BC, Laquis SJ, et al. Skin cooling before periocular botulinum toxin a injection. *Ophthalm Plast Reconstr Surg* 2002;18:441–2.
12. Onguchi T, Takano Y, Dogru M, et al. Lidocaine tape (Penles) reduces the pain of botulinum toxin injection for meige syndrome. *Am J Ophthalmol* 2004;138:654–5.
13. Sarifakioglu N, Sarifakioglu E. Evaluating the effects of ice application on the pain felt during botulinum toxin type-a injections: a prospective, randomized, single-blind controlled trial. *Ann Plast Surg* 2004;53:543–6.
14. Soylev MF, Kocak N, Kuvaki B, et al. Anesthesia with EMLA cream for botulinum A toxin injection into eyelids. *Ophthalmologica* 2002;216:355–8.
15. Bechara FG, Sand M, Altmeyer P, et al. Skin cooling for botulinum toxin A injection in patients with focal axillary hyperhidrosis: a prospective, randomized, controlled study. *Ann Plast Surg* 2007;58:299–302.
16. Smith KC, Comite SL, Balasubramanian S, et al. Vibration anesthesia: a noninvasive method of reducing discomfort prior to dermatologic procedures. *Dermatol Online J* 2004;10:1.
17. Flynn TC, Carruthers A, Carruthers J. Surgical pearl: the use of the Ultra-Fine II short needle 0.3-cc insulin syringe for botulinum toxin injections. *J Am Acad Dermatol* 2002;46:931–3.
18. Kashkouli MB, Salimi S, Bakhtiari P, et al. EMLA cream application without occlusive dressing before upper facial botulinum toxin injection: a randomized, double-blind, placebo-controlled trial. *Ann Plast Surg* 2008;60:353–6.
19. Dong H, Kerl H, Cerroni L. EMLA cream-induced irritant contact dermatitis. *J Cutan Pathol* 2002;29:190–2.
20. de Waard-van der Spek FB, Oranje AP. Purpura caused by Emla is of toxic origin. *Contact Derm* 1997;36:11–3.
21. Wahlgren CF, Quiding H. Depth of cutaneous analgesia after application of a eutectic mixture of the local anesthetics lidocaine and prilocaine (EMLA cream). *J Am Acad Dermatol* 2000;42:584–8.
22. Waton J, Boulanger A, Trechot PH, et al. Contact urticaria from Emla cream. *Contact Dermatitis* 2004;51:284–7.
23. Gebauer Company, Cleveland, OH. Gebauer's Pain Ease (Package Insert).
24. Allergan I, Irvine, California. Botox Cosmetic (botulinum toxin type A) Purified Neurotoxin Complex (Package Insert).
25. Mantha S, Thisted R, Foss J, et al. A proposal to use confidence intervals for visual analog scale data for pain measurement to determine clinical significance. *Anesth Analg* 1993;77:1041–7.
26. Lehmann JF, editor. *Therapeutic heat and cold. Rehabilitation medicine library*. Baltimore: Williams & Wilkins; 1990.
27. Meneghetti SC, Morgan MM, Fritz J, et al. Operating room fires: optimizing safety. *Plast Reconstr Surg* 2007;120:1701–8.