

Reduction of Pain and Anxiety Prior to Botulinum Toxin Injections With a New Topical Anesthetic Method

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Purpose: To evaluate the safety and efficacy of vapocoolants (topical skin refrigerants) to induce skin anesthesia and relieve patient anxiety and pain prior to cosmetic botulinum injections.

Methods: A paired (split-face) design was used in 52 patients where patient side (left vs. right) was randomized to receive either vapocoolant spray or no treatment control to test the study hypothesis of better anesthetic efficacy of vapocoolant spray versus no treatment control. A pain and anxiety questionnaire was administered before, during, and after the injections.

Results: A considerable percentage of patients either expected pain (35% of naïve patients expected moderate pain) or had experienced pain from their prior treatment (35% had experienced moderate pain). Among naïve patients, 15% had moderate or severe anxiety and among experienced patients, 31% had moderate anxiety. Pain was a factor in delaying the scheduling of cosmetic botulinum toxin treatments in 19% of naïve patients and 31% of experienced patients. Pain reported from actual injections was higher than what was anticipated prior to treatment. There was a significant reduction in pain at injection sites treated with vapocoolant ($p < 0.001$, paired t test). Overall, 67% of all patients reported that the vapocoolant method had less pain than no anesthesia and 54% preferred vapocoolant for their next treatment. Overall, 6% of all patients would schedule their next botulinum toxin treatment sooner if vapocoolant were available.

Conclusions: Vapocoolants represent a safe and effective means to reduce patient discomfort and anxiety before and during botulinum toxin type A treatments for glabellar area indications.

(*Ophthalm Plast Reconstr Surg* 2009;25:173–177)

Cosmetic botulinum toxin type A injection (Botox Cosmetic, Allergan Pharmaceuticals, Irvine, CA, U.S.A.) has become the most commonly performed cosmetic procedure in the United States since first described in 1992 to improve the appearance of glabellar folds.¹ Botulinum toxin type A was approved by the Food and Drug Administration as a safe and effective therapy for blepharospasm, strabismus, and hemifacial spasm in December 1989 and for cosmetic use in the glabellar area in April 2002. Botulinum toxin type A is also

used extensively for medical indications including adductor spasmodic dysphonia, oromandibular dystonia, torticollis, cerebral palsy, back spasms, blepharospasm, hemifacial spasm, migraines, and axillary hyperhidrosis, with new uses being discovered every day. The discovery of a better way to decrease the pain and discomfort of these and other types of injections will lead to decreased pain and morbidity in millions of people per year.

Botulinum toxin type A purified neurotoxin complex is a sterile, vacuum-dried purified potent neurotoxin, produced by the bacterium *Clostridia botulinum*. It exerts its effect at the neuromuscular junction, producing a weakness or flaccid paralysis of muscle, thus reducing the overlying wrinkles and the ability to frown. Specifically, botulinum toxin type A binds to acceptor sites on motor nerve terminals, enters the nerve terminals, and inhibits the release of acetylcholine. The reversible muscle weakening effects will usually be noticed between 2 and 7 days, and will last 3 to 5 months before returning to normal.

One noteworthy patient concern regarding botulinum toxin type A treatments is the actual and anticipated pain of injection with needles,² which may cause anxiety and discomfort before and during the procedure. This study was designed to examine these issues.

Modalities occasionally used or reported to reduce the pain of injection are topical application of ice packs,^{3–6} chilled air,⁷ numbing creams,^{8–10} and even a simple pinch technique.¹¹ In this study, the anesthetic methods previously used were no anesthesia (42%), ice compresses (19%), and EMLA (ASTRA Pharmaceuticals, Wayne, PA, U.S.A.) topical anesthetic (39%). The use of ice packs is cumbersome and not completely effective at reducing or eliminating injection pain. Numbing creams have limited effectiveness and are awkward to apply, in addition to requiring a topical application time of 20 to 60 minutes, a fact that has greatly limited their clinical use. Furthermore, dermal application of the numbing cream may cause transient, local blanching followed by transient, local redness, or erythema in up to 56% of patients.¹²

The study motivation derived from an observation that there was less pain, discomfort,⁶ and anxiety associated with botulinum toxin type A injections in patients treated with vapocoolant sprays immediately prior to injection.

Historically, the most frequently used vapocoolant in medicine is ethyl chloride (Gebauer Company, Cleveland, OH, U.S.A.), which has been used for more than 100 years. Topical anesthetic skin refrigerants (vapocoolant sprays) were formally described by Travell¹³ in 1955. Ethyl chloride spray was shown to be effective at reducing vaccination-associated pain by Reis et al.¹⁴ in 1998.

Vapocoolants are nonpharmaceutical topical anesthetics that are extremely effective at anesthetizing target areas to give rapid, relatively affordable pain management for a large variety

Accepted for publication October 15, 2008.

Supported by unrestricted scientific/educational activity grants from Allergan Medical, Inc., CA; and Gebauer Company, Cleveland, OH.

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DOI: 10.1097/IOP.0b013e3181a145ca

of procedures. They are intended for topical application to skin and intact mucous membranes (oral cavity, nasal passageways, and lips). When compressed or contained, such as in a can, the vapocoolants are in a liquid form. When sprayed in a warm atmosphere or onto warm skin, a phase change occurs to the vapor state. When contacting the skin, this phase change causes an endothermic or cooling reaction to occur, which refrigerates the point of evaporation from the skin surface. The coldness decreases the nerve conduction velocity of the C fibers and A-delta fibers that make up the peripheral nervous system, thus interrupting the nociceptive inputs to the spinal cord.¹⁵

The aerosol mist version of a new-generation hydrofluorocarbon-based, nonflammable vapocoolant compound consisting of a proprietary blend of 1,1,1,3,3-pentafluoropropane and 1,1,1,2-tetrafluoroethane (Pain Ease, Gebauer Company) was used exclusively in this study and is approved by the Food and Drug Administration for preinjection anesthesia for the skin, intact mucous membranes, and minor open wounds.¹⁶

METHODS

An independent investigational review board (Hoag Hospital, Newport Beach, CA, U.S.A.) prospectively reviewed and approved the study protocol prior to patient enrollment and monitored the clinical investigation.

Vapocoolant Comfort Shield. One obstacle to using a vapocoolant spray on the face was thought to be possible eye irritation from overspray. To address this concern, a “comfort” shield was created to protect the eye and limit the application of the anesthetic to a specific area through a central aperture (Fig.). Prestudy testing was performed to measure the spray diameter at various treatment distances to determine the optimum overall device diameter and also for materials compatibility. This shield was designed to be flexible enough to



Comfort shield in place over glabella.

conform to the irregular contours of the face in the periorbital region. A foam layer was used to wick any excess liquid away from the treated area and to provide a snug fit for further eye protection.

Procedure Description. Eligible patients were asked to complete a short preprocedure questionnaire prior to treatment. Pretreatment photographs and in some cases videos were obtained. Twenty U botulinum toxin type A was injected in 8 sites (2.5 U, 0.05 cc per site) in the glabellar area between the eyebrows and in the lower central forehead. The skin was marked with a lip liner in a standard pattern. By marking the injection spots with adequate lighting and magnification and injecting in a closely adjacent unmarked area, prominent and/or visible vessels were avoided.

Thirty-gauge needles were used, and the needle tips were examined under a micron scope (under sterile conditions) prior to use to ensure sharpness and lack of burrs. Needles were replaced as needed during treatment if they were suspected of being or becoming dulled as evidenced by tactile feedback or a “crunching” sensation.

One side of the treatment area (4 injection sites) had no anesthesia and the other side was anesthetized with vapocoolant spray immediately prior to injection. Before treatment, a bland eye ointment was placed in the eyes for protection from the vapocoolant spray application. Protective gauze eye pads were also used to protect the eyes. Furthermore, a shielding device (described earlier) was used to confine the vapocoolant spray to the treated area. The vapocoolant spray was applied through the central aperture of the comfort shield for approximately 4 seconds (~2.5 g) from a distance of 3 to 7 in until the skin just began to turn white without completely frosting the skin. The injection was then immediately performed, in some cases through the aperture of the shield while still in place. A corresponding site was then injected on the opposite side without vapocoolant. The patient was asked to rate injection discomfort at each site immediately after each injection and to compare the difference between each vapocoolant-treated and non-vapocoolant-treated pair and the overall difference for all the treatment sites for each side.

No other facial areas were treated on the study day nor were additional botulinum toxin injections administered in the glabellar area. After the injections, a gauze-wrapped ice pack compress was applied in the usual fashion for 1 to 3 minutes. The patient was then asked to complete a short posttreatment questionnaire.

Study Population. The study enrolled a total of 26 naïve patients (not previously treated with botulinum toxin injections) and 26 experienced patients (previously treated with botulinum toxin at the same anatomic location) for a total of 52 patients. Patients of either sex were required to be between 30 and 65 years of age, desiring to temporarily reduce or eliminate the function of glabellar and procerus muscles that cause frowning and wrinkles between the eyebrows and have a cosmetically enhanced appearance. Exclusion criteria were a history of an unusual sensitivity to pain; untoward result or allergic reaction to botulinum toxin; preexisting disorders affecting the neuromuscular junction function such as Eaton-Lambert syndrome, myasthenia gravis, amyotrophic lateral sclerosis and motor neuron disease; current use of aminoglycoside antibiotics; known untoward or allergic reaction to vapocoolant spray; pregnancy or lactation; excessive skin pigmentation thought to be at risk for pigment change; and anxiety disorders or current use of anxiolytic medications.

Anxiety Questionnaire. A 46-item anxiety/discomfort questionnaire was specifically developed to prospectively assess patient perceptions of anxiety, pain, outcome, future expectations, and whether pain or anxiety was a factor in delaying the scheduling of botulinum toxin treatments. Various questions were asked before, during, and 20 minutes, 1 day, and 1 month postprocedure. The data collection instrument was independently developed to meet the needs of this study. The form was to assess naïve and experienced patients. The form was not independently validated or modeled after any specific data collection

TABLE 1. Baseline characteristics

Baseline factor	Naïve	Experienced
Expected pain (0–4 scale)*	2.0 (35% moderate)	—
Pain from prior treatment	—	1.9 (35% moderate)
Anxiety (0–4 scale)*	1.0 (15% moderate/severe)	1.4 (31% moderate)
Pain a factor in delaying Botox treatment	19%	31%
Anesthetic method previously used	—	19% ice, 39% EMLA
Age, years	45	50

*0, none; 1, minimal; 2, mild; 3, moderate; 4, severe.

instrument. The 5-point ordinal rating scale deployed was modeled after a Likert scale with a low score being favorable (less anxiety).

Study Design. This study was designed to test the hypothesis that vapocoolant spray reduces patient anxiety and discomfort when administered prior to cosmetic botulinum toxin injections. A matched-pairs design was used where patient side was randomized to receive either vapocoolant or no anesthesia.

All study patients received botulinum toxin injections in the glabellar area and lower forehead. One side of each patient’s treatment area was anesthetized with vapocoolant, while the contralateral forehead was not anesthetized. Pain was assessed after each injection and after each complete treatment by subjective methods using a 5-point pain scale. Preprocedure and postprocedure questionnaires were used to assess anxiety using a 5-point ordinal scale.

Safety data were collected at the end of the procedure, a day later, and a month later to assess the overall incidence of pain, bruising, redness, pallor, swelling, abnormal pigmentation, ptosis, or other adverse events.

Sample Size Rationale. The study hypothesis is that the percent with pain immediately after the procedure will decrease from 60% to 20% favoring the vapocoolant spray versus no anesthesia using a matched pairs design with a total of 52 study patients (26 naïve, 26 experienced). Under the assumption that 60% were discordant pairs (different pain with anesthetic vs. control), each subgroup has 80% power and 5% type I error to detect a 40% advantage for vapocoolant spray. With 15 discordant patients (60%) per subgroup, the discordant hypothesis is established if 12 or more patients report less pain with vapocoolant spray.

Data Analysis. Each patient served as his/her own control for efficacy analyses. Bilateral data were compared using a McNemar’s paired comparison test. Patient-level data were summarized using proportions and 2-sided 95% confidence intervals. Subjective outcome measures were determined using a 5-point pain grading scale to evaluate the patient’s subjective pain levels. Objective outcome measures were generated using a validated pain scale.

The results postinjection were compared in the 2 groups using a marginal homogeneity test or paired *t* test to determine the statistical

TABLE 3. Patient anxiety: preprocedure*

	None, %	Minimal, %	Mild, %	Moderate, %	Severe, %
Naïve	38	38	8	12	4
Experienced	31	27	12	31	0
All	35	33	10	21	2

*Do you have any anxiety about the possible pain of the Botox injections? Anxiety rating: 0, none; 1, minimal; 2, mild; 3, moderate; 4, severe.

significance of any differences between the 2 treatment groups. Pain data were analyzed using the averaged outcome per side and using the worst outcome score per side. A paired *t* test was used to compare the sum of the mean changes across the 4 separate injection sites per treatment. Anxiety level and treatment preference were assessed per patient using 95% lower confidence bounds. The same analysis methods were used for the naïve and experienced populations.

RESULTS

Demographics and Preinjection Pain/Anxiety Questionnaire. The mean age was 45 years for naïve patients and 50 years for previously treated (experienced) patients (Table 1). Among naïve patients, the overall degree of pain expected was equally distributed between minimal (35%), mild (31%), and moderate (35%), with an average of mild (2.0). Among experienced patients, 58% used prior anesthetic (19% ice, 39% EMLA cream); the degree of pain reported for the prior treatment was equally distributed between none-minimal (31%), mild (35%), and moderate (35%), with a 1.9 average (mild).

Anxiety was minimal to mild for both naïve and experienced subgroups. Pain was a factor in delaying botulinum toxin treatment for 19% of naïve patients (4% yes, 15% somewhat) and 31% of experienced patients (12% yes, 19% somewhat) (Table 1).

Pain Reduction (Primary Efficacy Endpoint). The mean reduction in the mean summed pain at the 4 treatment-specific injection sites (Table 2) all favored vapocoolant at significant levels; the mean advantage was 2.3 units overall ($p < 0.001$, paired *t* test). Patients overall noted less pain with vapocoolant during treatment (65% vs. 19%, $p < 0.001$, marginal homogeneity test), at all times and among both groups. The vapocoolant-treated side also reported entirely no pain more frequently (40% vs. 6%) than control (Table 2).

The study met the planning assumptions with treatment discordant pain noted for 85% overall (88% for naïve patients, 81% for experienced patients) with a 46% vapocoolant advantage noted overall (58% for naïve patients, 35% for experienced patients). Thus, the study had the desired power to test the primary study hypothesis based on this primary efficacy endpoint.

Anxiety Reduction. Mean anxiety scores preprocedure (Table 3) showed that mild to severe anxiety about pain is present in 24% (16%

TABLE 2. Pain reduction advantages: during procedure

Pain endpoints	All		Naïve		Experienced	
	Control	Pain ease	Control	Pain ease	Control	Pain ease
Less painful side* (excludes no difference)	19%	65%	15%	73%	23%	58%
	$p < 0.001$		$p = 0.003$		$p = 0.08$	
Injection-site pain† (over summed sites)	5.2 (2.6)	2.9 (2.3)	5.2 (2.6)	2.3 (2.3)	5.2 (2.7)	3.4 (2.3)
	2.3 ($p < 0.001$)		2.8 ($p < 0.001$)		1.8 ($p = 0.006$)	

*Overall, which side was less painful for the group of 4 injections?

†How would you classify the pain of the injection site?
0, none; 1, minimal; 2, mild; 3, moderate; 4, severe.

TABLE 4. Patient anxiety relief (% reporting less anxiety than before procedure): postprocedure

Assessment times postprocedure	All			Naïve			Experienced		
	Less, %	Same, %	Greater, %	Less, %	Same, %	Greater, %	Less, %	Same, %	Greater, %
20 minutes	65	35	0	85	15	0	46	54	0
1 day	67	33	0	85	15	0	46	54	0
1 month	69	29	2	85	15	0	54	42	4

moderate-severe) of naïve botulinum toxin patients and 33% of all patients; mild to moderate anxiety is present in 43% (31% moderate) of experienced botulinum toxin patients. The increased incidence of anxiety among experienced patients is thought to be due to remembrance of pain from the prior procedure.

Patient anxiety was less at all postbaseline evaluations (Table 4). The naïve subgroup was relieved of anxiety to a larger degree than the experienced subgroup (85% vs. 54% at 1 month.) Among those who preferred vapocoolant at 20 minutes, 99% (85% none, 14% minimal) had little or no anxiety about the pain of the injection for their next treatment. This anxiety reduction was consistent at the later postprocedure evaluations.

Method Preferred. Patients preferred the vapocoolant method at 20 minutes posttreatment (52% vs. 29%, $p = 0.09$, marginal homogeneity test) and it was also the method preferred for the next treatment by a 2:1 margin at 20 minutes (Table 5). These vapocoolant preferences persisted at all time points and between groups.

Safety of Vapocoolant Method. One aspect of this study was to evaluate the safety profile and the efficacy of vapocoolant spray on the face. Risks that were considered included postinflammatory hyperpigmentation (skin darkening) or hypopigmentation (skin lightening), or frostbite if the product is not used as prescribed. These risks were thought to be minimal, given that only 1 case of skin hyperpigmentation has ever been received or reported to the Gebauer Company (personal communication). No significant safety issues or concerns were reported or discovered during this study.

Patient Satisfaction With Treatment Result. Patients overall were very pleased with their outcomes. At 1 month, 92.3% of patients were very satisfied (67%) or satisfied (25%) with their treatment result and 94% intended to schedule another treatment.

Effect of Pain and Anxiety on Patient Scheduling Frequency. Anticipated pain was a factor in delaying treatment scheduling in 19% of naïve and in 30.7% of experienced botulinum toxin patients. In addition, 6.4% of all patients (9% of naïve patients and 4% of experienced patients) would schedule their next botulinum toxin treatment sooner if vapocoolant were available.

DISCUSSION

The analgesia methods for botulinum toxin injection and patient expectations vary widely. Our results confirm

that there is sometimes significant pain associated with botulinum toxin injections. It is interesting to note that naïve patients experienced just about as much pain as they anticipated. Mild-moderate pain was expected in 65% (35% moderate) of the naïve patients, and mild-moderate pain was reported in 69% (35% moderate) of experienced patients' last botulinum treatment.

The remembrance of the actual injection pain may explain more anxiety among the experienced patients (11% mild, 31% moderate) than the naïve patients (8% mild, 11% moderate, 4% severe). The fact that anxiety about anticipated or previously experienced pain was a factor in delaying cosmetic botulinum toxin treatment for 19% of naïve patients and 31% of experienced patients (Table 1) strongly suggests that anxiety about pain is at least one of the factors in limiting more widespread acceptance of botulinum toxin injections, as is the fact that some (6.4%) would schedule retreatment sooner if vapocoolant was available.

It is a testament to the effectiveness of botulinum treatments and injector technique that 92% of all patients were happy with the results of their treatment at 1 month (67% very satisfied, 25% satisfied), while 94% intended to schedule another treatment.

However, the importance of the search for a better way to decrease injection pain is reflected by the fact that despite 58% of experienced patients having used some type of prior anesthesia (ice or EMLA), 70% reported mild (35%) or moderate (35%) pain. Any convenient method of decreasing injection pain and anxiety may increase patient acceptance and scheduling frequency.

Applicability to Clinical Practice. The vapocoolant method was roughly equivalent in time spent to using ice compresses and markedly reduced chair time compared with topical anesthesia. There was a rapid learning curve. Disadvantages include possible expense and that the method requires an assistant. One concern was that the overall vascular pattern could be masked by the pressure of the protective shield or blanched by the vapocoolant, but by premarking the injection spots with adequate lighting and magnification, prominent and/or visible vessels were easily avoided.

Ointment and protective gauze pads were used to protect the eye in this study. Ointment was rinsed out easily with generic lubricating eyedrops. Because of the efficacy of the protective

TABLE 5. Which method did you prefer? postprocedure (vapocoolant vs. no treatment)

Assessment time postprocedure	All		Naïve		Experienced	
	Control, %	Pain ease, %	Control, %	Pain ease, %	Control, %	Pain ease, %
20 minutes	29	52	27	54	31	50
1 day	31	48	31	50	31	46
1 month	33	42	31	50	27	42

shield, no leakage of the spray was seen in any patient and no patient complained of eye irritation. In addition, no patient reported feeling the coolness or the presence of the spray in an area other than the intended exposed and protected injection spot. Thus, it is not envisioned that ocular ointment or gauze pads would be necessary if this method was used in clinical practice.

Study Limitations and Future Directions. A split-face study was designed so that patients could act as their own control. Because pain and anxiety are highly variable and subjective, it was believed that a split-face design would produce the most useful data and answer the question: is this topical anesthetic method better than no anesthesia? One of the limiting factors of this study is that there was no mask and that a future masked study is needed (randomizing patients to each treatment) to eliminate any bias related to both injectors and patients being aware of which side of the face had each method.

Additional studies are needed to confirm our results in a multicenter study and to assess injector and staff compliance with this new method in different patient populations. We suggest that in addition to cosmetic and functional botulinum toxin injections, vapocoolant use be considered for other indications where less painful injections and less patient anxiety would be desirable, such as functional botulinum injections (especially in children), mass pediatric inoculations, venipuncture, and minor sports injuries.

In conclusion, significant pain and anxiety occurs prior to and during botulinum toxin type A injections that has a delaying effect on initial patient scheduling and the frequency of repeat visits. The current anesthetic method (vapocoolant) is safe, less painful, provokes less anxiety, is preferred to no anesthesia, and may lead to more frequent procedure scheduling in some patients.

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