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Review

Effectiveness of cold application on postoperative pain following botulinum toxin injections type a in the orofacial region: A systematic review of randomized controlled studies

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Abstract. *Objective:* This systematic review aims to evaluate self-perceived pain levels in patients undergoing a BoNT/A injection in the orofacial region with a cold application compared to other types of treatments. *Methods:* An electronic search was performed of indexed databases including PubMed, EMBASE, Scopus, ISI web of knowledge and Cochrane library up to and including April 2023. A Risk of Bias (RoB) assessment was conducted using the Cochrane tool for assessment. Due to a high heterogeneity of the included studies, a meta-analysis was not conducted. This study was registered in the PROSPERO database (CRD42023407290). *Results:* An initial electronic and manual search revealed a total of 496 and 5 manuscripts, respectively. After removing duplicates, 170 studies remained. Following the eligibility criteria, five randomized controlled trials (RCTs) were included. Four RCTs used the visual analog scale (VAS), and one used the numerical rating score (NRS) to assess post-operative pain. Three RCTs had a high, whereas two RCTs had a moderate ROB. *Conclusions:* the present review proves it inconclusive to identify the best cold modality protocol to alleviate pain in patients undergoing BoNT/A injections. However, 80% of the studies showed significant reduction in pain following injections and a positive outcome overall. Future standardized and power adjusted clinical studies are needed to identify cost effective and standardized cold treatment protocols in patients undergoing injections.

Key words: botulinum, neurotoxin, topical, EMLA, pain

Introduction

Botulinum toxin is an exotoxin produced by the bacterium Clostridium botulinum, an anaerobic gram-positive sporulating organism. Seven types of botulinum neurotoxins (BoNT) have been identified (A, B, C, D, E, F, G)[1,2]. However, BoNT types A and B are commercially available and predominantly utilized in clinical settings[1]. At present, there are three FDA-approved Botulinum A toxin products available: abobotulinumtoxinA (Dysport®, Ipsen, Paris, France), onabotulinumtoxinA (Botox®, Allergan, Irvine, CA, USA), and incobotulinumtoxinA (Xeomin®, Merz Pharmaceuticals GmbH, Frankfurt, Germany)[3]. Among many other uses, Botulinum neurotoxin type A (BoNT/A) has been widely used for medical and aesthetic purposes in the facial area, such as frown lines between the eyes, necklines, myofascial pain, bruxism, migraines, dystonia, hemifacial spasms, facial palsy, blepharospasm and strabismus[1,4,5]. The mechanism of action of BoNT is primarily characterized by paralyzing the muscles reversibly via inhibiting the release of

acetylcholine (AcH) at the presynaptic levels of the neuromuscular junction[6,7]. Botulinum toxin injections are relatively safe and have been approved by the Food and Drug Administration (FDA) for cosmetic and medical procedures[3]. However, some adverse effects are associated with the injections, such as bruising, swelling, redness, headaches, nausea, muscle weakness, paralysis of the nerves when injected in the target area, and pain[8]. Additionally, some patients refuse or are reluctant to have repeated injections because of the painful experience of the injection[9-11]. Repeated injections are often required as the mean duration of effectiveness is about 3 months[6,12,13].

Postoperative pain following BoNT/A injections is a common cause of acute pain and can vary from person to person. Some people experience mild discomfort, while others experience more intense pain[14,15]. Previous studies have suggested different techniques to reduce botulinum toxin injection discomfort and pain. These include dilution with sterile saline[16], using a 30-gauge insulin syringe[17] and integrating topical analgesia during the procedure such as topical anesthetic creams (e.g., EMLA) and the application of cutaneous cooling agents like topical refrigerant sprays, cold gel packs or ice packs[5,6,13,15,18,19]. However, several studies have shown that cold temperatures have a crucial effect on pain and discomfort reduction in different treatments such as those frequently used in physical therapy and anesthesia. In addition, it is helpful during childbirth, before and after minor surgical procedures, sports medicine, soft tissue trauma and orthopedics[19-22]. Pain receptors are free nerve endings predominant in the superficial layers of the skin and when a needle is inserted into the skin, pain is often experienced[9]. Moreover, cold temperature controls pain perception through its effect on sensory nociceptive inputs to the spinal cord. It decreases the nerve conduction velocity of pain fibers (C-fibers and A-delta fibers)[18,23,24].

There are some general considerations regarding cold application and BoNT that can influence the overall results. Cold application can potentially affect blood flow and vasoconstriction in the injected area. This may influence the distribution and uptake of Botox. The choice of injection site and the specific targeted muscle can also impact the overall effectiveness of BoNT. Different muscles may respond differently to cold temperatures and the neurotoxins. The timing of a cold application in relation to a BoNT injection can be of critical impact. The effects of cold temperatures on blood flow and tissue responsiveness might vary based on when it is applied in relation to the injection. Variability in individual responses to cold and BoNT can exist and factors such as skin thickness, muscle density and overall health may play a vital role. If a cold application is considered, it should be done according to established clinical protocols and guidelines, which presently are not standardized. Some advantages for patients include reduced discomfort, as a cold application can provide local anesthesia and reduce discomfort associated with the injection process. Furthermore, it can help minimize bruising and swelling by constricting blood vessels and reducing inflammation. It can enhance patient comfort during the injection procedure with the addition of a cold application and have potential for greater precision. Overall, it can lead to a positive patient experience, with minimized pain and side effects, and may contribute to the overall satisfaction of the patient with the treatment.

In a study by Chorney et al., they reported no significant difference in injection pain levels with vibration, ice packs or the absence of topical anesthesia[15]. In contrast, Iroken et al., reported that cooling of the skin with ethyl chloride spray significantly decreases the pain associated during BoNT injections compared to EMLA or in control groups[6]. Nonetheless, there has not been a statistical assessment comparing the cold application in patients undergoing BoNT/A injections in the orofacial region to evaluate post injection pain levels. Therefore, the primary aim of this systematic review was to evaluate the self-perceived pain levels and discomfort in patients undergoing a BoNT/A injection in the orofacial region with a cold application.

Material and methods

Protocol and registry

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[25]. The protocol was registered with PROSPERO (CRD42023407290). Due to the high heterogeneity of the included studies, a

meta-analysis was not conducted. An electronic search of indexed databases was performed, including PubMed, EMBASE, Scopus, ISI Web of Knowledge, and Cochrane library without a time restriction up to and including April 2023. The following keywords were used: (1) Botulinum neurotoxin type A, (2) Botulinum neurotoxin type A injection, (3) topical refrigerants, (4) topical anesthetic creams, (5) EMLA cream, (6) cutaneous cooling, (7) topical refrigerant spray, (8) cold gel pack, (9) ice pack and (10) pain. These keywords were combined using Boolean operators (OR, AND) to expand the search results (Table S1).

Eligibility criteria

The present systematic review included RCTs to evaluate self-perceived pain levels and discomfort in adult patients undergoing BoNT/A injections with a cold application compared to other types of treatments, based on the following approach: Participants-Interventions-Comparisons-Outcome-Study design (PICOS). (P): Adult patients undergoing a Botulinum neurotoxin type A injection in the orofacial region, (I): cold application before the injection, (C): other types of treatment, (O): self-perceived pain levels and discomfort, and (S): randomized controlled clinical trials. Case reports and case series, letters to the editor, commentaries, reviews, retrospective studies, experimental studies, non-randomized studies, and cross-sectional studies were excluded.

Focused question

The focused question was, "Does a cold application before a Botulinum neurotoxin type A injection result in reduced self-perceived pain levels compared to other types of treatment in the orofacial region?"

Study selection, data collection and risk of bias

Two authors (MA and RL) screened the titles and abstracts of the studies identified and full texts of the relevant studies were evaluated independently. In addition, handsearching was performed on the reference lists of relevant original studies and review articles to identify studies that might have been missed in the previous step. Disagreements were resolved through discussions and consultations with a third researcher (JK). All the information from the included studies was synthesized by tabulating the data according to (a) general characteristics of included randomized controlled clinical trials, (b) general characteristics of Botulinum neurotoxin type A injections, (c) general characteristics of the cold and other treatment groups, (d) general characteristics of outcome variables. Two authors (MA and OK) assessed the risk of bias (RoB) of the included studies using the Cochrane Collaboration's RoB tool for RCTs[26].

Results

Study selection

An electronic search revealed 496 articles. A PubMed search displayed 157 articles; an Embase search revealed 114 articles, a Scopus search resulted in 84 articles, a Web of Science search revealed 78 articles and a Cochrane Library search presented 63 articles. After removing duplicates, 170 studies remained. An additional 5 articles were added for screening after a handsearch of the references in relevant articles. After reading the titles and abstracts, 20 articles were fully evaluated, and 15 were excluded (Table S2). Five RCTs[5,6,13,15,19] were included in the present systematic review and processed for data extraction (Figure 1).

General characteristics of included studies

All the RCTs included in the present systematic review had a parallel group design and included an intervention group to refer to the use of the cold application, and a control group, meaning all other types of treatment or no treatment undergone. The number of participants in the included RCTs ranged between 22 to 60, and the mean age ranged between 43.9 ± 9.89 years to 58.15 ± 10.51 years reported in four studies[5,6,13,15]. One study did not report the mean age of its participants[19]. Three RCTs included male and female patients[5,13,19], and 2 RCTs included female patients[6,15]. All RCTs reported no dropouts for the patients. The study duration ranged between 4.5 to 8 months in two RCTs[5,13], while 3 studies did not report their duration[6,15,19] (Table 1).

General characteristics of botulinum neurotoxin type A (BoNT/A)

All the RCTs reported that Botulinum neurotoxin type A and Onabotulinum Type A were used in their studies. The injection of BoNT/A performed was performed by various health care providers, including three RCTs reporting that a doctor injected the BoNT/A[6,13,19], 1 study reported that a fellowship-trained facial plastic surgeon injected the BoNT/A[15], whereas 1 study did not report the person who injected the BoNT/A[5]. Two RCTs reported using a 30-gauge needle[6,15], 2 RCTs reported using a 20-gauge needle[5,19], whereas 1 study did not report the size of the needle used[13]. Four RCTs reported using sterile saline, as the dilution material[5,6,15,19], and 1 study did not report the type of dilution material they used[13]. There was a noticeable variety amongst the included RCTs regarding the diagnosis, the number of injections, the dosage of BoNT/A in the unit and the location of the injection (Table 2).

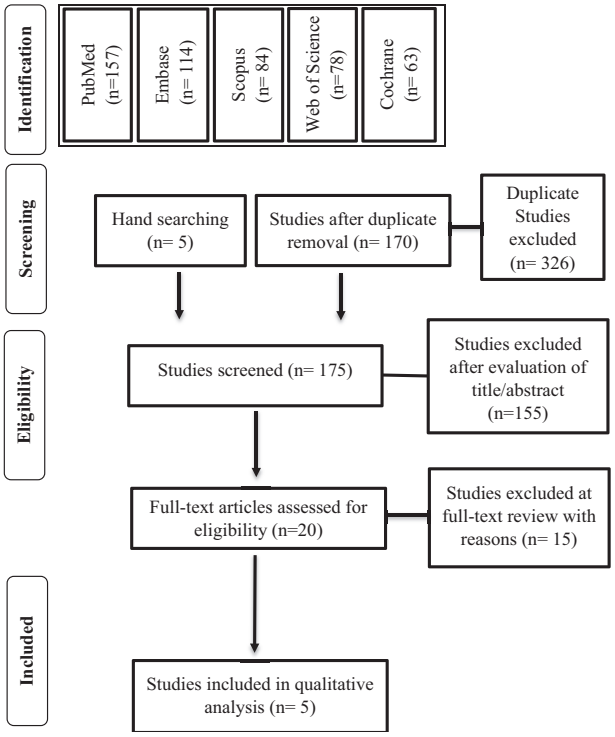

Figure 1. Study flowchart based on the PRISMA guidelines.

General characteristics of cold application and other treatment

Four RCTs reported following the treatment with a cold temperature or using an icepack[5,13,15,19] whereas one study reported using an ethyl chloride cooling spray[6]. All RCTs reported that the cold treatment was applied to the skin directly at the injection site before the BoNT/A injection. The reported duration of said cold treatment varied anywhere from 4-8 seconds[6], 1 minute[5,15] and up to 5 minutes[13,19] before the BoNT/A injection. Other treatments used in the control groups are summarized in (Table 3).

General characteristics of outcome variables

Four RCTs reported that the visual analog scale (VAS) was used to assess the self-pain level[5,6,15,19].

Table 1. General characteristics of included randomized controlled clinical trials.

Author et al.	Country of study	Total participants	Age (Mean ± SD) (range)	Gender	Intervention group	Control group	Duration of study
Chorney et al[16]	USA	22	43.9 ± 9.89 years (18- 65)	Male = 0 Female = 22	Cold pack	Vibration No treatment	NR
Iroken et al[8]	USA	45	46.73 ± 8.85 years (35-60)	Male = 0 Female = 45	Ethyl chloride spray	EMLA cream No treatment	NR
Pucks et al[7]	UK	35	44.17 ± NR years (NR)	Male = 8 Female = 27	Cold gel pack	Room-temperature gel pack	4.5 months
Saeliw et al[1]	Thailand	60	58.15 + 10.51 years (32-76)	Male = 11 Female = 49	Ice pack	No treatment	8 months
Sarifakioglu et al[20]	Turkey	24	NR	Male = 7 Female = 17	Ice pack	No treatment	NR

Abbreviations: SD, Standard Deviation; NR, Not Reported.

Table 2. General characteristics of Botulinum neurotoxin type A (BoNT/A).

Author et al.	Diagnosis	Type of BoNT/A	Provider who injected BoNT/A	Size of the needle	Dilution type and percentage	Number of injections	Dosage of BoNT/A	Injection site
Chorney et al[16]	Glabellar lines or furrowed brow lines	Onabotulinum Type A (Allergan, Irvine, CA)	Plastic surgeon	30 gauge	0.9% Sterile saline	5 injections per patient	4 Units	Bilateral corrugator supercilii muscles
Iroken et al[8]	Healthy patients /volunteers forehead wrinkles	Botulinum toxin type A (Allergan, Irvine, CA)	Doctor	30 gauge	0.9% Sodium chloride	4 injections per patient	2.5 Units	Frontal area
Pucks et al[7]	Chronic Synkinesis secondary to facial palsy	Botulinum toxin type A (Allergan, Marlow, UK)	NR	29 gauge	0.9% Sodium chloride	1 injection per patient	Varied according to patient treatment need	Platysma muscle
Saeliw et al[1]	Hemifacial spasm and Blepharospasm	Botulinum toxin type A (NR)	Doctor	NR	NR	NR	NR	Facial region
Sarifakioglu et al[20]	Bilateral lateral orbital wrinkles	Botulinum toxin type A (Allergan, Irvine, CA)	Doctor	29 gauge	0.9% Sodium chloride	8 injections per patient	5 Units	The lateral orbital zones (crow's feet area)

Abbreviations: NR, not reported.

Saeliw et al., reported that the numeric rating scale (NRS) was used to assess the self-perceived pain levels[13]. In three RCTs[5,13,15] the patient themselves documented the self-reported pain whereas in one study[6] it was the doctor, and in one study[19] the research assistant, who documented the pain levels. There was a variability noted among the included RCTs regarding the interval of the pain evaluation. Four RCTs[5,6,13,19] reported statistically significant differences regarding their pain levels between the cold treatment and other types of treatments (Table 4).

Risk of bias within studies

Three RCTs[5,13,15] had a high RoB, whereas two RCTs had a moderate RoB. The main reasons for that high RoB in the RCTs included the lack of blinding of allocation concealment, lack of blinding the participants and researchers, lack of blinding of the outcome assessment, and the inclusion of only female patients in two RCTs. All RCTs included a failure to disclose a power analysis for sample size estimation (Table 5).

Discussion

The pain and stress of injections can be a bothersome experience for the patient and can often lead to challenges in management, compliance, and cessation of treatment[6,12,27]. The use of botulinum toxin injections is getting more frequent and acceptable, for both medical and/or aesthetic reasons. Even though it is often a rather simple procedure, the injections can induce pain that may discourage patients from pursuing said treatment[6,12]. Various studies have reported substantial pain alleviation using topicals. However, topicals may have mild and temporary side effects including itching, burning, pain, erythema, purpura and edema[6,28]. One commonly used topical is EMLA, which is a combination of lidocaine and prilocaine that provides

Table 3. General characteristics of the cold and other treatment groups.

Author et al.	Type of cold treatment	Application of cold	Duration of the cold treatment	Type of the other treatments	Application of other treatments	Duration of other treatment
Chorney et al[16]	Small reusable cold pack	The cold pack was applied directly to the injection site.	1 minute before BoNT/A injection.	Buzzy vibration stimulus and control groups.	A vibratory distractor: applied and held within 2 cm of the injection sites. Control group: No topical anesthesia was applied.	NR
Iroken et al[8]	Ethyl chloride spray (Chlorethan 100 mL, ethyl chloride cooling aerosol spray)	Ethyl chloride spray was applied directly to the injection site until the skin turned white.	4-8 seconds before BoNT/A injection	EMLA cream (5% 25 g lidocaine, 25 g prilocaine) and control groups.	EMLA cream: applied directly to the injection site. Control group: Nothing applied.	45 min before BT injection.
Pucks et al[7]	Cold gel pack (3-5 °C)	Cold gel pack was applied directly to the injection site.	1 minute before the BoNT/A injection	Room temperature gel pack (20 °C)	Room temperature gel pack applied directly to injection site.	1 min before BT injection
Saeliw et al[1]	Ice pack	An ice pack was applied directly to the injection site.	Group 1: 5min before BoNT/A injection Group 2: 5min after BoNT/A injection	Group 3: No ice pack	No ice pack applied	No treatment
Sarifakioglu et al[20]	Ice pack (plastic bag (5x5 cm))	An ice pack was applied directly to the injection site.	5 minutes before BoNT/A injection	No ice pack	No ice pack applied	No treatment

Abbreviations: NR, not reported; BoNT/A, Botulinum neurotoxin type A

dermal analgesia. The effectiveness of pain relief associated with the application of EMLA is directly correlated to the time of application and is most effective after 45 minutes. Patients can either apply it at the office visit and wait or apply it before arriving. The cost of the product is also a substantial issue for some patients[18,29,30]. Several studies have compared EMLA cream to ice packs in reducing pain during botulinum toxin injections and have shown a considerable pain reduction after five minutes of cooling[18,19,31]. Local cooling works as an anesthetic by desensitizing pain receptors or low-temperature specific nerve impulses, which induce the synaptic inhibition of pain signals in the spinal cord[6,18,23,32]. Ice packs are inexpensive, relatively safe and readily available in most offices. In addition, they have shown to constrict surface blood vessels and significantly decrease post injection bruising and redness[15,31].

The internalization of BtxA involves its uptake through nerve terminals, where it acts on the synaptic vesicles preventing the release of acetylcholine and thereby causing muscle paralysis. BtxA Toxin is distributed mainly by convection, the bulk movement of the fluid determined by the fluid volume and the force of the injection. Enzymatic and protein-based processes, such as the internalization of toxins like BtxA, can be

Table 4. General characteristics of outcome variables.

Author et al.	Parameter used to assess pain	Pain assessment	Interval of pain evaluation	P-value	Outcome
Chorney et al[16]	VAS	Patient	Between each injection	P > 0.05	No significant difference in pain scale scores with the use of vibration, ice pack, or no topical anesthesia.
Iroken et al[8]	VAS	Doctor	NR	P < 0.05	Compared to EMLA or control groups, skin cooling with ethyl chloride spray significantly decreased the pain associated during forehead botulinum toxin injections.
Pucks et al[7]	VAS	Patient	Immediately after injection	P < 0.05	The application of a cold gel pack before BoNT/A injection significantly reduced the pain and discomfort associated with the procedure compared to control room-temperature gel pack application.
Saeliw et al[1]	NRS	Patient	Immediately after injection and 5 minutes after the injection	P < 0.05	Using ice application 5 minutes before or after injection no difference was reported. but both significantly reduced pain compared to without ice application.
Sarifakioglu et al[20]	VAS	Research Assistant	During injections	P < 0.05	The clinical findings indicated that pain significantly reduced on the side where the ice pack was applied.

Abbreviations: VAS, Visual Analog Scale; NRS, Numeric Rating Scale; NR, not reported.

Table 5. Risk of bias of the included randomized controlled clinical trials.

Domain	Chorney et al[16]	Iroken et al[8]	Pucks et al[7]	Saeliw et al	Sarifakioglu et al[20]
Random sequence generation	Low	Low	Low	Low	Low
Allocation concealment	High	Low	High	High	High
Blinding of participants and researchers	High	Low	High	High	Low
Blinding of outcome assessment	High	Low	High	High	Low
Incomplete outcome data	Low	Low	Low	Low	Low
Selective outcome reporting	Low	Low	Low	Low	Low
Other bias	High	High	Low	Low	Low
Summary	**High**	**Moderate**	**High**	**High**	**Moderate**

influenced by temperature. In general, lower temperatures may slow down enzymatic reactions and cellular processes. The internalization of BtxA involves endocytosis, a cellular process where cells engulf external material and can be affected by temperature, and lower temperatures might influence the efficiency of this process. The cellular uptake of proteins and toxins can be influenced by temperature-dependent changes in membrane fluidity and receptor activity. It is essential to note that future studies might be needed to directly address the effects of cold on BtxA internalization[39].

Several studies have suggested additional methods to relieve botulinum toxin injection pain and discomfort, including the use of a 30-gauge insulin syringe. It guarantees accurate delivery and minimizes the waste of the botulinum toxin due to its critical

needle design, which has no dead space in the needle hub[13,15,17]. Moreover, reducing needle wobble, perpendicular injection through the skin and a slow infiltration are essential standards to improve the injection technique and relieve the pain[15,33]. Furthermore, dilution with sterile saline is another way to alleviate botulinum toxin injection pain and discomfort[16,34].

The objective of the present study was to evaluate self-perceived pain levels with a cold application in subjects undergoing a BoNT/A injection in the orofacial region. After applying strict eligibility criteria, five RCTs were processed for data extraction. Chorney et al., reported no significant difference in pain levels during a BoNT/A injection with vibration or ice packs[15]. Iroken et al., reported that compared to EMLA or control groups, skin cooling with ethyl chloride spray significantly decreased the amount of pain associated with botulinum toxin injections in the forehead. In addition, the application of ethyl chloride for 4 to 8 seconds was sufficient to anesthetize the skin[6]. While an EMLA cream must be left for 45 minutes on the skin to achieve the maximal effect, the time lapse may not always be practical or optimal. Most patients favored ethyl chloride spray over EMLA cream as it had several advantages including cost, safety and quick acting effects[6]. Pucks et al., reported that the application of a cold gel pack 1 minute before a BoNT/A injection had significantly reduced pain and discomfort associated compared to room-temperature gel packs[5]. Furthermore, applying a cold gel pack for 1 min acted more rapidly and efficiently than applying ice for 5 minutes, which has been evaluated in previous studies[5,19,9,35]. Saeliw et al., reported that ice application 5 minutes before or after a BoNT/A injection showed no difference compared to the control group, but both significantly reduced pain[13]. Sarifakioglu et al. reported that injection pain significantly reduced on the side where the ice pack was applied[19].

The application of cold temperatures for the management of pain has been well documented in literature. It has been shown that before and after minor surgical procedures, laser therapy and dermal injections it can help reduce pain[19]. For example, Edmundo Marques et al., suggests that cryotherapy may have additional benefits in reducing pain following third molar surgery[36]. However, it is not effective on facial swelling and trismus. Another study shows that cold application can result in reduced pain and bruising following subcutaneous injections of low-molecular-weight heparin for up to 72 hours[37]. Chia-Te Chen et al., report that cold application is a safe and easy-to-administer non-pharmacological modality with immediate and persistent effects on pain and anxiety relief following chest tube removal in cardiothoracic surgery patients[38].

The strength of the present systematic review was that it included only RCTs, but the variability noted amongst the included RCTs made it challenging to perform a quantitative assessment (meta-analysis) of the extracted data. However, a limitation of this review was the methodological inconsistencies observed, such as the type of cold treatment or application, degree of cold application, duration of treatment, interval of pain evaluation, the scale used to assess the pain, the duration of pain evaluation and total duration of the study and a small sample size. This potentially decreases our knowledge of differences between groups due to poor power estimation. In addition, the amount of pain perceived during the intramuscular injection of BoNT/A was a limitation because it differs according to the depth of the needle and the injection technique. To underestimate this possible injection depth and technique variance, an experienced doctor performed the injection. It is worth mentioning that three RCTs[5,13,15] had a high RoB, whereas two RCTs[6,19] had a moderate RoB. The main reasons for that high RoB in the RCTs included the lack of blinding of an allocation concealment, lack of blinding of participants and researchers, lack of blinding of outcome assessment and inclusion of only female patients in two RCTs[6,15]. Moreover, all RCTs did not perform power analysis for sample size estimation, which certifies notice in interpreting statistical results due to the probability of Type II error. Not all RCTs reported multiplicity modifications when comparing intervention with control groups. The authors of the present systematic review perceive that p-values in all included RCTs should have been modified utilizing multiplicity correction to account for the multiple group comparisons amongst several time points. Based on these limitations, caution is recommended when interpreting individual study results.

From a clinical perspective, additional aspects should be considered before intervening with a cold

application for pain reduction before administering BoNT/A injections. Medical and cosmetic practices have used different types of cold applications and treatments. However, in this systematic review, the application of ice was the most practical modality used to alleviate pain. In addition, a pre-injection cold application sulted in less bleeding when compared to post injection cold application. Imminent studies must examine the role of topical anesthesia in cosmetic facial injections and handle patient-specific characteristics contributing to discomfort and pain. Future research should include power adjusted randomized controlled trials with a standardized methodological criteria and homogeneity to properly evaluate the association between cold application and pain. In addition, additional common clinical challenges such as swelling, ulceration, bleeding and facial paralysis should be addressed. It is also pertinent to mention that health care providers should inform prospective patients about the pain associated with using BoNT/A injections.

Conclusion

Based on the present review it is inconclusive to identify the best cold modality protocol to alleviate pain in patients undergoing BoNT/A injections. However, 80% of the studies showed significant reduction in pain following injections and a positive outcome overall. Future standardized and power adjusted clinical studies are needed to identify cost effective and standardized cold treatment protocols in patients undergoing injections.

Conflict of Interest: The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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Appendix – Supplementary files

Table S1. Search strategy for electronic databases.

Database Search	Keywords	Results
PubMed	(((((((Botulinum neurotoxin MeSH Terms]) OR Botulinum neurotoxin injection [Title/Abstract]) AND topical refrigerants spray [Title/Abstract]) OR cutaneous cooling [Title/Abstract]) OR cold gel pack [Title/Abstract]) OR ice pack [Title/Abstract]) AND topical anesthetic cream Title/Abstract]) OR EMLA cream AND pain [Title/Abstract]) OR discomfort [Title/Abstract])))))).	**157**
Embase	((((((((((((((‘Botulinum neurotoxin injection’) OR ((‘Botulinum’ /exp OR Botulinum) AND (‘neurotoxin’ /exp OR neurotoxin) AND (‘injection’/exp OR injection’) AND (‘topical’ /exp OR topical))) AND (‘refrigerants’ /exp OR refrigerants AND ((‘spray’ /exp OR spray) AND ((‘topical’/exp OR topical) AND (‘anesthetic’/exp OR anesthetic) AND (‘cream’/exp OR cream) AND (‘pain’/exp OR pain)) OR ((‘Botulinum’ /exp OR Botulinum) AND (‘neurotoxin’ /exp OR neurotoxin) AND (‘injection’/exp OR injection’) AND (‘cold’/exp OR cold))) AND (‘pack’/exp OR pack) AND (‘pain’/exp OR pain)) OR ((‘Botulinum’ /exp OR Botulinum) AND (‘neurotoxin’ /exp OR neurotoxin) AND (‘injection’/exp OR injection’) AND (‘treatment’/exp OR treatment) AND (‘ice’/exp OR ice))) AND (‘pack’/exp OR pack) AND (‘EMLA’ /exp OR EMLA) AND (‘cream’/exp OR cream) AND (‘pain’/exp OR pain)) OR ((‘Botulinum’ /exp OR Botulinum) AND (‘neurotoxin’ /exp OR neurotoxin) AND (‘injection’/exp OR injection’) AND (‘topical’ /exp OR topical))) AND (‘refrigerants’ /exp OR refrigerants AND ((‘spray’ /exp OR spray) AND ((‘topical’/exp OR topical) AND (‘anesthetic’/exp OR anesthetic) AND (‘cream’/exp OR cream) AND (‘discomfort’/exp OR discomfort) [Title/Abstract])))))).	**114**
Scopus	(((((((((TITLE-ABS-KEY (botulinum AND toxin AND injection AND topical AND anesthetic AND cream AND pain)) AND ((botulinum AND toxin AND injection AND cold AND gel AND pack AND pain)) OR (TITLE-ABS-KEY (botulinum AND toxin AND injection AND ice AND pack AND pain)) AND ((botulinum AND toxin AND injection AND emla AND cream AND pain)) AND (botulinum AND toxin AND injection AND cutaneous AND cooling AND pain) OR ((TITLE-ABS-KEY (botulinum AND toxin AND injection AND ice AND pack AND discomfort))))))))))).	**84**
Web of Science	(((((“Botulinum neurotoxin ”) OR TOPICO: (“Botulinum neurotoxin injection ”) ‘OR TOPICO: (“topical refrigerants spray ”) OR TOPICO: (“cutaneous cooling ”) ‘OR TOPICO: ((“cold gel pack ”) OR TOPICO: (“ice pack”) OR TOPICO: (“topical anesthetic cream ”) OR TOPICO: (“EMLA cream ”) OR TOPICO: (“pain ”) OR TOPICO: (“discomfort ”))))))).	**78**
Cochrane	(((((“Botulinum neurotoxin”): ti,ab,kw OR (“Botulinum neurotoxin injection”): ti,ab,kw OR (“topical refrigerants spray”): ti,ab,kw OR (“cutaneous cooling”): ti,ab,kw OR (“cold gel pack”): ti,ab,kw OR (“ice pack”) ti,ab,kw OR (“topical anesthetic cream”) ti,ab,kw OR (“EMLA cream”) ti,ab,kw OR (“pain”) ti,ab,kw OR (“discomfort”))))).	**63**

Table S2. List of excluded studies at full-text review with reasons for exclusion.

Reference	Reasons for the Exclusion
Orhan Elibol et al. (2007) PMID: 17413628	Not RCT
James S Linder et al. (2002) PMID: 12439058	Not RCT
Meltem F Söylev et al. (2002) PMID: 12424403	Focused question not addressed
Gülperi Çelik et al. (2011) PMID: 22022215	Focused question not addressed
Asghar Dalvandi et al. (2017) PMID: 28285862	Focused question not addressed
D E Page et al. (2010) PMID: 20682573	Focused question not addressed
Dirk Rüsch et al. (2017) PMID: 27590462	Focused question not addressed
Sharon E Mace et al. (2017) PMID: 28850378	Focused question not addressed
Sharon E Mace et al. (2016) PMID: 26979261	Focused question not addressed
Tracy Barbour et al. (2018) PMID: 29153919	Focused question not addressed
Jette Skiveren et al. (2008) PMID: 18709307	Focused question not addressed
Adel Alsantali et al. (2018) PMID: 29662322	Focused question not addressed
Barry L Eppley et al. (2004) PMID: 19336142	Focused question not addressed
Scott J Engel et al. (2010) PMID: 19716355	Focused question not addressed
Paula Monteiro et al. (2012) web of science	Not English study

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