A Comparative Study of Pain Intensity in Patients Receiving Cooling Botulinum Toxin (BTX) and Non-cooling BTX

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Objective: To compare pain intensity in the patients who receive both cooling Botulinum toxin (BTX) injections and non-cooling BTX injections around the periocular area.

Methods: A Prospective, randomized, single-blind controlled trial study of patients who had bilateral blepharospasm or bilateral hemifacial spasm between June 2021 and October 2022. Each patient received 10 points of BTX injections around the periocular area (randomized into 5 injection points each of cooling and non-cooling BTX respectively). A visual analog scale (VAS) was used to measure the pain intensity immediately after injection at each point. Main outcome measures: pain score and complication. cooling botox: 15-18°C, non-cooling botox: room temperature 25-27°C

Results: A cohort of 11 patients received 55 points for cooling BTX injections and 55 points for non-cooling BTX injections. The mean pain score of the cooling BTX group was 1.91 ± 1.59, while the non- cooling BTX group had a mean pain score of 1.89 ± 1.59, the difference was not statistically significant (p = 0.887). The highest pain levels in both groups were at the upper eyelids and lower (mean pain score of 2.0).

Conclusion: There was no significant difference in the pain intensity and complication between cooling BTX and non-cooling BTX injections.

Conflicts of Interest: none

Keywords: blepharospasm, hemifacial spasm, cooling botulinum toxin injection

Approved by the IRB of Samutprakarn Hospital; Research study code: Sh01564

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Introduction

Blepharospasm is an abnormal contraction of the orbicularis oculi muscle causing the closure of the eyelids and may affect vision.[1] Hemifacial spasm is a neuromuscular disorder causing involuntary twitches in the facial muscles which are supplied by the facial nerves. The symptom may occur on one side or both sides. The patients may have visual problems due to lid closing similar to blepharospasm.[2] Blepharospasm and hemifacial spasm are chronic diseases and Botulinum toxin (BTX) injection is the treatment of choice.[3,4]

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BTX has good efficacy, fewer systemic side effects, and is easy to use. Common side effects are redness and swelling at the injection site, ptosis, facial asymmetry, lagophthalmos, etc.[3,4] These side effects usually are transient. Some patients may produce autoantibodies to BTX, causing a decrease in efficacy.[5]

The BTX injections may be repeated every 3-4 months as a result of its temporary action. Some patients refuse treatment or feel nervous because of pain during the injection (approximately 10-12 points of injections in both blepharospasm and hemifacial spasm). Previous studies showed that pain from BTX injection can be relieved by cold compression or applying EMLA anesthetic to the skin before injection.[6-9]

Orhan Elibol, et al.[10] published a comparative study between the efficacy of EMLA and cold compression for pain relief. The study reported no statistically significant difference in the pain intensity when applying either EMLA or cold compression before BTX injections. The pain score of EMLA was 3.18 ± 1.31, and cold compression was 3.12 ± 1.31 compared to the control group (5.83 ± 1.98).

The pain can be relieved by cold compression which was supported by previous studies. Yuka Saeki[11] studied how cold reduces pricking pain sensation in the skin. He found that cold decreased the autonomic response by reducing blood flow (BF) and skin conductance level (SCL) at the fingertips. The research question is whether cooling BTX could decrease the pain sensation or not.

The purpose of this study is to compare pain intensity between cooling and non-cooling BTX injections.

Materials and Methods

A Prospective, randomized, single-blind controlled trial study was conducted in the Botox clinic, Samutprakarn Hospital from June 2021 to October 2022.

Subjects

All patients in the Botox clinic who had bilateral blepharospasm or bilateral hemifacial spasm were selected. Any skin lesions such as scars, acne, or inflammation in the periocular area were excluded.

All patients provided informed consent before entering the study. Each participant was randomized to be injected with 5 points of cooling and 5 points of non-cooling BTX around the periocular area.

Sample size

This study uses the below formula to calculate the sample size (the formula for randomized controlled trials for continuous data).

$$n_{trt} = \frac{(z_{1-\frac{\alpha}{2}} + z_{1-\beta})^2 \left[\sigma_{trt}^2 + \frac{\sigma_{con}^2}{r}\right]}{\Delta^2}$$

$$r = \frac{n_{con}}{n_{trt}}, \Delta = \mu_{trt} - \mu_{con}$$

μtrt = the mean outcome in the treatment group = 3.00

μcon = the mean outcome in the control group = 5.83

σtrt = the standard deviation in the treatment group = 1.70*

σcon = the standard deviation in the control group = 1.40**

Ratio (control/treatment) = 1.00

Alpha (α) the significance level = 0.01, Z (0.995) = 2.575829

Beta (β) the type II error probability = 0.10, Z (0.900) = 1.281552

Sample size: Treatments = 10, Controls = 10

*, ** the mean outcome and SD in the treatment group and control group based on the research of Orhan Elibol, et al.[10]

This study compares the treatment group (cooling BTX) and the control group (non-cooling BTX) in the same patient. Therefore, a total sample size of at least 10 patients will be included.

Methods

OnabotulinumtoxinA (Botox) concentration 1.25 unit/ml was prepared in an insulin syringe with a 30 gauge needle (using one needle per session) and then put in the refrigerator for 20 minutes to keep BTX cool (about 15-18°C), while non-cooling BTX was stored at room temperature (25-27°C). Cold compression was applied to the periocular area bilaterally 15 minutes before the injection. All participants were unaware of which form of BTX was injected (blind technique).

This study was carried out at the room temperature of 25°C because it is the general temperature used for work. And when the medicine is left over, it will be stored in the normal refrigerator compartment, of which the temperature was measured at 20 minutes to be 15-18°C.

All patients were informed about the procedure and pain score evaluation before starting the treatment and signed consent.

BTX injection points were shown in Figure 1. There were 10 points around the periocular area, 5 on the right side and 5 on the left side. Each of the same positions on each side would be randomly provided cooling or non-cooing BTX. There are 11 patterns of injected points. The injection points for cases with bilateral blepharospasm and bilateral hemifacial spasm were the same.

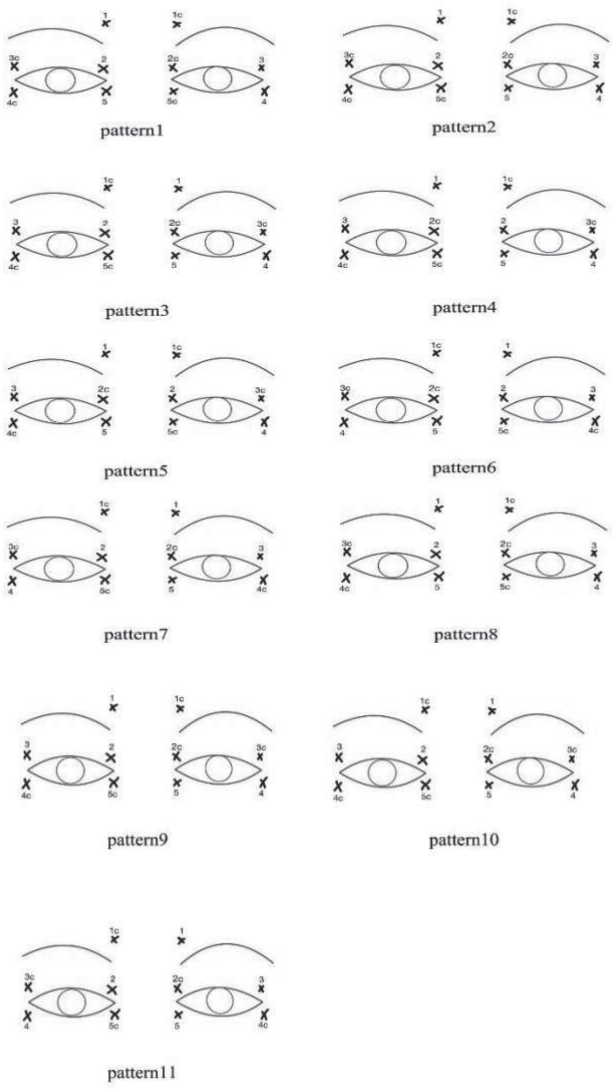

Figure 1: 11 pattern of injection points, 1 - 5 = non-cooling BTX, 1c - 5c = cooling BTX (1 = glabellar line, 2 = medial part of upper lid, 3 = lateral part of upper lid, 4 = lateral part of lower lid, 5 = medial part of lower lid)

Each patient received BTX injections at 10 points around the periocular area according to the patterns they received (5 points with cooling BTX, 5 points with non-cooling BTX). A visual analog scale (VAS) was used for measuring the pain intensity immediately after injection at each point.

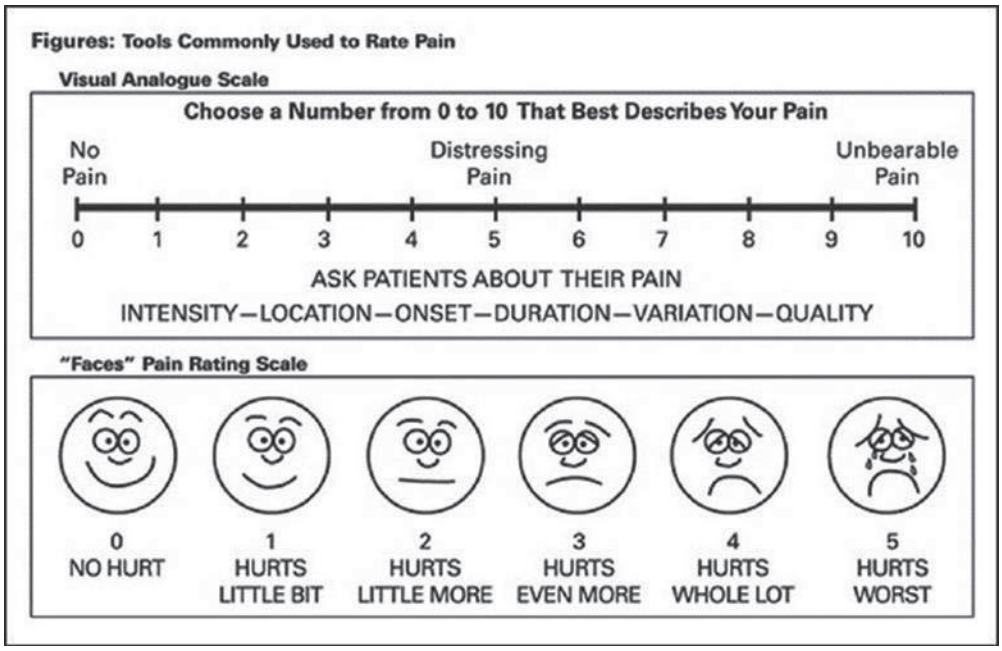

Figure 2: Visual Analogue Scale (VAS)

After the injections, all patients received cold compresses for 5 minutes to stop bleeding. All patients were informed about the procedure and pain score evaluation before starting the treatment and signed consent.

Statistical Analysis

A paired sample t-test was used to compare the means of pain intensity in cooling and non-cooing BTX points of injection.

Ethics

The study was approved by the institutional review board and human research ethics committee of Samutprakarn Hospital; Research study code: Sh01564. Informed consent was obtained from all participants and this study has no conflict of interest.

Results

During the study period, we had 11 cases (6 cases of bilateral blepharospasm, and 5 cases of bilateral hemifacial spasm), ages between 45-81 years old, and 6 cases (54.5%) had a history of cataract surgery. 7 cases (63.6%) had underlying diseases such as hypertension, old CVA, asthma, and hyperlipidemia. Each patient got a BTX injection of 10 points around the periocular area (5 points with cooling BTX, 5 points with non-cooling BTX). Therefore there were a total of 110 points, 55 points of cooing BTX and 55 points of non-cooling BTX injection. The mean pain score of the cooling BTX points was 1.91 ± 1.59, whereas it was 1.89 ± 1.59 on the non-cooling BTX points, the difference was not statistically significant ($p = 0.887$).

The highest pain levels in both groups were at injected points 4 and 3 representing the lateral lower eyelid and lateral upper eyelid respectively (mean pain score = 2.0). The minimum pain level was at injected point 2 which was the medial upper lid (mean pain score = 1.73).

There is no difference in bleeding and other complications between cooling and non-cooling Botox injected points.

Table 1: Demographic data (n = 11)

	Statistics data
Sex, n (%)	
Male	3 (27.3%)
Female	8 (72.7%)
Age	
Mean ± SD	64.27 ± 11.06
Min–Max	45-81
underlying disease, yes n (%)	7 (63.6%)
bilateral blepharospasm, yes n (%)	6 (54.5%)
bilateral hemifacial spasm, yes n (%)	5 (45.5%)
cataract surgery, yes n (%)	6 (54.5%)

Table 2: Pain score

Position	Cooling BTX	Non-cooling BTX	Mean difference (95%CI)	P-value
1 (glabellar line)	2.09 ± 1.76	1.64 ± 1.36	0.45 (-0.17, 1.08)	0.138
2 (medial upper lid)	1.73 ± 1.56	1.73 ± 1.74	0 (-0.42, 0.42)	1
3 (lateral upper lid)	2.09 ± 2.12	2.09 ± 1.81	0 (-0.6, 0.6)	1
4 (lateral lower lid)	2 ± 1.79	2 ± 1.79	0 (-0.42, 0.42)	1
5 (medial lower lid)	1.64 ± 1.75	2.09 ± 1.87	-0.45 (-0.92, 0.01)	0.053
Total	9.54 ± 7.94	9.55 ± 7.87	0 (-1.41, 1.41)	1
Mean	1.91 ± 1.59	1.89 ± 1.59	0.02 (-0.26, 0.29)	0.887

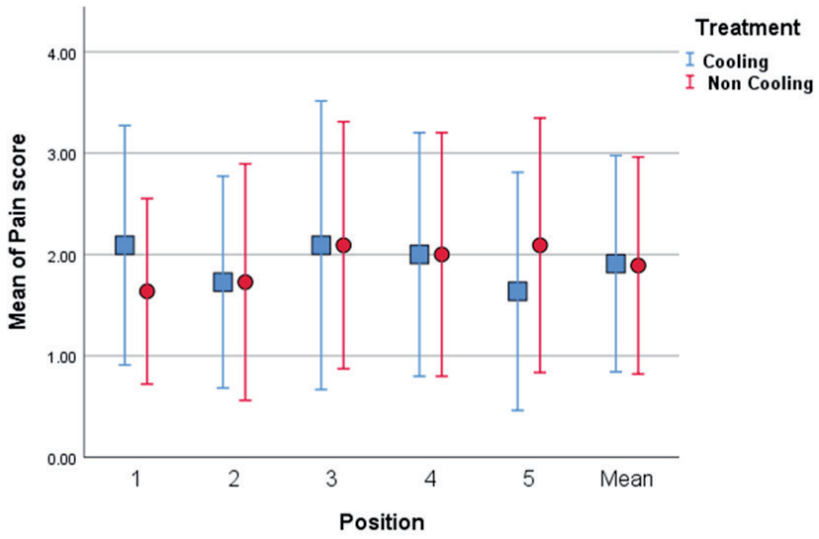

Figure 3: Shows the mean pain score in both groups.

Discussion

In this study, each patient blindly received both cooling and non-cooling BTX injections to compare pain intensity. The result shows that there is no statistically significant difference in the pain intensity between cooling BTX and non-cooling BTX injections. The complications of BTX injections are also not different in both groups which were minimal bleeding and bruised.

This is the first study comparing the pain intensity of cooling BTX and non-cooling BTX injections. There are some limitations in this study such as, only one brand of Botox used, a small sample size and a single-blind study. Therefore, further study should be conducted using other brands of BTX, double-blind method, and including a larger sample size.

In addition, the use of a visual analog scale (VAS) to measure pain level may not be accurate because the pain tolerance of each person is different. Moreover, some patients who want to please their doctor with the efficacy of the results may underreport the actual pain. This bias can be solved by using double-blind testing.

BTX injection is safe and efficient for treating blepharospasm and hemifacial spasm nowadays.[3,4]

More than 95% of blepharospasm improved after BTX injection.[12] BTX mechanism inhibits the presynaptic release of Acetylcholine at the neuromuscular junction causing muscle paralysis.[13-15] However, the action of BTX is not permanent.[5] The effects of BTX last about 3-6 months, so the patient has to repeat injections to continue its effect. Although BTX treatment is very effective, some patients refuse to repeat treatment or feel distressed due to pain while injecting.[12,16] EMLA and cold compression are applied to reduce pain before injection.[6-9,17], but the patients may still feel discomfort. The cold may reduce the pricking pain sensation by reducing blood flow and skin conductance level.[11]

The highest pain levels in both groups were at the lateral part of lower and upper eyelids, therefore the doctor should be careful when injecting these areas.

Conclusion

There was no statistically significant difference in the pain intensity and complication between cooling BTX and non-cooling BTX injections.

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