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Effect of cold compression before botulinum neurotoxin injection in hemifacial spasm

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Abstract

Objectives: To compare the effect of using cold compression before injecting botulinum toxin (BTX) versus not using cold compression, on pain and bleeding at the injection site, efficacy and the quality of life of patients with hemifacial spasm (HFS). *Methods:* A prospective, randomized, case crossover design was employed. One hundred fifty-nine (159) patients who were diagnosed as having primary HFS with BTX treatment in the botulinum toxin clinic were randomized during the period from May 2017 to November 2017. Patients were divided into two groups – with cold compression and without cold compression before BTX injection and then evaluated for the severity and frequency of HSF using the Jankovic Rating Scale and quality of life questionnaire. Immediate complications after injection such as pain and bleeding were also assessed. *Results:* Cold compression before BTX injection significantly decreased the severity and frequency of HFS ($p<0.001$). Pain in cases where cold compression was used before BTX injection was significantly lower than in those cases not receiving cold compression ($p<0.001$). Satisfaction scores and bleeding were significantly different ($p<0.001$). Quality of life was significantly improved after treatment with BTX ($p<0.001$).
Conclusion: Cold compression before BTX injection can improve the efficacy of treatment by reducing severity and frequency. This study confirms previous studies that using cold compression before BTX injection results in a good outcome in relation to satisfaction and bleeding. No significant complications were found. Additionally, BTX injection can also improve quality of life in hemifacial spasm patients.

Keywords: Cold compression, severity, frequency, botulinum, hemifacial spasm

INTRODUCTION

Hemifacial spasm (HFS) is an involuntary clonic or tonic contraction of the upper and lower facial muscles, typically with unilateral involvement but bilateral may occur <1% of the cases.[1] HFS is more common in women than men (ratio 1.5:1) with a prevalence of 14.5/100,000 population in women and 7.4/100,000 in men.[2] The mean age of onset is 55 years with a wide range of onset ages, from juvenile to late in life. Primary HFS is mainly attributed to vascular compression of the seventh cranial nerve at its exit zone from the pons.[3] The most common vascular abnormality is an aberrant or extatic intracranial artery, most commonly an overriding superior cerebellar artery (SCA) or anterior inferior cerebellar artery (AICA), but a vein may also be involved.[4]

Treatment options for HFS include oral pharmacologic therapies, surgery (microvascular decompression of the facial nerve), and local injections of botulinum toxin (BTX). Conventional medical treatments consist of benzodiazepines (clonazepam), anticonvulsants (carbamazepine) or GABAergic drugs (baclofen, gabapentin, pregabalin).[1] Botulinum toxin injection was pioneered by Elston in 1985 and the first study that assessed BTX in hemifacial spasm was conducted in 1986.[5]

Botulinum toxin is a protease exotoxin produced by a gram-positive, rod-shaped, anaerobic, spore-forming, motile bacterium called Clostridium botulinum.[6] The effect of BTX is blockage of acetylcholine release at the neuromuscular junction, which reduces excessive muscular contractions and leads to normalization of muscle activity. The effects of BTX are temporary and the mean duration of effect is 2.6–4 months.[7,8] Numerous trials of treatment of BTX in hemifacial spasm have demonstrated that

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BTX can reduce severity and frequency and also duration of improvement.

Pain during BTX injection is common. Cold compression prior to many interventions such as minor surgery, laser treatments, and skin injections can reduce pain.[9,10,11] Many studies have demonstrated that ice compression before BTX injection can significantly decrease bleeding and pain.[10,12,13]

The Jankovic Rating Scale is used to assess the effect of BTX treatment in hemifacial spasm to evaluate the severity and frequency of spasm. The HFS-7 questionnaire is a short and simple clinical tool to assess patient' quality of life (QoL) in hemifacial spasm. The seven questionnaire items were selected based on those of the HFS-30 questionnaires covering domains such as mobility, activities of daily living, emotional wellbeing, and stigma.[14,15]

The purposes of this study are to compare efficacy and complications of BTX injection in hemifacial spasm with cold compression and without cold compression groups. The efficacy is assessed by severity, frequency, duration of treatment and quality of life (QoL)[16]. For the complications, we evaluate pain by using a visual analog scale, bleeding during injection and other complications such as ptosis and facial asymmetry.

METHODS

Patients

Hemifacial spasm patients whom diagnosed by neurologist in Neurological Institute of Thailand, who were treated with BTX at the Botulinum Toxin Clinic at the Neurological Institute of Thailand during May-November, 2017 were enrolled in this study. Patients aged < 18 years old, unable to understand the Thai language, refused to join this study, or where there was a change in injection site or dosage of BTX during the study period and cases where follow-up was lost were excluded from this study.

Standard protocol approvals and patient consents

The study was approved by the Neurological Institute of Thailand Ethics Committee. All patients were required to sign informed consent.

Study design

This study employs a prospective, randomized, case crossover design to evaluate the relationship between using cold compression and not using cold compression before the same dose injection and the same sites of the same type of BTX injection in 2 session of treatment by the same neurologist, comparing its impact on the severity, frequency, duration of treatment effect and complications of HFS after BTX injection. Such as pain and bleeding. Quality of life (QoL) were also assessed.

Cold compression: We used ice in a 4.5x7-inch plastic bag as a compress on the facial skin at the injection site for two minutes prior to injection.

On the first visit (week 0), baseline demographic data was obtained and the QoL questionnaire HFS-7 was administered to the patients before the study. The patients were divided into two groups; group A received a cold compress before BTX injection; and group B did not receive a cold compress before BTX injection. During weeks 1-13, the patients evaluated severity and frequency of HFS manually by themselves once per week using the Jankovic Rating Scale.

On the second visit, (week 13), information on satisfaction after treatment in the first period was obtained. At this time, group A did not receive cold compression before BTX injection, and group B received cold compression before BTX injection. During weeks 14-26, the patients evaluated severity and frequency of HFS manually by themselves once per week using the Jankovic Rating Scale.

On the third visit (week 26), information on satisfaction after treatment in the second period was obtained and the QoL questionnaire HFS-7 after study was assessed (Figure 1).

We analyzed baseline characteristics: sex, age, side of HFS, duration of HFS, previous treatment with BTX injection, BTX brand, dose of BTX, number of injection sites each time, previous complications, combination treatment with clonazepam.

Severity and frequency: This study used the Jankovic Rating Scale (modified after Jankovic and Orman 1987) to evaluate the rating of spasm severity and frequency in HFS, defined as follows; 0=none; 1=slightly increased frequency of blinking; 2=eyelid fluttering lasting less than one second in duration; 3=eyelid spasm lasting longer than one second, but eyes open more than 50% of the waking time; 4=the involved eye functionally "blind" due to persistent eye closure more than 50% of the waking time.

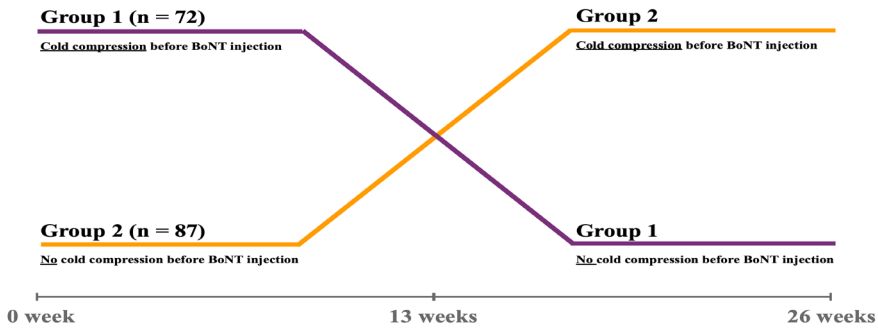

Figure 1. Case-crossover study design

Group 1 = Cold compression before BoNT injection in first visit, then no cold compression before BoNT injection in second visit
Group 2 = No cold compression before BoNT injection in first visit, then cold compression before BoNT injection in second visit

Complications: Complications from BTX injection were classified as bruising, eyelid ptosis, eyebrow ptosis, facial asymmetry, and leakage of fluid when drinking. We also recorded duration of complications in weeks.

Pain scale: This study used a numeric pain distress scale, with the numbers indicating the intensity of pain during injection. The pain scale ranged from 10 for the most unbearable pain to 0 for no pain.

Satisfaction: Satisfaction was rated from 100% for the most satisfied to 0% for unsatisfied.

Bleeding: Bleeding was noted where BTX was injected, the needle removed, and gentle compressed for 10 seconds, but when there was still bleeding.

Quality of life: The study used the QoL HFS-7 questionnaire to assess the patients' quality of life. The QoL HFS-7 questionnaire is a grading system that quantifies the severity of HFS based on functional impairment by evaluating the impact of HFS on activities of daily living. QoL is an important outcome measure in chronic diseases because it is a predictor of morbidity and mortality.[14,15] This questionnaire evaluates seven items: driving, reading, watching television/movies, feeling depressed, avoiding eye contact, feeling embarrassed about having the condition, and feeling worried about others' reactions. Severity grading is: 0=normal; 1=slight disability; 2=moderate disability, no functional impairment; 3=moderate disability, functional impairment; and 4=severely incapacitated.

Statistical analysis

Statistical analysis was conducted using SPSS 16.0 for Windows. Continuous variables were expressed as mean (SD) and median (IQR). Categorical variables were expressed as percentages. The Wilcoxon Signed Ranks Test was used for the Jankovic Rating Scale, pain scale, and satisfaction. The Pearson Chi-square test was used for overall complications from BTX injection. Paired *t*-tests were used for continuous variables for bleeding at the site after injection. The statistical significance cutoff was $p<0.005$.

RESULTS

This study enrolled 188 patients who were diagnosed as primary HFS during the period from May to November 2017, and were treated with BTX injection in Neurological Institute of Thailand. Twenty-nine (29) patients (15.4%) were excluded from the study due to nine lost follow-ups, eight incomplete clinical record forms and 12 changes in sites or dose of BTX injection. (Figure 2)

Patient characteristics: There were 159 HFS patients aged from 23 to 86 years with a mean age of 58.5 ± 11.2 years, comprising 40 (25.2%) males and 119 (74.8%) females. The median duration of disease was six years, and five patients were new cases. With regard to BTX brand, 138 (86.8%) patients were injected with Botox®, nine (5.7%) patients with Dysport® and 12 (7.5%) patients with Neuronox®. The mean total injection sites numbered 5.0 ± 1.4. Eighty-seven patients (54.7%) had previous complications from BTX injections: the most common complications were facial asymmetry followed by leakage of fluid

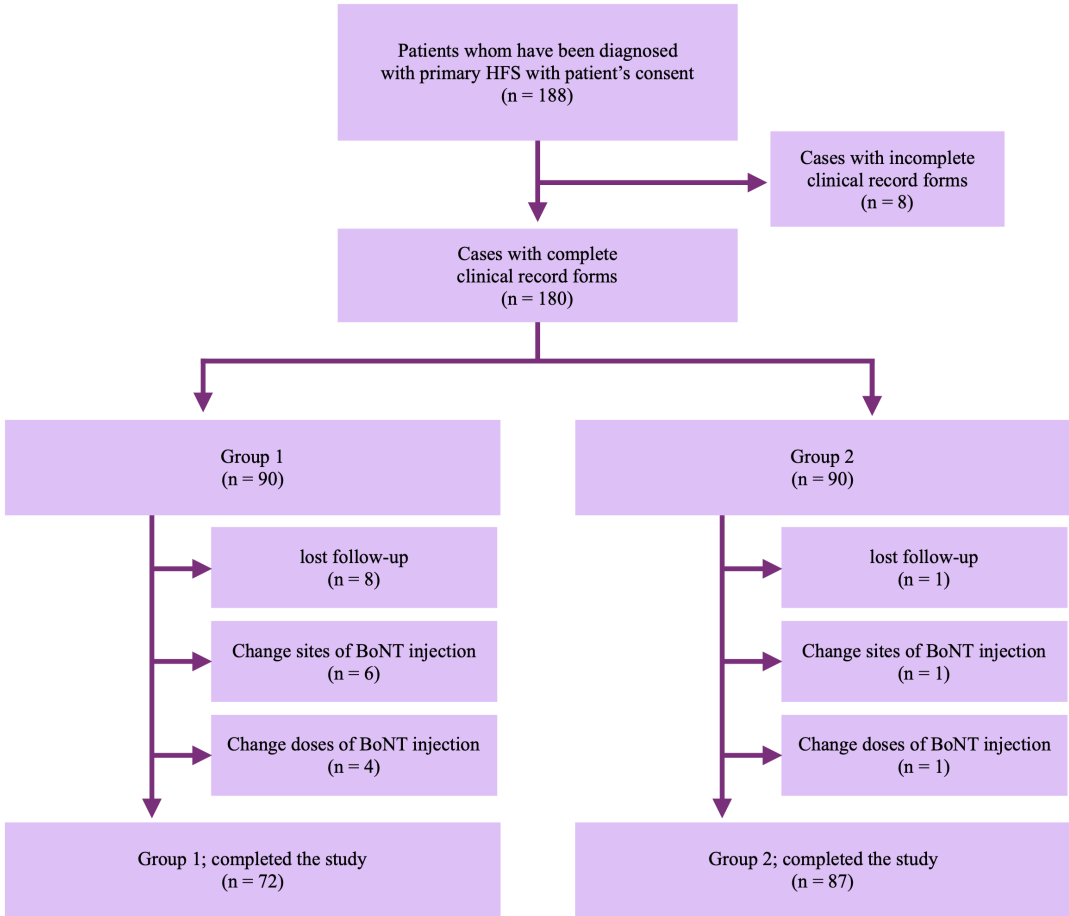

Figure 2. Flow chart of the patient data selection process

Group 1 = Cold compression before BoNT injection in first visit, then no cold compression before BoNT injection in second visit
Group 2 = No cold compression before BoNT injection in first visit, then cold compression before BoNT injection in second visit

while drinking and eyelid ptosis. Two-thirds of the patients (67.9%) received oral clonazepam in combination with BTX injection. There were no significant differences in patient characteristics between the two groups. (Table 1.)

Effect of cold compression before BTX injection: Cold compression before BTX injection significantly decreased severity and frequency of clinical symptoms after treatment as rated on the Jankovic Rating Scale ($p<0.001$). The mean Jankovic Rating Scale of cold compression and no cold compression before BTX injection is shown weekly for the entire 13 weeks showed that cold compression had significant less severity and longer treatment effect as shown by less median JRS in each week. (Figure 3)

Due to the crossover design of this study, the Jankovic Rating Scale was lower in the cold compression period as compared with the non-compression period in both groups at 26 weeks. ($p < 0.001$). (Figure 4) This demonstrated effect of cold compression before injection on clinical outcome of muscle spasm and had longer duration of the treatment effect in each group.

The pain scale ratings and number of bleeding sites after injection in the cold compression before BTX injection group were significantly lower than those without cold compression ($p<0.001$); while satisfaction was also significantly different ($p<0.001$). There were no significant differences in overall complications and duration of complications among the study groups. (Table 2)

Quality of life: This study used the QoL HFS-7 questionnaire to evaluate the patients' quality of life before and after the study (week zero and week 26). The mean (SD) of the QoL HFS-7 questionnaires was significantly different between the before and after study [7.3 (6.2) vs. 5.9 (5.4)],

Table 1. Patient characteristics

	All (n=159)	Group 1 (n=72)	Group 2 (n=87)	p value
Sex (male)	40 (25.2%)	20 (27.8%)	20 (23.0%)	0.488
Age (years; mean, SD)	58.5 (11.2)	59.7 (10.3)	57.4 (11.9)	0.202
Side of HFS				
Left	77 (48.4%)	35 (48.6%)	42 (48.3%)	0.966
Right	82 (51.6%)	37 (51.4%)	45 (51.7%)	
Duration of HFS (years; median, IQR)	6 (4.0-10.4)	7.0 (4.0-10.0)	6.0 (3.0-10.0)	0.320
Previous treatment with BoNT injection (times)				
Never	5 (3.1%)	2 (2.8%)	3 (3.4%)	0.963
1 time	1 (0.6%)	0 (0.0%)	1 (1.1%)	
2-4 times	17 (10.7%)	7 (9.7%)	10 (11.5%)	
more than 5 times	136 (85.6%)	63 (87.5%)	73 (84.0%)	
Trade name of BoNT				
Botox®	138 (86.8%)	60 (83.4%)	78 (89.7%)	0.492
Dysport®	9 (5.7%)	5 (6.9%)	4 (4.6%)	
Neuronox®	12 (7.5%)	7 (9.7%)	5 (5.7%)	
Dose of BoNT (units)				
Botox (units; median, IQR)	20.0 (15.0-30.0)	20.0 (15.0-30.0)	21.5 (15.0-30.0)	0.144
Dysport (units; median, IQR)	90.0 (60.0-100.0)	90.0 (57.5-100.0)	95.0 (67.5-122.5)	0.219
Neuronox (units; median, IQR)	15.0 (15.0-18.0)	18.0 (15.0-18.0)	15.0 (10.0-16.5)	0.679
Number of injection sites each time (sites; mean, SD)	5.0 (1.4)	5.0 (1.3)	5.0 (1.4)	0.991
Previous complication from BoNT injection	87 (54.7%)	37 (51.4%)	50 (57.5%)	0.443
Bruising	13 (9.2%)	7 (11.9%)	6 (7.3%)	0.371
Eyelid ptosis	33 (23.4%)	10 (16.9%)	23 (28.0%)	0.071
Eyebrow ptosis	7 (5.0%)	4 (6.8%)	3 (3.7%)	0.452
Facial asymmetry	52 (36.9%)	21 (35.6%)	31 (37.8%)	0.622
Leakage of fluid while drinking	36 (25.5%)	17 (28.8%)	19 (23.2%)	0.457
Combination treatment with clonazepam	108 (67.9%)	53 (73.6%)	55 (63.2%)	0.162

Group 1 = Cold compression before BoNT injection in first visit, then no cold compression before BoNT injection in second visit
Group 2 = No cold compression before BoNT injection in first visit, then cold compression before BoNT injection in second visit

($p<0.001$). When we consider all seven items of the QoL HFS-7 questionnaire, we found that they all were significantly different between the before and after study ($p<0.001$). (Table 3)

DISCUSSION

Cold compression on the skin can induce numbness and vasoconstriction in that area. A number of previous studies on BTX injection found that cold compression can reduce pain and the number of bleeding sites. According to previous studies, ice is also beneficial in local anesthesia through its ability to vasoconstrict in the skin, which reduces the incidence and severity of bruising post injection. This vasoconstrictive effect is evident down to approximately 15°C.[17]

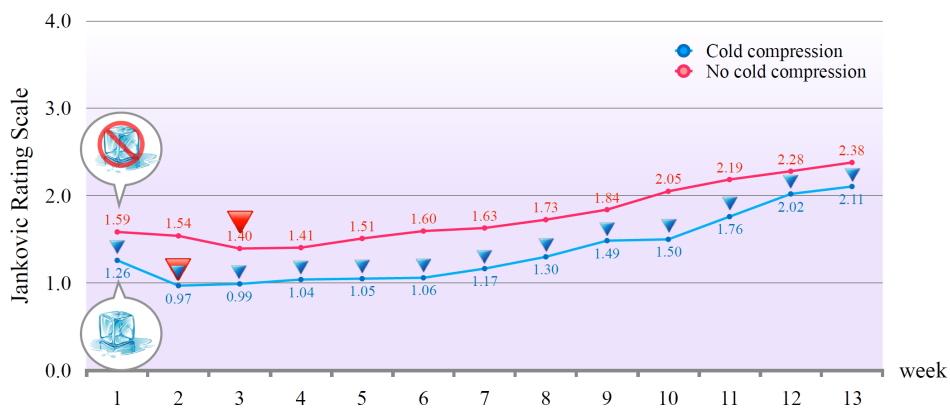

Figure 3. The mean Jankovic Rating Scale of Cold and No cold compression

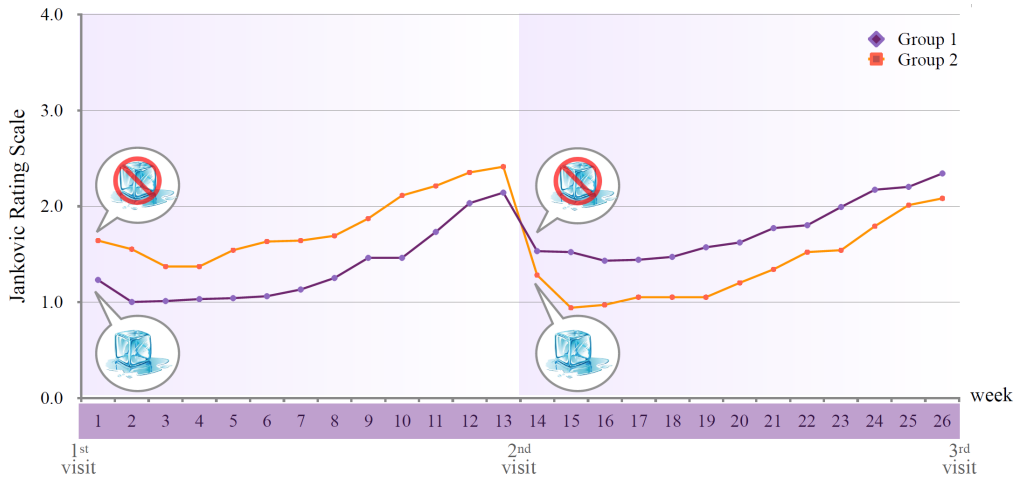

Figure 4. The mean Jankovic Rating Scale of Group 1 and Group 2 in 26 weeks

Group 1 = Cold compression before BoNT injection in first visit, then no cold compression before BoNT injection in second visit
Group 2 = No cold compression before BoNT injection in first visit, then cold compression before BoNT injection in second visit

Table 2. Categorized analysis

	Cold compression before BoNT injection	**No cold compression before BoNT injection**	**p value**
Jankovic Rating Scale (median, IQR)	1.2 (0.8-1.8)	1.7 (1.2-2.3)	<0.001*
Overall complication from BoNT injection (n, %)	8 (11.1)	12 (13.8)	0.237
Types of complication			
Bruising (n, %)	1 (12.5)	4 (28.6)	NA
Eyelid ptosis (n, %)	4 (50.0)	4 (28.6)	NA
Eyebrow ptosis (n, %)	0 0.0	1 (7.1)	NA
Facial asymmetry (n, %)	0 0.0	2 (14.3)	NA
Leakage of fluid when drinking (n, %)	3 (37.5)	3 (21.4)	NA
Duration of complication (week; median, IQR)	2.0 (1.0-2.3)	2.0 (1.3-3.0)	NA
Pain scale (median, IQR)	3.0 (2.0-5.0)	5.0 (3.0-7.0)	<0.001*
Satisfaction (median, IQR)	80.0 (70.0-90.0)	70.0 (60.0-80.0)	<0.001*
Sites of bleeding after injection (sites; mean, SD)	0.7 (0.9)	1.2 (1.1)	<0.001*

*significant at 99% confidence interval (p<0.001)

Table 3. QoL questionnaire HFS-7

HFS-7 items	**Before study** Median (IQR)	**After study** Median (IQR)	**p value**
1 Having difficulty in driving	0.00 (0.0-1.0)	0.00 (0.0-1.0)	<0.001*
2 Having difficulty in reading	1.00 (0.0-2.0)	1.00 (0.0-1.0)	<0.001*
3 Having difficulty in watching television/movie	1.00 (0.0-2.0)	0.00 (0.0-1.0)	<0.001*
4 Feeling depressed	0.00 (0.0-1.0)	0.00 (0.0-1.0)	<0.001*
5 Avoiding eye contact	1.00 (0.0-2.0)	1.00 (1.0-2.0)	<0.001*
6 Feeling embarrassed about having the condition	1.00 (0.0-2.0)	1.00 (0.0-2.0)	<0.001*
7 Feeling worried about others' reaction; mean (SD)	1.28 (1.3)	0.99 (1.1)	<0.001*
Overall QoL questionnaire HFS-7; mean (SD)	7.3 (6.2)	5.9 (5.4)	<0.001*

*significant at 99% confidence interval (p<0.001)

As skin temperature drops to 10°C, nerve conduction velocity is reduced by approximately 33%, resulting in a higher pain threshold.[18,20] *Patcharin S, et al*, studied the effect of cold compression before and after injection compared to a placebo and found that ice compression can reduce pain in both cold compression groups compare to a placebo, but only the cold compression before injection group experienced reduced bleeding.[12] In our study, we used ice compression on the skin area of injection for two minutes before injection. The pain scale ratings were lower in cold compression group which may be due to numbness low temperature induced numbness. Also, number of bleeding sites were significant lower in the cold compression group than in the no cold compression group which may explained by cold induce vasoconstriction. This explains the beneficial effect of cold compression before injection by reducing pain and bleeding as shown in previous studies.

Adding to the literature, this study is among the first that highlights the relationship between the effect of cold compression and the severity and frequency of hemifacial spasm by using the Jankovic Rating Scale. In addition, the study found that the cold compression group reached the lowest point on the scale in two weeks after injection compared to the no cold compression group, which reached the lowest point in three weeks this explain that cold compression may accelerate effect of BTN faster than the controls. (Figure 3). When we evaluated the duration of BTX treatment by the amount of time taken to reach the point of initial treatment, we found that the cold compression group experienced a longer duration than the no cold compression group.

With our crossover study design, we demonstrated that the effect of cold compression was the same in both groups: there was no effect on the scale results for both groups before and after intervention. (Figure 4) The scale results at the end of each period were lower in the cold compression groups for both groups. This confirmed that cold compression could improve efficacy and prolong the effect of BTX. The effect of cold compression on BTX treatment may be due to cold effect at the injection site may reduce diffusion of the toxin in that area, meaning that a greater amount of the toxin remained at the site.

In most studies, the Jankovic Rating Scale was evaluated monthly by physicians[9]; but in our study, we allowed patients to self-evaluate on the Jankovic Rating Scale weekly. This greater frequency could provide additional detail on the efficacy of cold compression in BTX injection. According to previous studies, there was no significant difference between different brands of BTX in terms of effect.[18] Thus, this study did not investigate the efficacy of the different brands in terms of severity and frequency of HFS. Another limitation is that this study did not evaluate the relationship between the patients who took clonazepam and those who did not, as well as compliance and other risk factors that can cause the disease to worsen. Also, we did not keep records of patients with bleeding risk factors such as those currently using antiplatelet or anticoagulant medication. Our study found a small number of subjects experiencing complications from BTX injection. With cold compression before BTX injection fewer complications were found than with no cold compression, but there was no statistical significance. Significance may be achieved in a larger population, however.

We found that BTX treatment can improve the quality of life for patients with hemifacial spasms on all seven questionnaire items.

In conclusion, ice compression for two minutes before BTX injection reducee pain and bleeding at the injection site. This ice compression also improved the effect of BTX, in the severity and frequency of facial spasm as assessed by the Jankovic rating scale and maximized the effect of BTX. The results confirmed the hypothesis and further suggested that reducing skin temperature by cold compression can reduce bleeding, which may result in a greater amount of BTX remaining in the skin, resulting in BTX acting more quickly and having a more sustained effect.

This study also confirmed previous findings and contributes additional evidence suggesting that patients experience a better quality of life after the treatment with BTX injection, and all of seven items of HFS-7 questionnaire showed significant differences before and after the study.

There are a few limitations to this study, however, which include the subjectivity of the Jankovic Rating Scale evaluation; and not having addressed the results among different BTX brands, BTX treatment in combination with clonazepam, or bleeding risks.

Further research should be undertaken to investigate complications after BTX injection in a larger population.

DISCLOSURE

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