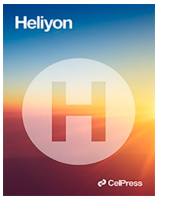
Heliyon 10 (2024) e24898

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Factors influencing short-term prognosis after botulinum toxin type A treatment for hemifacial spasm : A retrospective study

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ARTICLE INFO

Keywords:
Hemifacial spasm
Botulinum toxin
Prognosis
hypertension

ABSTRACT

Background: It is widely acknowledged that botulinum toxin type A (BTX-A) has been widely used in the treatment of hemifacial spasm (HFS). However, there is currently a lack of systematic analysis of the factors affecting its therapeutic effect. Therefore, this study aims to explore the influencing factors of BTX-A in the treatment of HFS and to identify risk factors for poor prognosis.

Methods: Retrospective study including 118 patients with HFS treated with BTX-A from 2019 January to 2023 April. Demographic and etiological variables as well as doses, number of sessions of BTX-A, infiltrated muscles, therapeutic response according to the Cohen evaluation scale, and side effects were analyzed. Logistic regression analysis was performed to identify the factors that are associated with the short-term prognosis of BTX-A for the treatment of HFS.

Results: Among the 118 patients with HFS included in this study, 57 achieved complete relief, 51 had significant relief, 7 had partial relief, and no improvement was observed in 3. The overall effective rate was 91.53 %. Results from the univariate analysis indicated that male, drinking, diabetes, and hypertension were all associated with poor short-term prognosis of BTX-A in the treatment of HFS. Multivariable logistic regression analysis further revealed that hypertension was an independent risk factor for poor short-term prognosis following BTX-A treatment for HFS (OR=5.847, $P<0.05$).

Conclusion: BTX-A was effective in treating HFS and had minimal adverse effects. Hypertension was an independent risk factor for poor short-term prognosis following BTX-A treatment of HFS.

1. Introduction

Hemifacial spasm (HFS) is a prevalent craniofacial nerve disorder, characterized by involuntary, periodic contractions or spasms of muscles supplied by the ipsilateral or bilateral facial nerves, such as orbicularis oculi, facial and orbicularis oris muscles [1]. These spasms are exacerbated by excitement or stress and can cause difficulties in eye-opening, mouth asymmetry, and auditory symptoms such as clicking sounds in severe cases [2]. The mean prevalence of HFS is approximately 10 in 100000 [3]. The average age at onset of primary HFS ranges from the fifth to sixth decades of life, and there is a higher prevalence among females [4,5]. The persistent attacks of HFS can significantly impact patients' daily lives, resulting in reduced confidence in social and professional situations [6]. Patients

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https://doi.org/10.1016/j.heliyon.2024.e24898
Received 13 July 2023; Received in revised form 17 December 2023; Accepted 16 January 2024
Available online 17 January 2024

with HFS often experience emotional and social difficulties that further complicate their health, family, and social lives [2,7]. Therefore, early and accurate diagnosis and treatment are particularly important for patients with HFS to improve their quality of life and psychological well-being.

The treatment of HFS includes medication, botulinum toxin injection, and surgery. Among them, local injection of botulinum toxin type A (BTX-A) has become one of the preferred treatments for HFS, with advantages such as rapid onset, minimal adverse reactions, and sustained therapeutic effects following repeated injections [8–10]. BTX-A is a neurotoxin produced by *Clostridium botulinum* that acts by inhibiting the release of acetylcholine at the neuromuscular junction, thereby blocking neural-muscular signal transmission and achieving biochemical denervation-induced muscle relaxation [11]. Currently, the safety and efficacy of BTX-A in treating HFS have been adequately confirmed. A retrospective study involving 162 patients with HFS found that BTX-A was effective in improving symptoms, with a total duration of treatment effect per injection of approximately 3.6 months and few side effects [12]. A prospective study analyzed changes in quality of life in 74 patients with HFS following treatment with BTX-A. The study found that throughout a five-year treatment period, BTX-A effectively improved symptoms and increased the patient's quality of life [13]. However, due to the current focus on exploring the efficacy of BTX-A therapy for HFS, few studies have analyzed factors affecting its short-term efficacy.

Therefore, this study aimed to retrospectively analyze clinical data of HFS patients treated with BTX-A and investigate the related factors that affect the short-term prognosis of BTX-A treatment for HFS. The objective was to identify the risk factors leading to poor short-term prognosis of HFS and provide more precise clinical guidance for treatment.

2. Materials and methods

2.1. Participants

A retrospective study was conducted including patients diagnosed with HFS and treated with botulinum toxin type A (Lanzhou Institute of Biological Products, Lanzhou, China) at the Department of Neurology of the Second Affiliated Hospital of Nanchang University from 2019 January to 2023 April. The Institutional Review Board of the Second Affiliated Hospital of Nanchang University approved this study. Informed consent was obtained from all participants.

All patients fulfilled the following inclusion criteria: (1) age equal or greater than 18 years; (2) symptoms and signs consistent with the diagnosis of HFS; (2) first-time BTX-A treatment with complete follow-up data; (3) underwent routine cranial magnetic resonance imaging (MRI) and three-dimensional time-of-flight magnetic resonance angiography(3D-TOF-MRA) examination, with clear vascular and neuronal imaging. The exclusion criteria were: (1) secondary HFS; (2) incomplete medical records; (3) patients with severe brain trauma or organic brain diseases. Based on these criteria, out of the initial sample of 133 patients treated with BTX-A during the study period, 118 patients were included in this study.

The administration of BTX-A was through subcutaneous or intramuscular injection. The selection of muscles, dosage of medication, and specific injection sites were personalized based on each patient's clinical presentation, considering factors such as the severity and distribution of symptoms. The injected muscles included the orbicularis oculi, frontalis, corrugator supercilii, zygomaticus major, orbicularis oris, and platysma, with a dosage range of 1–5 units.

2.2. Clinical assessment

The clinical and demographic data collected included: general characteristics (gender, age, education level), lifestyle habits (smoking, drinking), life events (history of head injury, hypoxia, poisoning), comorbidities (hypertension, diabetes, cardiovascular diseases), age of onset, disease duration, progression of symptoms, cranial MRI, dosage of BTX-A injection, and other relevant information.

The severity of HFS in patients was assessed using the Cohen evaluation scale before and after BTX-A treatment [14]. And the effectiveness information of the patients was obtained through telephone follow-up and video consultations. The assessment of therapeutic efficacy involved detailed questioning regarding changes in symptoms, documentation of adverse reactions following injection, and re-recording of videos during a follow-up visit 2–4 weeks after treatment. The grading system for the Cohen evaluation scale was as follows: 0 indicates no spasm, 1 indicates increased blinking caused by external stimuli, 2 indicates mild muscle tremors without functional impairment, 3 indicates moderate spasms with mild functional impairment, and 4 indicates severe spasms and functional impairment that affect work, such as difficulty in reading and driving. The changes in the degree of spasticity before and after BTX-A treatment were used as the evaluation criteria for efficacy, specifically as follows: complete relief was defined as the reduction from 1 to 4 to 0 after BTX-A treatment, marked improvement was defined as a reduction in grade from 2 to 3 to 1 or from 4 to 1–2, partial improvement was defined as a reduction in grade from 3 to 2 or grade 4 to 3, and no change was defined as ineffective. Both complete relief and marked improvement were considered effective, and any other response was considered ineffective [15].

3D-TOF-MRA is helpful in understanding the vascular distribution around the facial nerve, providing a 360° visualization of all vessels that are anatomically related to the facial nerve. The significance of this examination lies in its ability to identify the blood vessels in direct contact with the facial nerve, including their categorization, caliber, and degree of compression on the nerve. Therefore, we used this neuroimaging examination to assess the compression of the facial nerve by blood vessels in the brainstem region and the degree of compression. The assessment was carried out by two experienced neuroimaging physicians who were not aware of the patient's symptoms. The location relationship between blood vessels and nerves was classified into three categories based on axial, coronal, and sagittal images: (1) no contact, where no blood vessels are visible around the nerve, or the minimum distance between the surrounding blood vessels and the nerve is greater than the maximum diameter of the blood vessel; (2) close contact,

where there is contact between the surrounding blood vessels and the nerve, and the minimum distance between them is not greater than the maximum diameter of the blood vessel; (3) compression, where blood vessels cause impressions, displacement or indentation in the nerve's course [16]. Both close contact and compression are considered vascular contact.

2.3. Statistical analysis

The data were entered into SPSS 25.0 software for statistical analysis. Normality tests and descriptive statistics were performed on quantitative data, with mean ± standard deviation (mean±SD) used to represent normally distributed quantitative data, and median (interquartile range, IQR) used to represent skewed quantitative data. The significance of differences between the effective and ineffective groups was evaluated using the independent Student's t-test or the Mann-Whitney *U* test for continuous and ordinal variables, while Pearson's chi-square test or Fisher's exact test was used for categorical variables. Multivariate analysis was carried out with a logistic regression model to identify variables related to short-term prognosis following BTX-A treatment of HFS. The effective and ineffective groups were included as the dependent variables, whereas gender, alcohol consumption, diabetes mellitus, and hypertension were included as controlled variables. The logistic regression results are presented using odds ratios with 95 % confidence intervals. A P value < 0.05 indicated statistical significance.

3. Results

3.1. Demographic information and clinical characteristics

This study included 118 patients with HFS with an age range of 19–83 years and a mean age of 54.20 (11.95) years old. The mean age of onset for HFS was 51.46 (11.42) years old. Among males, the average age of onset was 51.31 (11.24) years, while among females, it was 51.55 (11.60) years. Of the participants, 45 were male and 73 were female. The duration of HFS ranged from 0.08 to 20 years, with a median duration of 2 (1–3.25) years. Among the patients, 27 had hypertension, 23 had diabetes, and 6 had a history of stroke. There were 24 smokers and 18 alcohol drinkers among the study population (Table 1).

Table 1
Baseline characteristics of study participants.

Characteristics	Overall (N = 118)
General characteristics	
Age(years), mean ± SD	54.20(11.95)
Onset age(years), mean ± SD	51.46(11.42)
Course of disease	2(1.00–3.25)
Sex, n (%)	
Male	45(38.13)
Female	73(61.87)
Education level, n (%)	
<Highschool	82(69.49)
Highschool	20(16.95)
>Highschool	16(13.56)
Lifestyle habits	
Smoking status, n (%)	
No	94(79.66)
Yes	24(20.34)
Drinking, n (%)	
No	100(84.75)
Yes	18(15.25)
Comorbidities	
Diabetes mellitus, n (%)	
No	93(78.81)
Yes	25(21.19)
Hypertension, n (%)	
No	91(77.12)
Yes	27(22.88)
Stroke, n (%)	
No	112(94.90)
Yes	6(5.10)
Vascular contact on the responsible side, n (%)	
No	43(36.44)
Yes	75(63.56)
Outcome, n (%)	
Ineffective	10(8.47)
Effective	108(91.53)

Abbreviations: Values are medians (IQR) unless otherwise indicated.

3.2. Effect of BTX-A in the treatment of HFS

During the 2–4 weeks follow-up period after BTX-A treatment, complete relief was achieved in 57 cases, marked improvement was observed in 51 cases, partial improvement was noted in 7 cases, and no change was seen in 3 cases. Among them, there were 37 males and 71 females who demonstrated a positive response to the treatment. The overall effective rate was 91.53%. A total of 55 individuals (46.61%) reported adverse effects, with an average age of 53.96 (11.92). Among them, 27 were female, and there were 11 individuals with hypertension, 10 with diabetes, 2 with a history of stroke, and 4 with cardiovascular diseases. The reported adverse effects included facial rigidity, crooked mouth, and drooping eyelids. However, these symptoms resolved spontaneously without specific intervention after BTX-A treatment, typically within 5–10 days.

3.3. Univariate analysis of short-term prognosis of HFS treated with BTX-A

According to the results of the univariate analysis shown in Table 2, significant differences were observed in gender, alcohol consumption, hypertension, and diabetes among different prognostic groups ($P<0.05$).

3.4. Multivariate analysis of short-term prognosis of HFS treated with BTX-A

Logistic regression analysis was conducted to determine the factors that affect the short-term prognosis of BTX-A treatment for HFS. The effective and ineffective groups were set as dependent variables, while gender, alcohol consumption, diabetes mellitus, and hypertension were set as control variables. Results from the logistic regression analysis showed that hypertension is an independent risk factor for poor short-term prognosis of BTX-A treatment for HFS (OR=5.847, $P<0.05$) (Table 3).

4. Discussion

This study was the first to investigate the factors affecting the short-term prognosis of BTX-A treatment for HFS. The results demonstrated that BTX-A can effectively improve symptoms of HFS without causing serious adverse reactions. Furthermore, we found that hypertension was an independent risk factor for the short-term prognosis of BTX-A treatment for HFS.

Among 118 HFS patients, 28 had concurrent hypertension in our study, and all patients took anti-hypertensive drugs. Both

Table 2
Univariate analysis of the prognostic factors of hemifacial spasm after botulinum toxin type A treatment.

Variable	Effective	Ineffective	*P* Value
General characteristics			
Age(years)	53.97(12.01)	56.70(11.64)	0.492[a]
Onset age(years)	51.11(11.39)	55.20(11.63)	0.281[a]
Course of disease	1(1.00–2.75)	2(0.94–4.00)	0.423[b]
Sex			0.004
Male	37	8	
Female	71	2	
Education level			0.589
<Highschool	74	8	
Highschool	18	2	
>Highschool	16	0	
Lifestyle habits			
Smoking status			0.428
No	87	7	
Yes	21	3	
Drinking			<0.001
No	96	4	
Yes	12	6	
Comorbidities			
Diabetes mellitus			0.011
No	90	5	
Yes	18	5	
Hypertension			<0.001
No	88	3	
Yes	20	7	
Stroke			0.460
No	103	9	
Yes	5	1	
Vascular contact on the responsible side			0.658
No	40	3	
Yes	68	7	

Abbreviations: [a] Student's t-test was used for comparison between groups; [b], Mann-Whitney *U* test was used for comparison between groups; Pearson's chi-square test was used for comparison between groups unless otherwise indicated.

Table 3
Multivariate analysis of the prognostic factors of hemifacial spasm after botulinum toxin type A treatment.

Variable	Standard Error	Wald	OR (95 % CI)	*P* Value
Sex	1.069	0.623	2.325(0.268–18.890)	0.430
Drinking	0.948	2.262	4.159(0.649–26.640)	0.133
Diabetes mellitus	0.781	0.916	2.111(0.457–9.748)	0.339
Hypertension	0.788	5.016	5.847(1.257–27.422)	0.025

Abbreviations: OR, odds ratio; CI, confidence interval.

univariate and multivariate analysis results suggested that concurrent hypertension was a risk factor for poor short-term prognosis of BTX-A treatment in HFS patients. Studies indicate a significant correlation between hypertension and the severity of HFS [17]. A retrospective study has indicated that there is a higher risk of adverse reactions after microvascular decompression treatment among patients with HFS who have hypertension [18]. He et al. [19] found that HFS combined with hypertension was independently associated with postoperative delirium after microvascular decompression. Although the effectiveness of BTX-A in treating HFS has been widely recognized, there is currently a lack of research on the short-term prognosis effect of hypertension on BTX-A treatment for HFS. In our study, we have made the novel discovery that hypertension was an independent risk factor for poor short-term prognosis following BTX-A treatment of HFS. Therefore, these results suggested that in the process of clinical diagnosis and treatment, it was important to explore alternative treatment options such as microvascular decompression surgery for HFS patients with hypertension. In addition, multi-center, larger sample sizes, and prospective cohort studies are needed to further verify this conclusion.

Hypertension may exert adverse effects on the short-term prognosis of BTX-A treatment for HFS, and its mechanisms mainly include the following aspects: Firstly, hypertension can cause vasoconstriction and increased resistance in small blood vessels, thereby affecting the microcirculation function of local tissues [20]. After BTX-A injection, it needs to be absorbed and diffused through local tissues [21,22]. If there is a local microcirculatory disorder, it will affect the absorption and efficacy of the drug, which is speculated to be one of the main reasons for the poor response of hypertensive patients to drug treatment. Secondly, hypertension patients undergo long-term antihypertensive drug therapy, and some drugs inhibit or affect neurotransmitter release, affecting the excitation of neuromuscular junctions, which may aggravate HFS [23,24]. BTX-A inhibits the excitation of neuromuscular junctions. If the excitability of neuromuscular junctions is already poor at this time, it may lead to an unsatisfactory therapeutic effect. Finally, hypertension patients have neuroregulatory imbalance and enhanced sympathetic nervous system activity [25–27], which may lead to worsened HFS. BTX-A treatment for HFS mainly blocks the release of acetylcholine, inhibiting muscle contraction and alleviating symptoms [28]. However, this mechanism may conflict with the neuroregulatory imbalance of hypertension, affecting the therapeutic effect. In summary, when diagnosing and treating HFS, doctors need to consider whether patients have underlying conditions such as hypertension and adjust the treatment methods accordingly to improve the therapeutic effect.

In the univariate analysis, we also found a significant correlation between male, alcohol consumption, and comorbid diabetes with poor short-term prognosis of BTX-A treatment for HFS. However, we did not observe any significant associations in the multivariate analysis. Some studies have found that there are no significant differences between genders in the treatment outcomes of BTX-A [29–31]. These findings supported our conclusion. Research has shown that drinking can exacerbate the severity of facial muscle spasms in HFS [32]. However, there was a lack of evidence regarding the impact of alcohol consumption on the efficacy of BTX-A in the treatment of HFS. Considering that alcohol consumption can potentially affect the nervous system and exacerbate symptoms of certain neurological disorders [33], as well as impact vasodilation and microcirculation [34], which may influence the absorption and efficacy of BTX-A, we recommend that patients avoid drinking during treatment to ensure optimal effectiveness. Although some studies have found that diabetes may be associated with the severity of HFS, no specific study has investigated the influence of diabetes on the efficacy of BTX-A treatment [35]. However, diabetes may cause neurological and microvascular complications [36], which could potentially affect the diffusion, absorption, and therapeutic effects of BTX-A. Patients with diabetes may also experience peripheral neuropathy [37], which could worsen the symptoms of HFS and impact the efficacy of BTX-A. Further research is needed to clarify the effects of diabetes on the efficacy of BTX-A in treating HFS. In summary, the effects of gender, alcohol consumption, and diabetes on the short-term prognosis of BTX-A treatment for HFS still need more studies to verify and confirm in the future. In clinical practice, healthcare professionals will consider the individual circumstances of each patient and rely on their clinical experience to determine the most appropriate treatment plan.

This study has some limitations as a retrospective analysis. Firstly, the study was based on a single-center sample and may not fully represent the overall characteristics of the population under investigation. Secondly, due to the limited number of patients included in this study, there was no further screening or balancing of baseline data among HFS patients. Future studies using a prospective cohort design are needed to validate our findings. Thirdly, other confounding factors that could influence the efficacy of BTX-A treatment for HFS were not taken into account in this study. In addition, our study relied on existing medical records and data, which may be incomplete, and there may be differences in the quality and accuracy of the data that could affect the findings. Finally, the follow-up period of this study was relatively short, which may have limited our ability to assess the long-term outcomes of BTX-A treatment for HFS. Therefore, larger-scale studies with longer follow-up periods are required to confirm these findings and provide more robust evidence.

5. Conclusion

In summary, BTX-A was an effective treatment for HFS with minimal adverse effects. Our study results demonstrated that hypertension was an independent risk factor associated with poor short-term prognosis following BTX-A administration in the management of HFS.

6. Institutional Review Board statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of the Second Affiliated Hospital of Nanchang University (approval number: 102).

Funding

This work was supported by the Jiangxi Province Postgraduate Innovation Special Fund (Grant numbers: YC2022–B065 and YC2021–B049), National Natural Science Foundation of China (Grant numbers: 82160227), Natural Science Foundation of Jiangxi Province (Grant numbers: 20224BAB206036), Jiangxi Provincial Department of Education Science and Technology Program Project (Grant numbers: GJJ210125) and Clinical Research Project Supported by the Second Affiliated Hospital of Nanchang University (Grant numbers: efy2022C02).

Data availability statement

The original contributions presented in the study are included in the article material, further inquiries can be directed to the corresponding author.

CRediT authorship contribution statement

Sheng Tian: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Heqing Zheng:** Project administration, Investigation, Formal analysis, Data curation. **Lanxiang Wu:** Methodology, Formal analysis. **Wei Wu:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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