Botulinum Toxin Type A as an Effective Prophylactic Treatment in Migraine: an Open-label Study

Hu Yueyu, Hu Xingyue
(Department of Neurology, Sir Run Run Shaw Hospital,
Medical School of Zhejiang University, Hangzhou Zhejiang 310016 China)

Abstract

Objective: To evaluate the efficacy and adverse reactions of botulinum toxin type A in migraine prophylaxis.

Method: We performed a 3-month open study that enrolled 30 adult migraineurs, and botulinum toxin type A was injected into multiple sites of pericranial muscles. During 3-month baseline period and other 3 month following injection, subjects kept daily diaries recording migraine frequency, duration and severity together with acute migraine medication usage, and the occurrence of treatment-related adverse reactions

Results: After comparing with those of pretreatment, subjects received pericranial intramuscular administration of botulinum toxin type A, showed significant reduction for migraine medication usage for at least three months (P<0.01), and no severe treatment-related adverse reactions were observed.

Conclusion: Pericranial intramuscular injection of botulinum toxin type A is safe and effective treatment significantly reducing the frequency, severity, duration, and acute medication usage of migraine.

Key words: Botulinum toxin type A; Migraine; Drug therapy

Migraine is a common neurological disease with the incidence rates for male and female being 6% and 18% respectively and at age 25 to 55 [1]. For patients having severe migraine, they are commonly associated with nausea, vomiting, photophobia, phonophobia. The repeated occurrence seriously interferes with the patient's daily routine, however, the current therapeutic approaches will cause relatively more adverse events and the therapeutic efficacy is uncertain. Oversea studies indicated that injection of botulinum toxin type A (LANTOX) into the pericranial muscles can probably be an effective way to treat migraine [2], but the writer could not find any related literatures reported in China. We performed a study that enrolled 30 adult migraineurs, and botulinum toxin type A was injected into pericranial muscles, and the results were reported as follows.

Clinical Information

During September 2003 to May 2004, 30 migraineurs, including 11 males and 19

females, were selected. Their age ranged from 17 – 65 (36 ±*s*13), and their courses of disease ranged from 0.4 to 20 years (7±4). 14 of them took analgesic [mainly compound paracetamol (Saridon)], 10 tablets monthly. Intake standard: (1) Meet the 1988 International Headache Society (IHS) classification of headache system; (2) Above 3 months of migraine history; (3) The migraine frequency is at least twice a month; (4) The migraine condition (frequency, duration and severity) is relatively stable; (5) If other drugs were taken to treat migraine before the treatment, the dosage has to be remain unchanged 1 month prior to the treatment; (6) No abnormal finding in skull MRI or CT. Exclusion standard: (1) Migraine occurs more than 15 days in a month; (2) Dependence on analgesic; (3) Application of drugs that strengthen the blockage of transmission at the neuromuscular junction within a week; (4) Suffer from myasthenia gravis, Lambert-Eaton syndrome or peripheral neuropathic diseases, like motor neuropathy ; (5) Presence of infection at the proposed injection site, malfunction in blood clotting, serious heart, liver or kidney diseases, pregnant or breastfeeding women and former BTX users.

Treatment Method

LANTOX produced by Lanzhou Institute of Biological Products, with the no. of (97) Drug Approval License (LAN) No. S201 was used for injection. It was lyophilized crystal toxin, stored in vial containing 110U at -5℃ to -20℃ low-temperature fringe. To apply, sodium chloride injection was used to dilute to 25000UL-1 (25UmL^{-1}), by mean of 1ml skin test syringe and no.4 syringe needle, it can be applied within 0.5 hour. The combined application of 2 methods, fixed-site method and follow-the-pain approach, generally includes frontalis muscle, temporal muscle, corrugator muscle and occipitalis muscle, and the injection dosage is 35-100U. The information about the occurrence of migraine before the treatment was collected and the patients were asked to record well their conditions in their migraine dairies. After the treatment, their conditions were followed once a month, for totally 3 times, over the phone or through subsequent consultation in order to assess any changes in migraine conditions and the treatment-related adverse reactions.

Efficacy Evaluation

1. Classification According to the Headache Severity

According to the headache level and the influence of headache on patient's daily routine [GELMERS HJ. Nimodipine, a new calcium antagonist in the prophylactic treatment of migraine. *Headache*, 1983; 23(3): 106-112]: Class 0 – without headache; Class I (mild headache) – mild headache, do not affect daily routine; Class II (moderate headache) – relatively severe headache, affect daily routine; Class III

(acute headache) – severe headache, cannot continuous with the daily routine, even being bed-ridden.

In order to classify the headache level precisely, further numerical grading method was used, numbers 1 to 10 represent different headache levels. 0 represents no headache at all while 10 represent the most acute headache. Mild headache – 1 to 3; Moderate headache – 4 to 6 and; acute headache – 7 to 10.

2. Efficacy Assessment

Based on the 3-month baseline period, the headache conditions were measured by the headache frequency (time), duration (hour), severity (grade), analgesic usage and treatment-related adverse condition. According to the improvement in frequency, duration and severity, the cases can be classified as: (1) Complete remission – 100% improvement in the mentioned aspects; (2) Significant effectiveness – 50% to 100% improvement in the mentioned aspects; (3) Effectiveness – >1% to 50% improvement in the mentioned aspects; (4) Ineffectiveness – <1% to 50% improvement in the mentioned aspects.

3. Statistical Techniques

The statistical analysis and efficacy assessment were based on the 3-month post-treatment migraine diaries recorded by the patients with their conditions followed by the professional physicians from time to time. All values were represented in form of median or percentage. A Compaq Pentium III/1000 computer installed with SPSS/11.0 program was used for the analysis and Krusja-Wallis H was used for checking. A significant difference resulted when $P<0.05$ and an extremely significant difference resulted when $P<0.01$.

Result

1. Efficacy Evaluation

After the LANTOX injections in the 30 cases, in comparison with the situation before the treatment, the proportion of patients without headache and with mild headache obviously increased ($P<0.01$) 1 to 3 months after treatment, while the constituent ratio between the different classes remained no significant difference during the 3-month postinjection ($P>0.05$). (Table 1)

Table 1 Proportion of each severity – scale subjects before and after administration of LANTOX among 30 migraine patients

Severity	Before Treatment	After treatment		
		1 month	2 month	3 month
Without headache	0 (0)	8 (27) [cd]	9 (30) [cd]	10 (33) [cd]
Mild headache	1 (3)	6 (20) [cd]	14 (47) [cd]	11 (37) [cd]
Moderate headache	23 (77)	16 (53) [cd]	7 (23) [cd]	9 (30) [cd]
Acute headache	6 (20)	0 (0) [cd]	0 (0) [cd]	0 (0) [cd]

After checking by Krusja-Wallis H, the constituent ratio between the different classes and different time-intervals after the treatment in comparison with that before the treatment : [c]$P<0.01$; comparison among different time-intervals after the treatment : [d]$P>0.05$

After the LANTOX injections in the 30 cases, in comparison with the situation before the treatment, the migraine frequency was significantly reduced ($P<0.01$), the severity was significantly relieved ($P<0.01$) and the duration of headache was also significantly shortened ($P<0.01$) 1 to 3 months after treatment. However, the migraine frequency (as well as the severity and the duration) did not differ significantly among the 3-month interval after the treatment ($P>0.05$). (Table 2)

Table 2 Results of headache attacks before and after treatment with LANTOX for 30 patients with migraine

Items	Before Treatment	After treatment		
		1 month	2 month	3 month
Monthly migraine frequency / time	4.5	2.0 [cd]	1.0 [cd]	1.0 [cd]
Severity / score	6.0	4.0 [cd]	3.0 [cd]	2.5 [cd]
Duration / hour	7.0	3.5 [cd]	2.0 [cd]	2.0 [cd]

After checking by Krusja-Wallis H, the parameters between the different classes and different time-intervals after the treatment in comparison with that before the treatment : [c]$P<0.01$; comparison of the parameters among different time-intervals after the treatment : [d]$P>0.05$

After the LANTOX injections in the 30 cases, the number of cases and the corresponding ratio of patients with their headache frequency, duration and severity being completely relieved, significantly reduced or reduced were relatively higher. (Table 3)

Table 3 Proportion of subjects getting headache symptoms improvement after administration of LANTOX among 30 migraine patients

Items	Complete remission	Significant effectiveness	Effectiveness	Ineffectiveness
Frequency	8 (27)	15 (50)	4 (13)	3 (10)
Severity	8 (27)	14 (47)	6 (20)	2 (6)
Duration	8 (27)	10 (33)	5 (23)	5 (17)

2. Analgesic Usage

After the LANTOX injections in the 30 cases, the number of cases that demand analgesic was reduced. There was no significant difference between the baseline and 1 to 2 months after treatment ($P>0.05$), however, there was a significant difference between the baseline and 3 months after treatment ($P<0.05$). The analgesic dosage is significantly reduced. There was a significant difference between the baseline and 1 to 3 months after treatment ($P<0.01$). (Table 4)

Table 4 Comparison of analgesics usage before and after administration of LANTOX among 30 migraine patients

Items	Before Treatment	After treatment		
		1 month	2 month	3 month
Cases with analgesic usage / case (%)	14 (47)	9 (30) [a]	9 (30) [a]	5 (17) [b]
Monthly analgesic usage / tablet	10	2[c]	1[c]	1[c]

After checking by Krusja-Wallis H, in comparison with the conditions before the treatment: [a]$P>0.05$, [b]$P<0.05$, [c]$P<0.01$.

3. Adverse Reaction

After the LANTOX injections in the 30 cases, weakness in head elevation occurred in one case, and ptosis of eyebrow occurred in another case, however these adverse events disappeared within the second week postinjection spontaneously. Pain at the injection sites occurred in another case, but it disappeared within the first week postinjection.

Discussion

LANTOX is a neural-like cell exotoxin produced by Botulinum, and is widely applied to treat diseases such as blepharospasm, facial spasm and spasmodic torticollis with high efficacy [3-5]. It was a coincidence that the LANTOX intramuscular injection was discovered to ameliorate migraine symptoms during the LANTOX treatments in blepharospasm, facial spasm and cosmetic wrinkle removal. After that, studies

concerning the LANTOX treatment on migraine develop continuously.

In this study, after the LANTOX injections in the 30 cases, improvement shown in the following one month as the migraine frequency, severity, duration and analgesic usage were all reduced. The efficacy sustained for 3 months postinjection which coincide with the findings in the oversea studies [8-10]. The mechanism for the LANTOX treatment in migraine is complex and potential mechanisms are (1) LANTOX relaxes the muscles by inhibiting the release of neurotransmitter, acetylcholine chloride, at the presynaptic membrane of the neuromuscular junction selectively; (2) LANTOX inhibits neurogenic inflammation by inhibiting the release of neuropeptides and therefore reducing the impulses transmitted through the nucleus tractus spinalis nervi trigemini; (3) Through the negative transmission to the central nervous system, inhibits the activity of trigeminal nerve- vascular system directly by adjust the presence of substance P and cephalin and therefore relief the headache. Due to the complexity of the migraine mechanism and the variety of clinical types, this research did not further discuss the effect of LANTOX treatment towards different clinical types. Moreover, as no journals in such area being reported, further research will be carried out.

Clinically, the dosage in treating migraine by LANTOX is 25-100U, and the toxic dosage is 30 to 120 times of that dosage [11]. At this moment, none of the many clinical researches indicated that LANTOX treatment will result in systemic disease or acute adverse reactions. Only small number of patients reported mild and temporary treatment-related adverse reactions, including blepharoptosis, diplopia, ptosis of eyebrow and weakness, pain or hematoma at the injection sites [6, 7]. In this research, weakness in head elevation occurred in one case, and ptosis of eyebrow occurred in another case however these adverse events disappeared within the second week postinjection spontaneously. Pain in the injection sites occurred in another case, but it disappeared within the first week following injection. Some studies indicated that if the time interval in between injection treatment is short (<3 months) and the injection dosage is high (>300U), production of antibody becomes possible. Yet, the long-lasting efficacy (>3 moths) of a single injection and the low dosage (<100U) will not lead to antibody production, thus, repeated injections will not result in efficacy reduction. Another research even indicated that repeated multiple injections will result in higher efficacy than a single injection [11]. Therefore, LANTOX treatment can be a new drug for treating migraine due to its high and long-lasting efficacy in treating migraine and minor treatment-related adverse reactions. In addition, repeated treatment will result in unchanged efficacy. Application of LANTOX in treating migraine is full of prospects and further research and promotion should be done.

Up to now, different doses and injection sites were employed in different clinical studies. Concerning the clinical studies done, 25-100U dosages were commonly used. There are yet no information indicating the connection between the dosage and efficacy [11]. The LANTOX injection sites are not standardized in a system yet, however, the three common methods are: (1) the fixed-site method; (2) the follow-the-pain approaches and; (3) a combination of the two approaches. In this study, a combination of the fixed-site and follow-the-pain approaches was employed. Depending on where the patient feels pain and the associated severity, the locations of injection sites and doses can be confirmed, in order to produce a satisfactory result. The confirmation of the best doses and injection sites of LANTOX treatment is left for further study.

Under the theory and budget limitation, this study did not employ double-blind, randomized and placebo-controlled trial. Moreover, due to the lack of consultation time, the exact effect and duration of LANTOX were not fully explored.

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