The Egyptian Journal of Hospital Medicine (October 2021) Vol. 85 (2), Page 3827-3830

Intralesional Injection of Botulinum Toxin for Post-Herpetic Neuralgia: A Pilot Study

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ABSTRACT

Background: When someone has herpes zoster and the rash goes away in spite of persistence of pain, they are defined to have post-herpetic neuralgia (PHN). Herpes zoster is frequently accompanied by post-herpetic neuralgia. Clostridium botulinum produces botulinum toxin (BTX-A), a neurotoxic protein that is used to treat various ailments.

Objective: Intralesional botulinum toxin injections were tested for their efficacy in the treatment of post herpetic neuralgia.

Patients and methods: An intralesional BTX-A injections pilot trial including 19 patients with PHN was carried out. Quality of life scale (QLS), neuropathy pains scale (NPS), and pain analyses by visual analogue scale (VAS) were used for all patients after comprehensive history-taking process.

Results: After a six-months therapy follow-up period, we found significant differences comparing before and after treatment in the neuropathy pain scale, VAS score, and the QLS (SF-36). Pain at site of injection was found in all patients while redness or erythema was found in 13 patients.

Conclusion: Treatment with botulinum toxin via local injection is beneficial for post-herpetic neuralgia (PHN). BTX could be alternative therapeutic modality in treating PHN in the future.

Keywords: Post-herpetic neuralgia, Botulinum toxin A.

INTRODUCTION

Most people who get herpes zoster develop post-herpetic neuralgia (PHN), which is neuropathic pain caused by the virus. The standard definition of herpes zoster pain is dermatomal discomfort that lasts at least 90 days after the rash appears. PHN leads in significant pain and suffering for those affected, as well as a financial and social cost on society as a whole [(1)].

PHN is characterized by a stabbing sensation, burning, or pain induced by light touch with non-painful stimuli and affects nerve fibers and skin. Post-herpetic neuralgia pain is notoriously difficult to cure and can last for years, making several negative impacts on patient social life [(2)].

Central neurons sodium channels are inactivated through action of a neurotoxin made by the bacterium Clostridium botulinum that is called Botulinum toxin (BTX-A), which also can suppress peripheral neurotransmitters as well as inflammatory mediators [(3)]. BTX's effectiveness in PHN has been the subject of several studies. On 60 PHN patients **Xiao *et al.*** [(4)] conducted a double-blind randomized placebo-controlled study with the following groups: BTX, 0.5 percent lidocaine, and 0.9 percent saline groups. When compared to the other two groups, the BTX-treated patients showed the largest improvement on VAS and in terms of sleep quality.

Intralesional botulinum toxin injections were tested for their efficacy in the treatment of post herpetic neuralgia in this research.

PATIENTS AND METHODS

Pilot research including 19 people with PHN was carried out in the Dermatology and Neurology departments.

Ethical approval:

Patients signed a valid written agreement to participate in the study, and it was authorized by the Zagazig University Faculty of Medicine's Research Ethical Council (ZU-IRB). The study complied with the World Medical Association's Code of Ethics for Human Research (Declaration of Helsinki).

Inclusion criteria: Cases with post herpes zoster persistent dermatomal pain ≥ 90 days, patients with variable degree of PHN, males or females, and age ≥ 18 years.

Exclusion criteria:

Individuals suffering from motor neuron disease, myasthenia gravis, severe organ failure, Eaton-Lambert syndrome, mental disorders, cognitive impairment and a history of infectious diseases, recent fever or having asthma. Patients taking medication for aggravated transmission disorders of neuromuscular junction, one week prior to the study. History of allergy to the same used materials. Pregnant and lactating women. Coagulation abnormality, including use of coumarin or anticoagulants. The affected dermatome is infected with bacteria on the skin, and immunocompromised patients.

Received: 8/7/2021
Accepted: 4/9/2021

All patients were subjected to the following: Complete history taking include duration of pain, complete general examination, NPS, QLS (SF-36), and Pain analysis measured by VAS. **VAS** is a tool for assessing the intensity of pain. 0 denotes no discomfort, whereas 10 denotes the most agonizing pain**. NPS** was also utilized to gauge the degree of pain a person is experiencing. A value of 0 indicates no pain, whereas a value of 10 indicates severe pain.

Quality Life Scale (SF-36): is indicator of overall health status. From 0 to 100. Higher scores are associated with fewer disabilities, while lower scores indicate more.

Patients received the botulinum toxin as follow:

- Lyophilized crystalline BTX-A. Each vial of BTX-A contain 50 IU and stored at a temperature between 2 and 8 ºC. Before injecting, it was diluted in 2cc of saline. Five units per point of BTX-A will be injected intralesional for one session (full dosage ranges from 50 to 100 units).
- Follow up: Pain re-analysis two weeks following injection, followed by monthly assessments for the next six months.

Statistical analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test (χ^2) was used to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD. Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). P value ≤ 0.05 was considered significant.

RESULTS

Table (1): Study subjects' characteristics, including age and gender

Variable	**Mean ± SD**	
Age: (years)	66.16 ± 7.64	
Variable	**No**	**%**
Sex:		
Male	14	73.7
Female	5	26.3

t: Independent t test, SD: Standard deviation, χ^2: Chi square test NS: Non-significant (P higher than 0.05)

Table (1) showed that the included patients were 19 and the mean age was 66.16 ± 7.64 years. They were 14 males and 5 females.

Table (2): Visual analogue score among the studied group atdifferent times of follow up

VAS		Mean ± SD
Base line:	**Mean ± SD** **Median**	**6.63 ± 1.86** **7**
1st follow up:	**Mean ± SD** **Median**	**5.21 ± 1.65** **5**
2nd follow up:	**Mean ± SD** **Median**	**4.63 ± 1.46** **4**
3rd follow up:	**Mean ± SD** **Median**	**3.73 ± 1.15** **4**
4th follow up:	**Mean ± SD** **Median**	**3.11 ± 1.37** **3**
5th follow up	**Mean ± SD** **Median**	**2.79 ± 1.13** **3**
6th follow up:	**Mean ± ds** **Median**	**2.74 ± 1.41** **3**
7th follow up:	**Mean ± SD** **Median**	**2.90 ± 1.37** **3**
% of reduction		**52.74%**

MW: Mann Whitney. t: independent t test .SD: Standard deviation F: Friedman test NS: Non-significant (P>0.05)*:Significant (p<0.05)**: Highly significant (P<0.01)VAS: visual analogue scale.

Table (2) showed that there was a significant difference regarding VAS score before and after treatment follow up for six months. Mean VAS score dropped from 6.63 at baseline to 5.2 at the first follow-up visit. At last visit pain was described as stronger but bearable by all patients and mean VAS score was 2.90.

Table (3): Neuropathy pain scale among the studied group at different times follow up

NPS		Mean ± SD
Base line:	**Mean ± SD** **Median**	**52.42 ± 15.79** **51**
1st follow up:	**Mean ± SD** **Median**	**43 ± 12.56** **36**
2nd follow up:	**Mean ± SD** **Median**	**36.42 ± 9.81** **33**
3rd follow up:	**Mean ± SD** **Median**	**31.16 ± 9.03** **30**
4th follow up:	**Mean ± SD** **Median**	**27.16 ± 9.38** **28**
5th follow up	**Mean ± SD** **Median**	**23.95 ± 10.01** **26**
6th follow up:	**Mean ± SD** **Median**	**24.26 ± 11.75** **27**
7th follow up:	**Mean ± SD** **Median**	**25.53 ± 12.60** **25**
% of reduction		**46.54%**

SD: Standard deviation **t: independent t test MW: Mann Whitney** F: Friedman test NS: Non significant (P>0.05) *: Significant (p<0.05) **:

Highly significant (P<0.01)NPS = neuropathy Pain scale

In Table (3), a significant statistical difference was found regarding NPS before and after treatment follow up for six months. Mean NPS dropped from 52.42 ± 15.79 at baseline to 43 ± 12.56 at the first follow-up visit. At last visit NPS was 25.53 ± 12.60.

Table (4): Quality of life scale among the studied group at different times of follow up

QLS		Mean ± SD
Base line:	**Mean ± SD** **Median**	**28.73 ± 8.69** **29.1**
1st follow up:	**Mean ± SD** **Median**	**37.97 ± 16.29** **35.4**
2nd follow up:	**Mean ± SD** **Median**	**42.51 ± 15.12** **37**
3rd follow up:	**Mean ± SD** **Median**	**47.89 ± 14.99** **44.6**
4th follow up:	**Mean ± SD** **Median**	**52.04 ± 16.07** **45.9**
5th follow up	**Mean ± SD** **Median**	**53.58 ± 18.75** **43.8**
6th follow up:	**Mean ± SD** **Median**	**52.95 ± 19.22** **43.8**
7th follow up:	**Mean ± SD** **Median**	**52.29 ± 20.38** **46.27**
% of increase		**89.13%**

SD: Standard deviation **t: independent t test** **MW: Mann Whitney** F: Friedman test NS: Non significant (P>0.05) *: Significant (p<0.05) **:

Highly significant (P<0.01)QLS: quality life scale.

Table (4) showed that there was a significant difference regarding QLS before and after treatment follow up for six months. Mean QLS raised from 28.73 ± 8.69 at baseline to 37.97 ± 16.29 at the first follow-up visit. At last visit QLS was improved and raised to 52.29 ± 20.38.

Table (5): Side effects of treatment among the studied groups

Variable	No	%
Side effect:		
No	0	0
Pain at site of injection	19	100
Redness or erythema	13	68.4

χ^2: chi square test NS: Significant (P>0.05)

Table (5) showed that pain at site of injection was found in all patients while redness or erythema was found in 13 patients.

DISCUSSION

It is more prevalent in the elderly than in children to experience post-herpetic neuralgia after herpes zoster. PHN-induced pain is either constant or burning or alternates with a stinging sensation [5].

Clostridium botulinum produces botulinum toxin-A, a powerful neurotoxin that inhibits acetylcholine release at neuromuscular junctions and relaxes muscles. According to animal research, there are various plausible methods by which BTX-A works as an analgesic. The release of pain mediators from both motor and sensory neurons is inhibited; calcitonin-produced peptide and other neuropeptides are also prevented from being released [3]**.** By blocking neurotransmitter release and deactivating the sodium channel in central nervous system neurons, BTX-A lowers chronic inflammation and acute injury, showing promise as an analgesic for trigeminal neuralgia, other neuralgic conditions, and PHN [6]**.**

It was our goal to see if intralesional botulinum toxin was effective in treating post-herpetic neuralgia in 19 patients who had received the botulinum toxin.

There was a significant difference in VAS score before and after a six-month therapy follow-up, according to the results of the current study. Mean VAS score dropped from 6.63 at baseline to 5.2 at the first follow- up visit. At last visit pain was described as stronger but bearable by all patients and mean VAS score was 2.90.

Our results regarding treatment with BTX injection are in agreement with **Li *et al.*** [7] they made a meta-analysis BTX-A treatment for PHN. Patients who got BTX-A for PHN had significantly decreased VAS pain scores after two months of follow-up. Patients who got BTX-A for PHN had considerably decreased VAS pain scores three months after treatment, according to the results of the current study. Additionally, our results are in agreement with **Xiao *et al.*** [5] who aimed to see if BTX-A could help treat patients with PHN. Prior to therapy, patients had evaluations for VAS pain on day 1, day 7, and three months after treatment ended. Pain scores on the VAS decreased 7 days after therapy and 3 months later.

Although the results obtained from **Emad *et al.*** [8] study VAS pain score was decreased after injection with botulinum toxin but it was not statistically significant as VAS pain was measured during the follow-up visits of the patients. The patients' VAS pain was assessed during follow-up visits. The VAS ranged from 0 to 10, with a mean of 6.4 ± 4.4 on the second day. The mean was 4.2 ± 7.2 in the second week. The VAS was also measured in the fourth week, with lowest value of 3.7±7.6. Additionally, our findings match those of a previous study looking at the curative effects of BTX for PHN treatment [9]. There were 58 PHN patients and treated them with hypodermic injection of BTX-A. They measured and compared VAS pain score before and after treatment follow up for six months. VAS score was significantly reduced compared with before treatment.

The current study showed that there was a significant difference regarding NPS before and after treatment followup for six months. Mean NPS dropped from 52.42 ± 15.79 at baseline to 43 ± 12.56 at the first follow-up visit. At last visit NPS was 25.53 ± 12.60. **Ding *et al.*** [9] reported that there were 58 PHN

patients and treated them with hypodermic injection of BTX-A. They measured andcompared NPS pain score before and after treatment follow up for six months. NPS score was significantly reduced compared with before treatment.

After a six-month follow-up, the results of the current study demonstrated a substantial difference in QLS scores. Mean QLS raised from 28.73 ± 8.69 at baseline to 37.97 ± 16.29 at the first follow-up visit. At last visit QLS was improved and raised to 52.29 ± 20.38, which is in agreement with **xiao *et al.*, [(5)]** where QLS were assessed before therapy, on day one, on day seven, and three months after treatment ended. On day 7 and three months after therapy, QLS had improved in all three groups when compared to pretreatment. However, as compared to the lidocaine and placebo groups, the BTX-A group ($p < 0.01$) showed a significant improvement, unfortunately, six months following therapy, not all of the participants in the study by **Xiao *et al.* [(5)]** were evaluated by the authors.

Our results regarding treatment with BTX injection are in agreement with **Apalla *et al.* [(10)].** BTX patients showed a significantimproved in QLS, which lasted for approximately four months. Unfortunately, **Apalla *et al.* [(10)]** did not evaluate all the subjects for 6 months after treatment.

Our results regarding treatment with BTX injection is in agreement with the study of **Ding *et al.* [(9)]**. There were 58 PHN patients and treated them with hypodermic injection of BTX-A. They measured and compared QLS before and after treatment follow up for six months and SF-36 score was significantly improved ($P < 0.01$).

Regarding to side effects of treatment, most of the participants inthe study experienced pain at site of injection and redness or erythema, these may be attributed to hypersensitivity at these sites, also personal and technical variation may contribute.

CONCLUSION

Local injection of botulinum toxin has potential as an effective treatment for post-herpetic neuralgia. It relieves the pain of PHN and had more efficacy and satisfaction results. Botulinum toxin could be an alternative therapeutic modality in treating PHN in the future.

RECOMMENDATION

We recommend further studies on the role of BTX-A as a treatment of PHN and other types of neuralgia with bigger sample size and longer duration of the study.

Financial support and sponsorship: Nil.
Conflict of interest: Nil.

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