Effect of COVID-19 Vaccination on Management of Chronic Migraine with Botulinum Toxin: A Case Series

Delara Hazegh Fetratjoo, Elham Jafari and Mansoureh Togha

1School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
2Headache Department, Iranian Center of Neurological Research, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran
*Corresponding author: Headache Department, Iranian Center of Neurological Research, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran. Email: toghae@sina.tums.ac.ir

Received 2023 January 18; Revised 2023 June 20; Accepted 2023 June 25.

Abstract

Introduction: Headache worsening has been previously reported following the coronavirus disease 2019 (COVID-19) vaccination. However, COVID vaccination's influence on managing chronic migraine (CM) with botulinum toxin is yet to be studied.

Case Presentation: In this case series, we present five cases of CM, who had responded to abobotulinum toxin type A (BTX-A), but their number of headache days increased after COVID vaccination.

Conclusions: In the case of vaccination with COVID vaccines, during the first month of administering botulinum toxin for the management of CM, there might be a decrease in the efficacy of botulinum toxin, which should be explained to the patients. The authors suggest that physicians postpone the administration of BTX-A for chronic migraine management to a later time at their discretion.

Keywords: COVID Vaccination, COVID-19, Chronic Migraine, Botulinum Toxin, Case Series

1. Introduction

Chronic migraine (CM), with an estimated global prevalence of 1.4% - 2.2%, is a disabling neurologic disorder with limited treatment options (1). Botulinum toxin has been widely prescribed for the management of CM since 2011 after the Food and Drug Administration's approval.

It has been three years since the outbreak of coronavirus disease 2019 (COVID-19) and the development of different vaccines. While some adverse effects of these vaccines remain unknown, headache after COVID vaccination was reported as the third most common adverse event in clinical trials among 1.57 million participants (2). The incidence of headaches following COVID vaccination was generally higher in patients with pre-existing headaches (3).

In this case series, we present five cases of CM that had a good response to abobotulinum toxin type A (BTX-A) treatment. However, their number of headache days increased after receiving COVID vaccines.

2. Case Presentation

For the following cases, BTX-A (either Dyston, manufactured by Imen Vaccine Alborz, or Dysport®, manufactured by IPSEN) was injected according to a fixed-site-fixed-dose protocol similar to The Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) clinical program (4), for the management of CM as part of an ongoing clinical trial (ethics code: IR.TUMS.MEDICINE.REC.1400.1227, clinical trial registration number: IRCT20201040492653). All the patients experienced fewer headache days, but a relapse occurred following the COVID vaccination.

A routine neurological examination was done for all the patients. The optic discs were sharp, and no abnormal finding was observed in the patients' magnetic resonance imaging (MRI). The patients were instructed to complete headache diaries, which were assessed monthly to measure the number of headache days, intensity of headaches, and abortive medications. Non-prohibited concomitant pharmacologic and non-pharmacologic...
treatments were instructed not to be changed during the study.

All patients were diagnosed with CM according to the third edition of the International Classification of Headache Disorders (ICHD-3) criteria (5). After assessing the eligibility criteria and signing written informed consent, they were enrolled in the clinical trial. Then, 500 IU BTX-A was injected for them with the same protocol by the same physician at the headache clinic of Sina Hospital located in Tehran, Iran. Face-to-face visits were scheduled every four weeks, and each patient was followed for three months after the BTX-A injection. The demographic and baseline data of the patients are presented in Table 1.

The first case was a 50-year-old woman diagnosed with CM without aura with medication overuse headache (MOH) and a medical history of hypertension controlled with losartan 25 mg twice a day. She had a dramatic response to botulinum toxin in the first month (visit 1, four weeks after injection) that decreased in the second month (visit 2, week eight) after the third dose of Sinopharm COVID vaccine that was injected four weeks after the toxin injection (her headache days increased from four days to 20 days per month). For abortive management of her headaches, a short duration of NSAIDs was initiated and then tapered off (100 mg celecoxib capsules were initiated every six hours for three days, decreased every three days to every eight hours, 12 hours, once daily, and then discontinued). The patient responded well, and her days with a headache decreased again (Table 2).

The second case involved a 31-year-old woman diagnosed with CM without aura with medication overuse headache (MOH) and a medical history of gastroesophageal reflux disease and asthma. Her concomitant medications were amitriptyline 25 mg every night, topiramate 50 mg twice a day, and a salbutamol (albuterol) inhaler PRN. She responded well in the first two months post-toxin injection. However, her headache days increased by 10 days in the third visit after the third dose of Sinopharm, injected in the seventh week.

The third case was a 41-year-old woman diagnosed with CM without aura with MOH and a medical history of hypertension controlled with losartan 25 mg twice a day, and a salbutamol (albuterol) inhaler PRN. She responded well in the first two months post-toxin injection. However, her headache days increased by 10 days in the third visit after the third dose of Sinopharm, injected in the seventh week.

The fourth case was a 40-year-old woman diagnosed with CM without aura with MOH, with no past medical history. Her concomitant medication was zolpidem 5 mg PRN. She responded well in the first two months post-toxin injection. However, her headache days increased from eight to 14 days after the fourth dose of the AstraZeneca COVID vaccine, injected in the ninth week.

The fifth case was a 45-year-old woman diagnosed with CM without aura with anxiety as a comorbid condition. Her concomitant medications were nortriptyline 10 mg every night and citalopram 20 mg daily. She had about a 50% reduction in her headache days in the first month (visit 1, four weeks after injection). However, her headaches worsened from 15 to 23 days in the second month (visit 2, week eight) after the second dose of the Sinopharm COVID vaccine injected five weeks after the toxin injection. In order to control the patient’s headaches, we increased nortriptyline gradually to 25 mg daily in the second visit. At the end of the study, topiramate was prescribed and titrated to a final dose of 50 mg twice daily. The trend of headache days per month is represented in Figure 1 and detailed in Table 2.

3. Discussion

Worsening migraine headaches has been previously reported following COVID vaccination (6). A retrospective cohort study assessed 45 patients and concluded that COVID-19 mRNA vaccination reduces the efficacy of botulinum toxin type A when administered for aesthetic indications (7). A study presented two cases of sub-acute hypersensitivity reactions to botulinum toxin type A, injected for cosmetic purposes following COVID-19 vaccination. It recommended that botulinum toxin should be administered at least two to three months after COVID vaccination (8).

The five cases presented in the current study experienced headaches worsening after vaccination, despite achieving a proper response to botulinum toxin. This finding might be contrary to an expert opinion that concluded COVID vaccines and their antibody production are not reasonable to lessen the efficacy of migraine preventive therapies. No delay would be necessary regarding the timing of vaccination (9).

Due to the limited number of cases, and lack of understanding of the possible mechanism of COVID vaccines that aggravate migraine headaches, no direct conclusions can be reached whether these vaccines could reduce BTX-A’s efficacy. Previous studies have demonstrated that the effect of botulinum toxin decreases gradually after two and a half to three months (10), which makes it even more difficult to relate the worsening effect of COVID vaccines on headaches in cases number two to four that received their vaccines during the second and third months after toxin injection. Their relapse might have been due to the natural elimination of botulinum toxin’s effect. On the other hand, a systematic literature review and meta-analysis showed that the onset of headache after COVID vaccination was within
Table 1. Baseline and Demographic Data of the Cases

<table>
<thead>
<tr>
<th>Case Number</th>
<th>Age</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>BMI (Kg/m²)</th>
<th>Smoking</th>
<th>Family History of Migraine</th>
<th>Diagnosis</th>
<th>Overused Medication(s)</th>
<th>Age of Migraine Diagnosis</th>
<th>Age of Chronic Migraine Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case one</td>
<td>50</td>
<td>Female</td>
<td>60</td>
<td>23.43</td>
<td>No</td>
<td>Yes</td>
<td>CM+MOH (without aura)</td>
<td>Acetaminophen, NSAIDs, ergot alkaloid, caffeine</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td>Case two</td>
<td>31</td>
<td>Female</td>
<td>70</td>
<td>29.13</td>
<td>No</td>
<td>No</td>
<td>CM (without aura)</td>
<td>None</td>
<td>27</td>
<td>30</td>
</tr>
<tr>
<td>Case three</td>
<td>41</td>
<td>Female</td>
<td>63</td>
<td>23.14</td>
<td>No</td>
<td>Yes</td>
<td>CM+MOH (without aura)</td>
<td>Triptan, NSAIDs</td>
<td>31</td>
<td>39</td>
</tr>
<tr>
<td>Case four</td>
<td>40</td>
<td>Female</td>
<td>62</td>
<td>24.83</td>
<td>No</td>
<td>Yes</td>
<td>CM+MOH (without aura)</td>
<td>Triptan, NSAIDs</td>
<td>18</td>
<td>40</td>
</tr>
<tr>
<td>Case five</td>
<td>45</td>
<td>Female</td>
<td>64</td>
<td>24.30</td>
<td>No</td>
<td>Yes</td>
<td>CM (without aura)</td>
<td>-</td>
<td>25</td>
<td>30</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CM, chronic migraine; MOH, medication overuse headache; NSAIDs, non-steroidal anti-inflammatory drugs.

Figure 1. The trend of headache days per month throughout the study. An increase in the number of headache days was observed following COVID vaccine administration. Vaccination times are marked with arrows (→).
Table 2. Headache days per month and maximum headache intensity of the cases in each visit. The baseline visit shows the number of headache days and maximum intensity of headaches one month before abobotulinum toxin injection.

<table>
<thead>
<tr>
<th>Case Number</th>
<th>COVID Vaccine Injection Time (Weeks After Enrollment)</th>
<th>Headache Days per Month (Baseline)</th>
<th>Maximum Headache Intensity (Baseline)</th>
<th>Headache Days per Month (Visit 1, Week 4)</th>
<th>Maximum Headache Intensity (Visit 1)</th>
<th>Headache Days per Month (Visit 2, Week 8)</th>
<th>Maximum Headache Intensity (Visit 2)</th>
<th>Headache Days per Month (Visit 3, Week 12)</th>
<th>Maximum Headache Intensity (Visit 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case one</td>
<td>4</td>
<td>16</td>
<td>10</td>
<td>4</td>
<td>10</td>
<td>20*</td>
<td>10*</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Case two</td>
<td>7</td>
<td>20</td>
<td>9</td>
<td>6</td>
<td>10</td>
<td>1</td>
<td>5</td>
<td>11*</td>
<td>8*</td>
</tr>
<tr>
<td>Case three</td>
<td>8</td>
<td>20</td>
<td>8</td>
<td>16</td>
<td>6</td>
<td>6</td>
<td>7</td>
<td>10*</td>
<td>6*</td>
</tr>
<tr>
<td>Case four</td>
<td>9</td>
<td>24</td>
<td>9</td>
<td>7</td>
<td>8</td>
<td>8</td>
<td>6</td>
<td>14*</td>
<td>7*</td>
</tr>
<tr>
<td>Case five</td>
<td>5</td>
<td>29</td>
<td>6</td>
<td>15</td>
<td>6</td>
<td>23*</td>
<td>8*</td>
<td>20</td>
<td>8</td>
</tr>
</tbody>
</table>

* Show an increase in headache days after vaccination.

the first day from injection and lasted four to 72 hours (2). Therefore, the increased number of headache days in these cases, which were all more than three days, could be due to the diminished efficacy of botulinum toxin caused by the vaccines.

To the best of our knowledge, no study has been published reporting the effect of COVID vaccination on the efficacy of botulinum toxin for chronic migraine management. Further studies are suggested to discover the possible underlying mechanisms of the decreased efficacy and to find the optimum time interval for these injections.

3.1. Conclusions

In the case of vaccination with COVID vaccines, during the first month of administering botulinum toxin for the management of CM, there might be a decrease in the efficacy of botulinum toxin, which should be explained to the patients. The authors also suggest that physicians postpone the administration of BTX-A for chronic migraine management to a later time at their discretion.

Acknowledgments

The authors would like to thank the patients for participating in this study. This case series has not received any financial support from any organization.

Footnotes

Authors’ Contribution: D.H.F. collected the data and drafted the manuscript. E.J. contributed to the conception of the study. E.J. and M.T. conducted the study visits and revised the manuscript.

Clinical Trial Registration Code: IRCT20201104049265N3.

Conflict of Interests: The authors have no conflicts of interest to disclose.

Data Reproducibility: The dataset presented in the study is available on request from the corresponding author during submission or after publication. The data are not publicly available in order to maintain the privacy of the cases.

Ethical Approval: IR.TUMS.MEDICINE.REC.1400.1227.

Funding/Support: This case series has not received any financial support from any organization.

Informed Consent: Patients signed the written informed consent.

References


