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Evaluation of the effectiveness of botulinum toxin injection on reducing phantom pain in patients

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ABSTRACT

Objective: Phantom pain is very common in amputations and is associated with severe pain followed by distress and poor quality of life. The aim of this study is to evaluate the effectiveness of botulinum toxin injection in reducing phantom pain in patients referred to Imam Hossein Hospital.

Materials and methods: In this double-blinded placebo study, 30 patients with phantom pain referred to Imam Hossein Hospital were included. The participants were divided into two groups of 15 intervention and placebo. In the intervention group, botulinum toxin A was injected to reduce pain in patients and normal saline was injected in placebo group. Patients' pain relief was assessed at 0, 2, 4, 8, and 16 weeks of the treatment. Data were analyzed using SPSS 23 software.

Results: Botulinum toxin A injection significantly reduced phantom pain in intervention group at 0, 2, 4, 8, and 16 weeks of the treatment $p < 0.05$. This reduction was also seen in regard to the cause of amputation, such as war, accidents, and unknown causes.

Conclusion: The use of botulinum toxin A seems to be effective in reducing pain in patients with phantom pain. Comparative studies and comparisons of the effect of botulinum toxin with common treatments are recommended.

1. Introduction

Neuropathic pain is one of the pathological pains that is caused by damage to the peripheral or central nervous system [1]. International Association for the Study of Pain defines the term neuropathic pain as pain caused by a lesion or disease of the locomotor nervous system [2].

One of the most common neuropathic pains is phantom limb pain [3], which occurs after amputation and is felt at the missing limb. It has a profound effect on the performance and well-being of patients and occurs in 81 % of patients with amputation [4], which can occur in 72 % of patients within a week [5]. Annually, due to factors such as disease, trauma, and birth defects, about 211 to 511 million amputations are performed [6]. Phantom pain has negative effects on daily activities and quality of life [7,8]. Half of patients experience severe pain for about a week every month and more than 25 % experience pain for more than 15 h a day [9]. Unfortunately, there is no satisfactory treatment for phantom pain and it remains a challenge to date. Pharmaceutical interventions have been studied in this regard such as beta-blockers, calcitonin, anticonvulsants, antidepressants, inhibitors Selective serotonin reuptake inhibitors, anesthetics, opioids, tramadol, analgesics, nonsteroidal anti-inflammatory drugs, and nerve blocks. Phantom pain is very common in amputation cases and has been studied as a global topic by many researchers. 511 years ago, the sensation of a phantom limb was described by a French military surgeon, Ambrose Pare [10]. In fact, phantom pain is one of the most common neuropathic pains [3].

Phantom limb pain may go away in a few months to a year if left untreated, but there are some patients who may suffer from this pain for years. Common treatments include pharmacotherapy, adjuvant therapy, and surgery. There are several types of medications that can be used for treatment. These medications include tricyclic antidepressants, opioids, and NSAIDs [11].

Botulinum toxins are potent toxins produced in nature by anaerobic bacteria called Clostridium botulinum. Seven types of Clostridium toxin have been identified, including A to G, and a new serotype called H has

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recently been discovered [12]. Clostridium botulinum toxin is a potent bacterial neurotoxin that acts at the nerve-muscle junction and blocks the secretion of acetylcholine from the pre-synaptic cholinergic nerves, thereby inhibiting sympathetic stimulation of smooth muscle tone [13,14]. The effect of this neurotoxin is dose-dependent and lasts for an average of 4 to 6 months. Today, the injection of this toxin is used in the treatment of various diseases such as strabismus, muscle spasms of the limbs, a number of gastrointestinal disorders including esophageal achalasia, non-relaxation of Udi snipe in biliary dyskinesia, pain treatment in chronic anal anus, hemorrhoidectomy and persistent constipation after pull-through surgery in Hirschsprung patients [13,14].

Botulinum toxin type A is used in the treatment of neurological, muscular, and autonomic disorders. It has been reported to have analgesic effects [15]. Recent studies have shown that intramuscular injection of botulinum toxin A toxin, in addition to being uncomplicated, also reduces spasm. This toxin reduces muscle spasm, improves limb condition, and improves mobility and limb function. In addition, the injection of this drug is done simply and without the need for anesthesia and is not associated with complications [16].

The aim of this study is to evaluate the efficacy and safety of botulinum toxin type A among patients with phantom pain.

2. Methods

In this double-blind clinical trial patients referred to Imam Hossein Hospital with phantom pain from June 2020 – August 2020, aged 18 – 65 years were included. Patients with a history of botulinum toxin allergy, localized infection, lumbar radiculopathy (based on clinical signs, clinical examination, EMG), neurological and mental illness, history of alcohol and drug use, known kidney disease, history of myasthenia gravis and consumption of aminoglycosides were excluded from the study. Written consent was obtained from all the patients prior to their participation in the study.

After participants were included in the study, individuals were assigned to the intervention group or placebo (without being told) using the last digit of their national code. If their last national code number is even, they were assigned intervention group (A) and otherwise placebo group (B). Patients were divided into two groups of 15 using random allocation and considering bilateral blindness. After assigning individuals to the two groups, before injecting any drug, their pain was first measured using the VAS (visual analog scale). Following the treatment, the pain was measured at 2-, 4-, 8- and 16-weeks VAS and NPS (neuropathy pain scale).

All patients, in both groups, received standard treatment (gabapentin 311 mg capsules once daily). Patients in group A received, 111units of Xeomin® (incobotulinumtoxinA) dissolved in 1 ml of normal saline in 21 points (with insulin syringe and 5 syringe lines at each point), intradermally at the amputation site. Group B received normal saline using the same method. Side effects such as headache, cold symptoms, and injection pain were also evaluated in both groups.

The data was computerized and statistically analyzed using SPSS v23.

3. Result

In group A, 5 patients were female and 10 were male, and in group B, 4 were female and 11 were male. The mean age of the patients in group A was 56.13 years and that of group B was 53.86 years. In group A, 40 % of the patients were in the age group of 51–60 years and 61 years and above, respectively. In group B, 4 % of the patients were in the age group of 61 years and above.

In terms of cause of amputation, 53.3 % of patients were amputated because of the war, 20.2 % because of an accident, none because of burns, and in 26.7 % of patients the cause of amputation is unknown. Before the intervention, the mean pain score in groups A and B was 4.63 and 5.21, respectively, which was not significantly different. Fig. 1 shows pain score after intervention at 0, 2, 4, 8, and 16 weeks. T-test independent samples with Bonferroni correction showed that there was a significant association between pain scores in groups A and B at 0, 2, 4, and 8 weeks, $p = 0.01$, $p < 0.001$, 0.004, $p < 0.001$, respectively.

Pain score among subgroups showed that war, accident, and unknown cause was significantly different in terms of intervention and control, $p < 0.001$, respectively. Whereas, in burns group, due to insufficient data, an analysis could not be performed.

T-test independent samples with Bonferroni correction showed that there was a significant association between pain S scores in the two groups at 2, 8, and 16 weeks, $p < 0.001$, respectively but there were no significant associations at 0 and 4 weeks (Fig. 2A). This difference was also significant in war and accident groups.

In pain D group, there was a significant association just in week 2 (Fig. 3A), $p = 0.02$. Also, the test showed that for pain D group, Botox was statistically effective just in an unknown group (Fig. 3B and 3C).

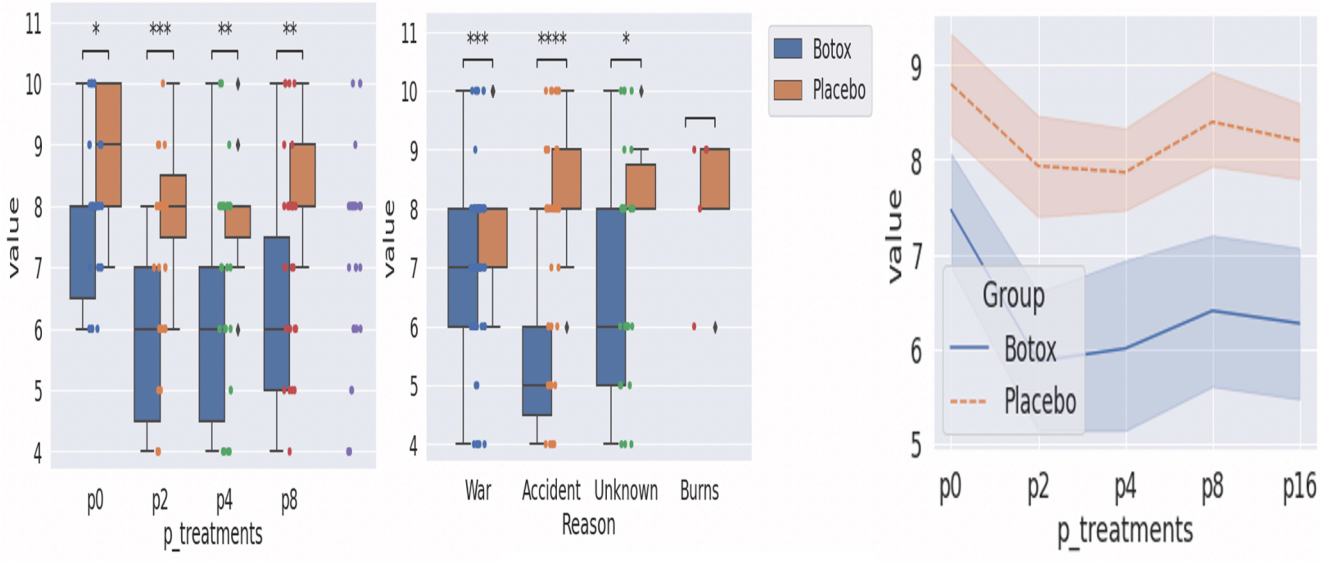

Fig. 1. 1A. Pain scores in Botox and Placebo groups in different injection times (week 0, 2, 4, and 8). Fig. 1B. Pain scores in Botox and Placebo groups in different groups. Fig. 1C.

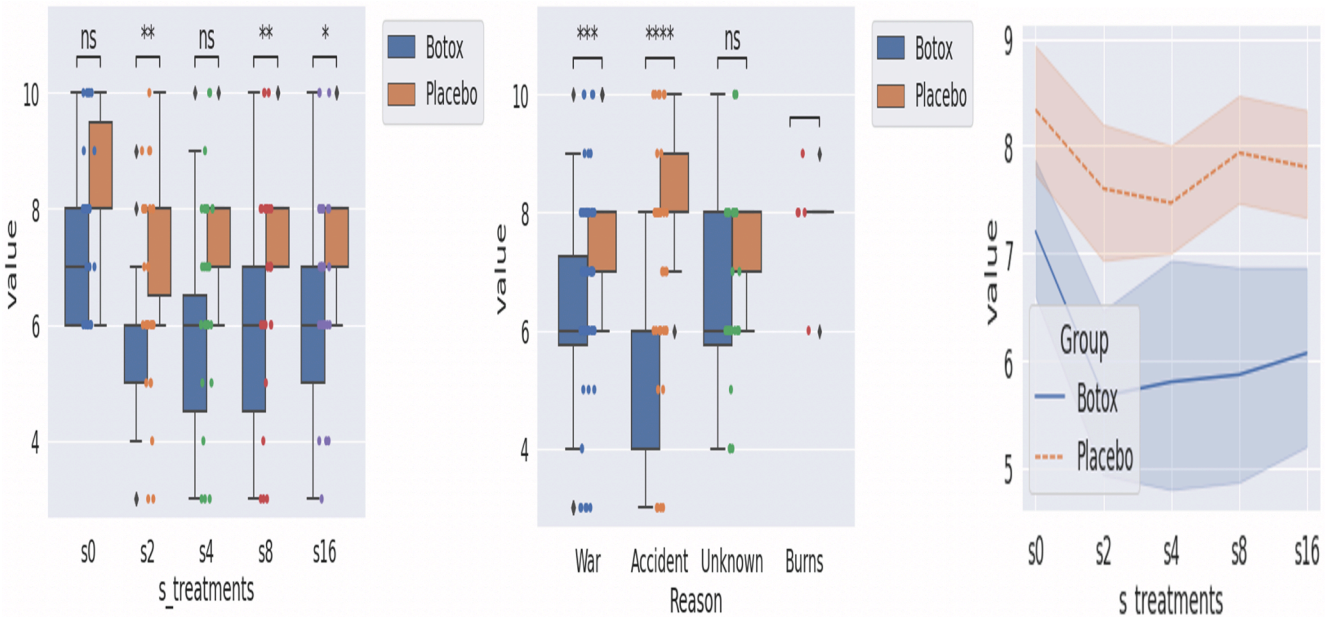

Fig. 2. 2A. Pain S scores in Botox and Placebo groups in different injection times (week 0, 2, 4, 8 and 16). Fig. 2B. Pain S scores in Botox and Placebo groups in different groups. Fig. 2C.

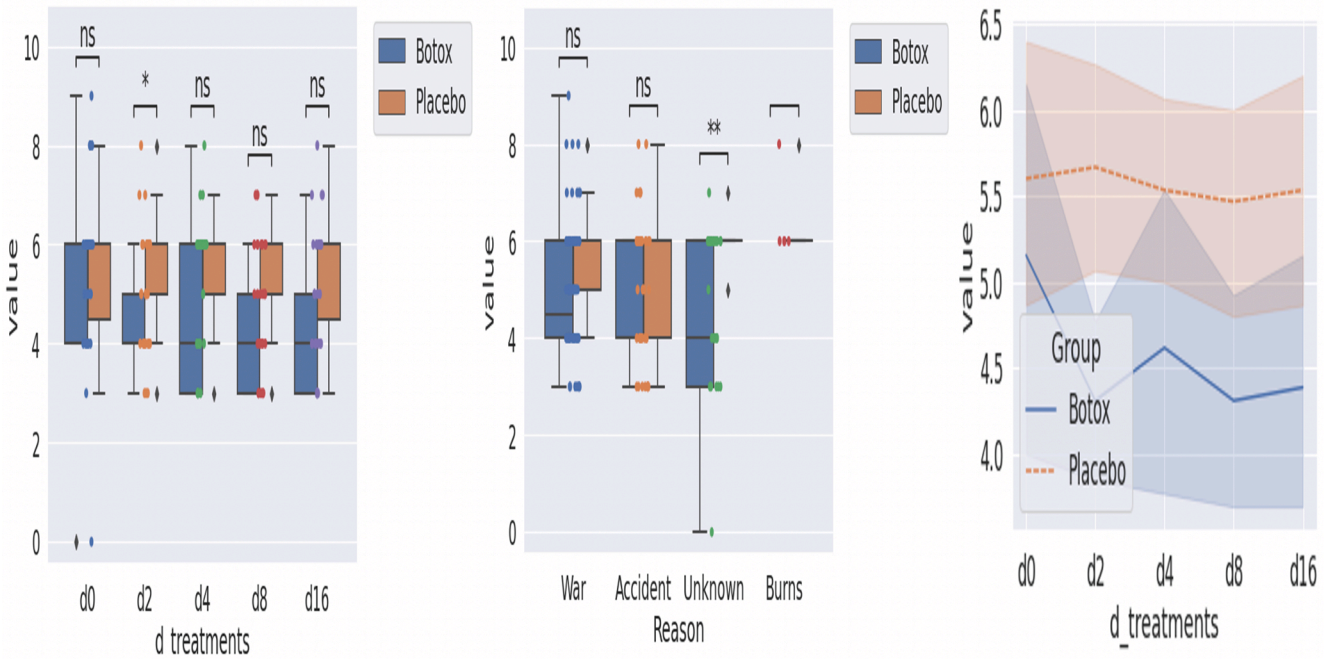

Fig. 3. 3A. Pain S scores in Botox and Placebo groups in different injection times (week 0, 2, 4, 8 and 16). Fig. 3B. Pain S scores in Botox and Placebo groups in different groups. Fig. 3C.

T-test independent samples with Bonferroni correction did not find a significant association in both Pain H and C groups between the two groups (A and B). The test showed that in both, Pain H and C groups, there was just a significant association in Unknown group.

In F group, T-test independent samples with Bonferroni correction showed that intervention was statistically effective just at 4 weeks (Fig. 4A), $p = 0.03$. Intervention was also significantly effective in accident and unknown groups.

In both, I and De pain groups, the test showed that there was no significant association between the two groups at any time. Regarding the cause of amputation, an intervention was effective for Accident subgroup in De pain group, but not in Pain I group.

In Pain U group, *t*-test showed that except at 4-week, an intervention was significantly effective in comparison to Placebo group (Fig. 5A) (week 0, $p = 0.003$, week 2, $p = 0.02$, week 8, $p < 0.001$ and week 16, $p = 0.001$). Intervention was significantly effective for war, accident, and unknown subgroups. Because of small sample size in burns group, we could not find the association type (Fig. 5B and 5C).

Pain Su group.

In Pain Su group, the *t*-test showed that intervention was effective just for week 16, $p = 0.015$. It was also effective in accident and unknown groups (Fig. 6A and 6C).

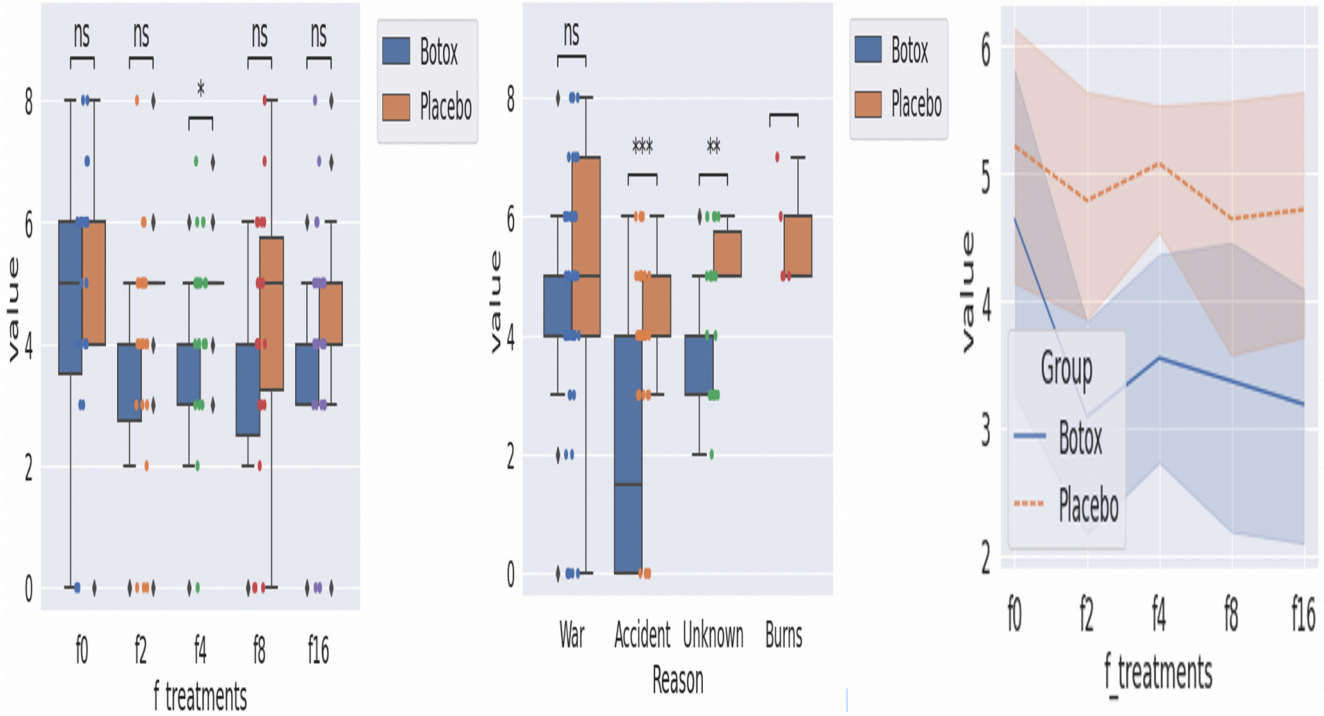

Fig. 4. 4A. Pain S scores in Botox and Placebo groups in different injection times (week 0, 2, 4, 8 and 16). Fig. 4B. Pain S scores in Botox and Placebo groups in different groups. Fig. 4C.

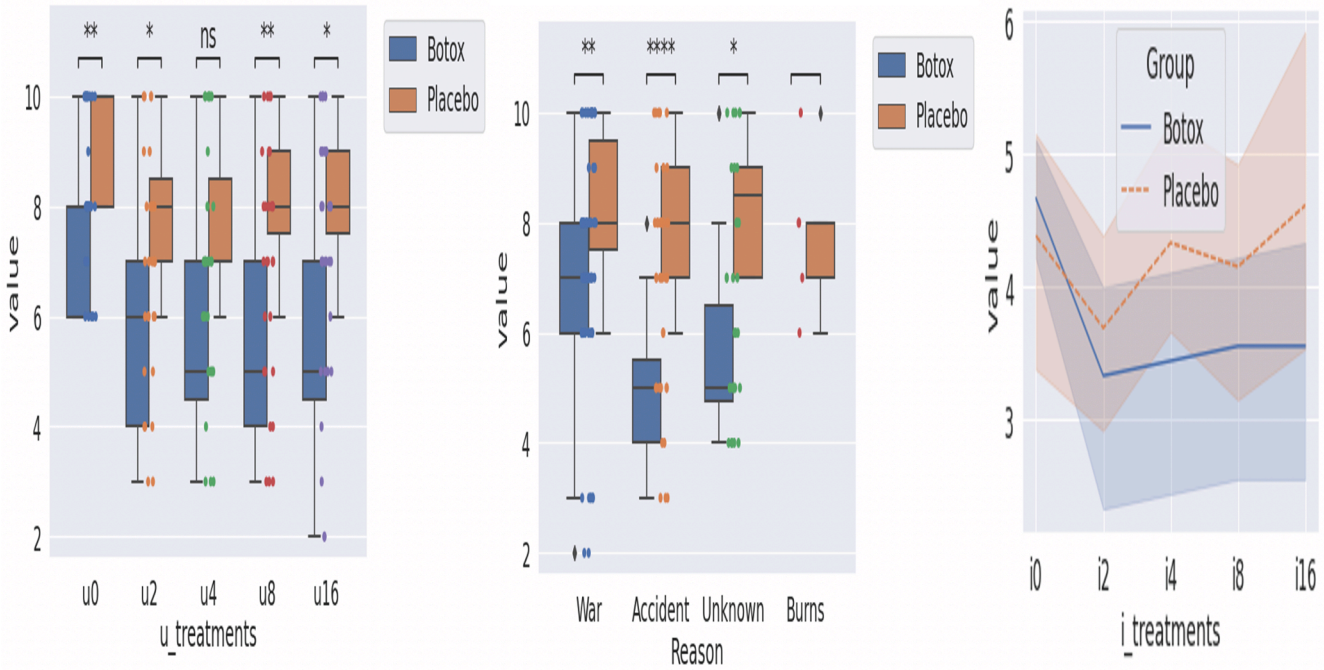

Fig. 5. 5A. Pain S scores in Botox and Placebo groups in different injection times (week 0, 2, 4, 8 and 16). Fig. 5B. Pain S scores in Botox and Placebo groups in different groups. Fig. 5C.

4. Discussion

In the present study, we investigated the effect of botulinum toxin injection on phantom pain in patients. Based on the results of the present study, injection of botulinum toxin A in the intervention group significantly reduced patients' pain compared to the placebo group. Also, the mean pain of patients in the pre-test stage was significantly different from their mean pain in the post-test stage, and also the mean of pre-test pain with the mean pain in the follow-up of the first stage, follow-up of the second stage, and follow-up of the third stage. This result is similar to the results obtained in the study of Kern et al. [17,18]. However, in the study of Kern et al., only three patients were studied, while in the present study, a total of 30 patients were studied in two groups of 15 people. In the study of Ethel et al. (62), which was similar to the present study,

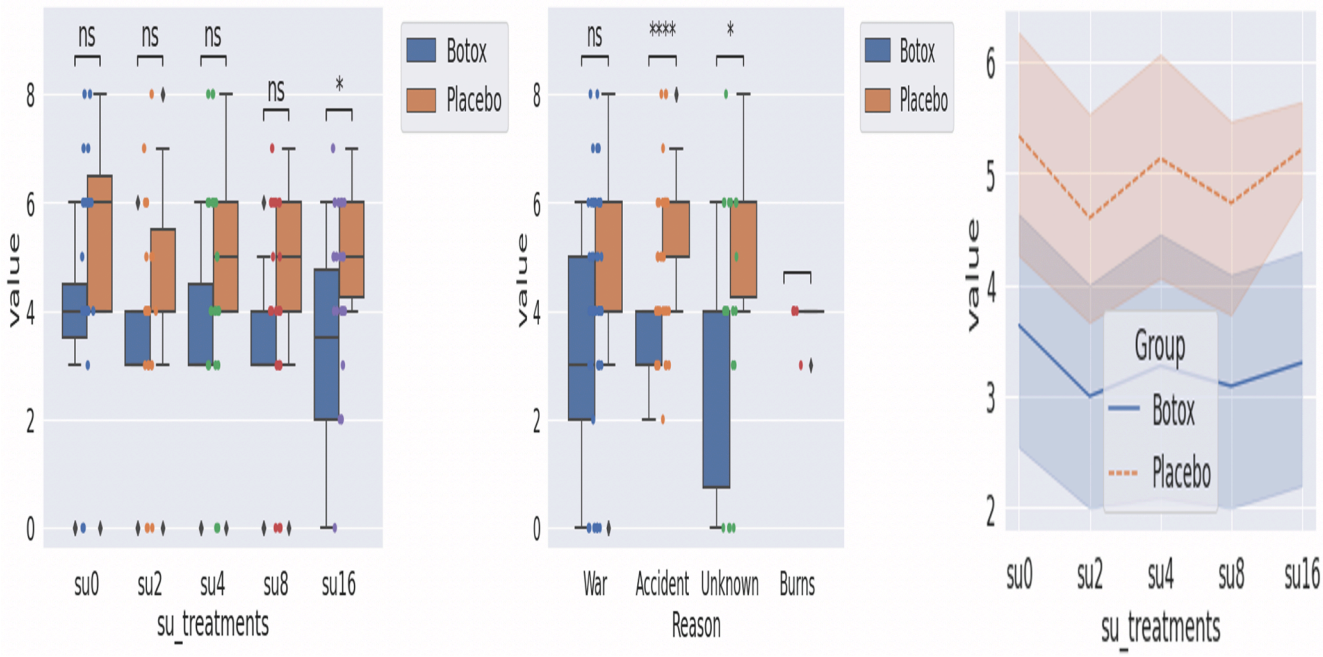

Fig. 6. 6A. Pain S scores in Botox and Placebo groups in different injection times (week 0, 2, 4, 8 and 16). Fig. 6B. Pain S scores in Botox and Placebo groups in different groups. Fig. 6C.

injection of toxin A reduced peripheral neuropathy in patients. In the study of Koule et al. [19] that studied the effects of botulinum toxin on phantom pain in 3 amputated patients, botulinum significantly reduced phantom pain. On the contrary, the study of Wu et al. [20] showed that in 14 amputated patients toxin A reduces residual limb pain but has no effect on limb phantom pain.

Our study was blinded using national numbers, which it could have impaired the blinding of the treatment. Furthermore, a sample size of 15 cannot give us an absolute outcome in sub-group analysis.

5. Conclusion

We recommend studies with larger sample sizes, a comparison of botulinum with other pain killers, used to treat phantom pain and an assessment of complications and recurrence of the pain in future studies.

The results of the present study show that injection of botulinum toxin A can effectively reduce phantom pain in patients. This effect does not affect some of the pain properties such as hot and cold pain and itching pain. It seems that botulinum toxin A can be used in the future as an effective treatment in patients with phantom pain and improve the quality of life of patients.

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Availability of data and material: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Ethical approval and consent to participate.

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to participate: from the under 16 years old was given by a parent or legal guardian.

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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