

1 **Introduction**

2 Cervicogenic headache (CH) was first reported by Sjaastad in 1983 (1). Fredriksen et al.
3 presented a more detailed description in a patient diagnosed as CH in 1987 (2). CH was added
4 as a headache disorder in the International Headache Society Classification published in 2004
5 (3). CH may be due to many factors associated with the back of the head and neck. Lesions
6 that affect nerves, ganglia, nerve roots, vertebrae, joints, the periosteum, muscles, and
7 ligaments may be etiological in CH (4-7).

8 The reported prevalence of CH varies. For example, the prevalence of CH in migraine
9 patients was 0%, versus 80% in patients with only headache (8,9). In the general population
10 the prevalence of CH is between 0.4% and 2.5%, and between 15% and 20% in patients with
11 headache (10-14). Shah and Nafee reported that 20.9% of CH patients were male and 79.1%
12 were female (15). Traumatic and degenerative changes increase the incidence of CH (16).

13 CH is unilateral and always located on the same side. CH typically begins at the back of the
14 head, neck, and ear, and spreads over the zygomatic region. Pain associated with CH is
15 sometimes throbbing. The most important feature of CH is that it is caused by mechanical
16 triggers. Compression of the great occipital nerve may cause pain. Additionally, head and
17 neck flexion, extension, and rotation may cause pain; the sensitivity and specificity of this
18 maneuver is 91% and 90%, respectively (17). The pain may begin up to 30 min or
19 immediately after these maneuvers. The duration of a CH attack is variable and may be
20 several days or several weeks.

21 The pathophysiological mechanism of CH is thought to be related to the trigeminocervical
22 nucleus, which is located at the C1-C3 level (18,19). Any kind of direct or indirect effects on
23 the great and small occipital nerves might cause cervicogenic pain, yet despite surgical
24 evidence, this is not a fully proven theory. All structures associated with the trigeminocervical
25 nucleus may cause CH (18,19).

26 Simple analgesics, ergotamine, oxygen inhalation, triptans, amitriptyline, botulinum toxin
27 type A (BoNTA), sterile water, nerve blockades, epidural blockade, steroids, and surgical
28 procedures have been used as treatment for CH (20-29). Few studies have assessed the
29 usefulness of BoNTA treatment for CH. Studies have reported variable findings concerning
30 the usefulness of BoNTA for the treatment of CH (30). One of the most important findings
31 was obtained in a placebo-controlled study that included 33 patients with CH; analgesic use
32 and duration of pain were found to be decreased in BoNTA group, as compared to the placebo
33 group (31). The present study aimed to investigate the effectiveness of BoNTA in the
34 treatment of CH by comparing and placebo group and a BoNTA treatment group consisting of
35 medically resistant CH patients.

36

37 **Materials and Methods**

38 Patients that presented to our clinic with complaints of head and neck pain that were
39 diagnosed as CH were included in the study. Among these patients, those 18-65 years of age
40 with normal general physical and neurological examination results, a ≤ 6 -month history of
41 one-sided cervical pain radiating to the occulo-fronto-temporal region, no cervical
42 abnormalities related to their complaints observed with MRI, no complaints of painful
43 periods, and resistance to medical treatment were included in the BoNTA treatment group.

44 Patients that were treated with cervical and cranial surgery, received interventional treatment,
45 had a diagnosis of any psychiatric disease, used antipsychotic, antidepressant, or antiepileptic
46 drugs during the 3 months preceding the study, were receiving coagulopathy, were pregnant,
47 had a neuromuscular disease, were responsive to medical treatment, and previously received
48 BoNTA treatment were excluded from the study.

49 The study protocol was approved by the local ethics committee and all the participants
50 provided written informed consent. In total, 40 patients were included in the study, according

51 to inclusion and exclusion criteria. Demographic characteristics of the patients are
52 summarized in Table 1. Prior to receiving BoNTA treatment all patients were evaluated for
53 severity of pain using the Visual Analog Scale (VAS) and **frequency of pain scores were**
54 **recorded.**

55

56 *Administration of BoNTA*

57 Patients in the BoNTA group (n = 20) were bilaterally administered 10 U of BoNTA
58 (Dysport®) to the frontal muscles, 20 U to the temporal muscles, 15 U to the semispinalis
59 capitis, 15 U to the splenius capitis, and 15 U to the trapezius muscles (total: 150 units).
60 Patients in the placebo group (n = 20) received 0.2 mL of saline administered to the same sites
61 (Table 2). Following administration of BoNTA and saline both groups were observed for 30
62 min for side effects. All participants were evaluated 6 and 12 weeks post treatment; **side**
63 **effects, VAS and frequency of pain scores were evaluated.**

64

65 *Statistical analysis*

66 Statistical analysis was performed using SPSS v.16. Two groups in their pre-treatment, the
67 frequency of the 6th and 12th weeks, and VAS scores were evaluated using the Wilcoxon test.
68 Comparison of the 2 groups was performed using the Mann-Whitney U test.

69

70 **Results**

71 Significant differences were not observed in age, or pre-treatment pain intensity and
72 frequency between the BoNTA and placebo groups ($P > 0.05$). In BoNTA group, pain
73 intensity and frequency 6 and 12 weeks post treatment were significantly lower than pre-
74 treatment levels (**all $P < 0.05$**)(**Table 3**).

75 In the placebo group the severity of pain 6 weeks post treatment was significantly lower than
76 the pre-treatment level (P : 0.029), but there wasn't a significant difference in the severity of
77 pain between pre-treatment and 12 weeks post treatment (P : 0.441). There wasn't any
78 difference in the frequency of pain between 6 and 12 weeks post treatment in the placebo
79 group (P : 0.086 and P : 0.496, respectively).

80 The severity of pain at 6 weeks post treatment did not differ significantly between the 2
81 groups (P : 0.071), but the frequency of pain in the BoNTA group was significantly lower
82 (both P < 0.001 and P < 0.001). The intensity and frequency of pain in the BoNT-A group
83 were lower than in the placebo group at the second visit as 12th week (P: 0.006 and P<
84 0.001, respectively) (Table 3).

85 All patients were carefully monitored for serious adverse effects. We did not observed any
86 serious side effects resulting in the need to withdraw from the study. Side effects are
87 summarized in Table 4.

88

89 **Discussion**

90 The present study's results indicate that BoNTA can be a beneficial treatment for patients
91 with CH. The BoNTA group had significantly lower severity and frequency of pain 6 and 12
92 weeks post treatment, as compared to pre-treatment levels. Despite a significant decrease in
93 the severity of pain in the placebo group 6 weeks post treatment, there wasn't a significant
94 difference between pre-treatment and 12 weeks post treatment. The results show that BoNTA
95 therapy was superior to saline.

96 BoNTA has been used to treat many types of headache, and some randomized, double-blind
97 placebo-controlled studies examined the use of BoNTA as a prophylactic treatment for
98 migraine and tension headaches; however, there are only a few case reports on BoNTA
99 treatment for cluster headache, and overall the results have been inconsistent (32). Despite the

100 fact that in Schnider et al.'s randomized, double-blind placebo-controlled study there wasn't a
101 significant difference in the severity of pain between the BoNTA and placebo groups, the
102 duration of pain in the BoNTA group decreased (31).

103 Clostridium botulinum an anaerobic bacteria synthesizes toxins that target presynaptic
104 proteins and block acetylcholine secretion. BoNTA is a presynaptic neurotoxin that causes
105 dose-dependent weakness or paralysis of skeletal muscles by blocking calcium-mediated
106 release of acetylcholine in the motor nerve terminals; parasympathetic and sympathetic
107 cholinergic synapse activity also decreases. Inhibition lasts between weeks and 3-4 months,
108 and requires a germination for nerve function recovery. Protective (immune) resistance
109 develops in response to long-term use (33).

110 It was reported that BoNTA is associated with substance P release from neuronal cell cultures
111 obtained from dorsal root ganglia of mouse embryos and CGRP release from neuronal cell
112 cultures obtained from trigeminal ganglia (34). Subcutaneous BoNTA administration to the
113 paws of mice significantly reduced the inflammatory response induced by subcutaneous
114 formalin, which has an analgesic effect by blocking glutamate release from peripheral axons.
115 Moreover, reduced activity was observed in dorsal root neurons in the spinal cord (34). The
116 direct inhibitory effect of BoNTA on nociceptors due to inhibition of neuropeptide release
117 might be responsible for central or peripheral pain pathway sensitization and
118 neurotransmission. In addition to being a potent inhibitor of acetylcholine release, as BoNTA
119 inhibits neurotransmitters and neuropeptides, it has anti-inflammatory and analgesic effects
120 (34).

121 To further elucidate BoNTA's inhibitory effects on nociceptors additional research is needed.

122 There are 4 possible mechanisms by which BoNTA decreases pain signals (34):

123 Normalization of muscular hyperactivity;

124 Normalization of excessive muscle activity;

125 Neuronal retrograde flow to the central nervous system (CNS);
126 Inhibition of neuropeptide release from nociceptors in peripheral tissues and the CNS.
127 Release of neuropeptides and inflammatory mediators in response to injury stimuli causes
128 peripheral sensitization. Peripheral sensitization of the trigeminal nucleus and spinal cord
129 causes an increase in the impulse, resulting in CNS sensitization. BoNTA directly limits
130 peripheral sensitization via inhibition of the release of neurotransmitters that occurs after
131 nociceptive stimulation or peripheral nerve injury, and indirectly limits central sensitization
132 by inhibiting such neurotransmitters as glutamate and substance P (35).
133 Most likely, a complex of mechanisms rather than a single mechanism are involved.
134 Headaches arise from nociceptors in the occipital region of the head and neck. Myelinated A
135 delta fibers transmit high-speed pain signals and unmyelinated C fibers slow-speed burning
136 pain signals; data in the literature are compatible with peripheral nerve/nerve root dysfunction
137 or lesions. Ongoing neuropathic pain causes CNS sensitization and over time leads to chronic
138 pain (18,19).
139 Hobson and Gladish reported the efficacy of BoNTA treatment in a CH patient (24). These
140 may be evidence that muscles play a role in the formation or spread of pain. Freund et al.
141 reported a significant reduction in the frequency and severity in headaches in patients with
142 chronic cervical pain treated with BoNTA (22); however, patients in this study had chronic
143 pain secondary to cervical vertebrae injury. As such, these patients were reported as cervical-
144 associated headache instead of cervicogenic headache.
145 The absence of clinically significant side effects in the present study indicates the reliability
146 of BoNTA as a prophylactic treatment for CH. The findings and doses reported herein are
147 specific for the formula produced by Ipsen Biopharm Ltd. (UK). Differences in the results of
148 different studies are due to many factors, such as BoNTA dose, BoNTA administration
149 method, and patient population. According to the present results (similar to other published

150 results) BoNTA can be an effective treatment method in patients with CH. The results of
151 controlled studies on patients with chronic daily headache show that BoNTA is well tolerated
152 and effective in reducing the frequency of painful episodes and the number of painful days
153 (36-37).

154 The present study has some limitations; the patients received only 1 dose of BoNTA, the same
155 dose, and at the same sites. Larger placebo-controlled trials on BoNTA that use multiple
156 dosing, different doses, and different administration methods are needed to more definitively
157 demonstrate the therapeutic efficacy of BoNTA.

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