1. Title
Ultrasound-guided greater occipital nerve block with botulinum toxin for patients with chronic headache in the occipital area: A randomized controlled trial.

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3. Running Title
Ultrasound-guided GON block

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Ultrasound-guided greater occipital nerve block with botulinum toxin for patients with chronic headache in the occipital area: a randomized controlled trial

Running title: Ultrasound-guided GON block
Abstract

Background: The ultrasound guided greater occipital nerve (GON) block has been frequently used for various types of headache and botulinum toxin has recently begun to be used in patients with headache. Our study presents the long term effect of botulinum toxin on the GON block using ultrasound in patients with chronic headache in occipital area.

Methods: Patients with occipital headache were divided into two groups (bupivacaine: group BUP (n=27), botulinum toxin: group BTX (n=27)) and ultrasound-guided GON block was performed on C2 level. The GON was detected using ultrasound technique and distance from the GON to midline, from the skin surface to the GON and size of GON was measured in both groups. The VAS scores and Likert scale were assessed at pretreatment, 1 week, 4 weeks, 8 weeks and 24 weeks after treatment on both groups.

Results: The GON had a distance of 18.9 ± 4.4 mm (right) and 17.3 ± 3.8 mm (left) from the GON to midline. The depth from the skin was 12.9 ± 1.5 mm (right) and 13.4 ± 1.6 mm (left). The size of GON was measured as 3.1 mm on both sides. VAS score and patient satisfaction score (Likert scale) of 4 weeks, 8 weeks, 24 weeks after injection were superior in botulinum toxin group.

Conclusions: Ultrasound-guided GON block using botulinum toxin is effective in reducing short-term and long-term pain in patients with chronic headache in occipital area.

Key Words: Botox; Greater occipital nerve block; Headache; Likert scale; Long term follow up; Ultrasound; Visual analogue scale
Introduction

Headache is a commonly experienced pain that is caused by a variety of causes. Primary headache can be categorized as tension-type headache, migraine, trigeminal autonomic cephalalgia, and other primary headache disorders according to the 3rd International Classification of Headache Disorders [1]. The greater occipital nerve (GON), which derives most of its fibers from the C2 dorsal root, is the main sensory nerve of the occipital area [2]. The GON block is a commonly used method in the treatment of these various headaches, especially occipital headache, and there are a number of articles mentioning practical usefulness [3-8]. However, conventional methods using only anatomical landmarks for finding the GON is difficult to demonstrate accurate nerve blockage and thus may raise questions about therapeutic efficacy. We have confirmed through preliminary test that ultrasound guided block at the origin of the GON is more accurate and effective than in the conventional method. In addition, local anesthetic agents or steroids can be used for treatment of headache, and opinions on the possibility of using botulinum toxin for prolonging the treatment effect have been recently reported [9, 10].

We compared the treatment effect of botulinum toxin injected group with that of local anesthetics group by using real-time ultrasound guided block, which is a more accurate method in headache patients. The effect of botulinum toxin on the GON block in the chronic headache in the occipital area with various causes and anatomical parameters for more accurate procedure was investigated.

Therefore, the primary aim of this study was to assess the effectiveness of the GON block using ultrasound and evaluate the satisfaction of patients in the treatment of the chronic headache in the occipital area up to 6 months. Secondary aims included obtaining the values of the anatomic
parameters for safe technique and confirming the occurrence of adverse events.
Materials and Methods

This double-blinded, randomized controlled trial was approved by the Research Ethics Board at Hanyang university Guri Hospital (20110021167).

Inclusion criteria & exclusion criteria

Inclusion criteria were 18-85 years old patients undergo primary headache on the occipital area over three months included tension-type headache, migraine, new daily persistent headache, and cluster headache. Exclusion criteria were 1) patients who have baseline pain of less than 30 mm (0-100 mm VAS) pain intensity, 2) patients with infection in the area of the injection site, 3) patients who had used acute pain medications within 24 hours prior to the study visit, 4) patients with evidence of serious cardiovascular diseases or neurologic disorders, 4) patients with known hypersensitivity to the study drugs, 5) pregnant or breast feeding women, and 6) patients who refuse to signed a written informed consent after being told the purpose of the study, procedures involved, and potential risks and benefits of the study.

After a written informed consent was obtained for all patients, 54 patients with chronic headache on the occipital area were enrolled in this study. We randomized the enrolled patients using the closed-envelope technique into two groups: group BUP and group BTX. The allocation sequence was generated using a random number table. Group BUP (n=27) was defined as patients receiving the ultrasound-guided GON block with levobupivacaine and dexamethasone and group BTX (n=27) as patients receiving the ultrasound-guided GON block with the botulinum toxin type A (Fig. 1).
Methods

The GON blockades were performed in the prone position with mild neck flexion as previously described [11] using either a linear-array high frequency (6-13 MHz) ultrasound probe (Sonosite, USA). Some parameters were measured before needle insertion. Patients were placed in the prone position with mild neck and head flexed. After confirmed the spinous process of C2, the probe was placed parallel to the laminae of C2 and slightly rotated to the long axis of the obliquus capitis inferior muscle (OCI) (Fig. 2). The relationship of the GON to the OCI is reliable and constant. Therefore obliquus capitis inferior muscle is used as the primary landmark for searching for the GON [12]. After measurements of the distance from the GON to midline, the distance from the skin surface to the GON and the size of the GON, a 23-gauge, 50mm block needle was inserted and advanced until the tip was seen to lie just deep to the greater occipital nerve. Patients with both side headache were injected on the both side on the same day with the same drug. The anatomical parameters were measured on both sides, but VAS score and the pain satisfaction was assessed for more severe side.

A total of 1 ml of 0.1% chirocaine (Levobupvacaine, Abott, USA) and 1 mg dexamethasone (Yuhan, Korea) was prepared for group BUP [13]. One milliliter of 50unit of the botulinum toxin type A (BoNT-A) (Allergan Inc., Irvine, CA, USA) was prepared for group BTX. The same amount of drug for each group were contained to 3 ml syringes and injected by a practitioner who does not know about the drugs in the syringes. For both groups, we evaluated the success of the block 15 minutes after the injection of medication. We checked for the sensory or motor changes such as numbness or paralysis of the dermatome. A successful block was defined as the absence of
light-touch sensation in the dermatome of the GON [12]. The side effects of injection were
determined by clinical symptoms.

Demographic data was collected. The practitioner performing the block, the patient, and the
personnel responsible for data collection were blinded to study group allocation. Headache severity
was assessed on a visual analogue scale (VAS) score and patient satisfaction was assessed on Likert
scale in a blinded manner. Patients were assessed prior to being injected and 1 week, 4 weeks, 8
weeks, and 24 weeks after treatment for pain severity. Patients were asked to note the satisfactory
score after injection (1, 4, 8, 24 week) on a 5-point scale (Likert scale: 1-excellent, 2-good, 3-fair,
4-poor, 5-no effect) when they visited outpatient. Telephone follow-up was also performed at 24
weeks (6 months) postoperatively to assess satisfactory score if they did not visit. If patients feel a
headache during the evaluation period, they are given acetaminophen 500mg twice a day.

Statistical analyses

Assuming a power of 80% and an alpha level of 0.05, clinical significance (ε) is generally
considered to be clinically significant when the difference of VAS is about 20 mm. The study
sample size was set at 27 patients per group considering the expected dropout rate of 20%.
Statistical analysis was performed by SAS 9.4 (SAS Institute Inc., Cary, NC). Continuous data were
tested for normality using the Shapiro-Wilk W statistic. Parametric data were analyzed using
Student’s t-test and non-parametric data were analyzed using the Mann-Whitney U test. Numerical
quantitative data were presented by “mean ± SD” and tested by an independent t-test, and
categorical data were presented by “frequency (%)” and tested by a chi-square test or a Fisher’s
exact test for demographic data and anatomical parameter. The differences in VAS score at pretreatment, 1 week, 4 weeks, 8 weeks, and 24 weeks after injection were analyzed using the unpaired \( t \)-test. The differences in Likert scale at 1 week, 4 weeks, 8 weeks, and 24 weeks after injection were analyzed using the unpaired \( t \)-test. A \( P \) value of 0.05 was chosen as the significance level.
Results

Seventy patients were screened for enrolment in the study, of which a total of 54 patients were recruited and randomized to receive either 0.1% chirocaine and 1 mg dexamethasone or a BoNT-A injection (Fig. 1.)

There were 25 patients with tension-type headache, 12 patients with migraine, 9 patients with cluster headache, and 8 patients with new daily persistent headache in our study. Eleven tension-type headache patients, 7 migraine patients, 5 cluster headache patients, and 4 patients with new daily persistent headache were included in group BUP.

The each anatomical parameter was collected in both groups. Fifteen cases were measured on the right side, 9 cases on the left side, and 3 cases on both sides in group BTX. In group BUP, 17 cases were measured on the right side, 9 cases on the left side, and 1 case on both sides. There were no significant differences in patient demographics between the two groups (Table 1).

The greater occipital nerve had a distance of 21.2 ± 4.9 mm on the right and 16.5 ± 3.9 mm on the left from the GON to midline (spinous process) in group BTX, and a distance of 15.0 ± 3.6 mm on the right and 19.6 ± 4.0 mm on the left from the GON to midline in group BUP. The depth from the skin was 13.4 ± 1.4 mm on the right and 13.5 ± 1.5 mm on the left in group BTX, and 12.3 ± 1.7 mm on the right and 13.3 ± 1.7 mm on the left in group BUP. The size of GON was measured as 3.1 mm on both sides in both groups (Table 2).

There were no statistical differences of the VAS scores before injection and at 1 week after treatment between group BTX (66.8 ± 3.1 and 24.9 ± 3.9) and group BUP (63.0 ± 2.8 and 27.5 ± 4.5), respectively. The VAS scores at 4, 8, and 24 weeks after treatment were significantly lower in
group BTX (13.9 ± 3.3, 9.3 ± 2.6 and 12.3 ± 3.8) compared to group BUP (27.2 ± 4.1, 31.0 ± 4.2 and 34.8 ± 5.8), respectively (all p<0.05) (Fig. 3).

There was no statistical difference of the Likert scale at 1 week after treatment between group BTX and group BUP (2.1 ± 0.2 vs 2.4 ± 0.2). The Likert scales of 4, 8, and 24 weeks after treatment were significantly lower in group BTX (1.6 ± 0.2, 1.4 ± 0.1 and 1.5 ± 0.2) compared to group BUP (2.4 ± 0.2, 2.8 ± 0.2 and 3.1 ± 0.3), respectively (all p<0.05) (Fig. 4).

Adverse effects such as direct paralysis, flu-like symptom, dizziness, vaso-vagal syncopal attack, allergic reaction, exaggerated headache, and major complications were not reported.
Discussion

Headache disorders are among the most common disorders of the nervous system. It has been estimated that 46% of the adult population have headache at least once within last year in general [14]. Because of its high prevalence, socioeconomic and personal effects are very significant. It can be categorized as cervicogenic headache, occipital neuralgia, tension headache, migraine, cluster headache according to the 3rd International Classification of Headache Disorders [1].

The blocking sensory nerve is a useful method for reducing pain immediately. Several studies have suggested that blocking GON is effective for various kinds of headaches, such as cervicogenic headache [3-5], occipital neuralgia [15], tension headache [5,8], primary headache [16], cluster headache [17], and even migraine [6,7]. The reason for using the GON block in the treatment of headache can be explained by the convergence of the sensory input to the trigeminal nucleus caudalis neurons from both trigeminal and cervical nerve fibers [6,18], and its role in antagonizing a putative "wind-up-like effect" that can explain headache improvement [4].

Many practitioners still perform GON injections using a conventional approach with or without ultrasound, depending entirely on conventional anatomic landmarks to injectate local anesthetic and corticosteroid around the nerve at the level of the superior nuchal line [13, 19]. They are increasingly using ultrasound for peripheral nerve block because of determining the exact location of the nerve, minimizing complications and increasing chances of success with small quantities of the drug.
The GON originates from the medial branch of the posterior division of the second cervical spinal nerve with variable contribution from the C3 dorsal ramus, and traverses the posterior scalp and neck. Ducic et al. [20] reported that the GON proceeds between obliquus capitis inferior (OCI) and the semispinalis capitis muscle and then pierces medially to the semispinalis capitis muscle. It courses obliquely, in a superolateral fashion and is considerably more lateral at the level of the occipital prominence [15, 21].

Greher et al [11] described a proximal approach at the level of C2, targeting the GON superficial to the OCI muscle. They mentioned that the GON blockade at the level of C2 has a higher success rate and more precise compared with site at the level of the superior nuchal line using ultrasound guidance [11]. The block success rate was 80% (95% confidence interval: 58–93%) at classic site vs 100% (95% confidence interval: 86–100%) at new proximal site in that study. In our study, proximal block at the level of C2 using ultrasound guidance was 100% successful. They measured that the distance from GON to the C2 spinous process (NSD) was 27.6 mm (18.9-32.6 mm) in their cadaver study. In our study, NSD was 21.2 ± 4.9 mm on the right and 16.5 ± 3.9 mm on the left in group BTX, and 15.0 ± 3.6 mm on the right and 19.6 ± 4.0 mm on the left in group BUP. The depth from the skin was 17.5 mm (9.8-29.0 mm) in their cadaver study. In our study, the depth was 13.4 ± 1.4 mm on the right and 13.5 ± 1.5 mm on the left in group BTX, and 12.3 ± 1.7 mm on the right and 13.3 ± 1.7 mm on the left in group BUP. In our study, NSD and depth from the skin were shorter, which could be predicted as a result of the difference in height, weight, and BMI of the patients between the two studies.
We used a mixture of 1 ml of 0.1% chirocaine 0.1 and 1 mg dexamethasone with reference to previous study [13]. Such a small amount would be enough for GON block under ultrasound guidance according to that reference. The dose of BoNT-A used for chronic headache or myofascial pain syndrome varies from 5 U to 100 U [22, 23]. Kapural L, et al. [24] mentioned that the mean VAS score was significantly reduced from $8 \pm 1.8$ to $2 \pm 2.7$ and the Pain Disability Index (PDI) was reduced from $51.5 \pm 17.6$ to $19.5 \pm 21$ using botulinum toxin 50U in occipital nerve block for the treatment of severe occipital neuralgia and the duration of the pain relief was increased to an average of $16.3 \pm 3.2$ weeks. Therefore we used a total of 1 ml of 0.1% chirocaine and 1 mg of dexamethasone for group BUP and 1 ml of 50 units of BoNT-A for group BTX respectively [13, 17, 24, 25].

Botulinum toxin (BTX) is a neurotoxic protein produced by the bacterium Clostridium botulinum and related species [26]. It prevents the release of the neurotransmitter acetylcholine from axon endings at the neuromuscular junction and thus causes flaccid paralysis. BTX exerts its effect by cleaving key proteins required for nerve activation. First, the toxin binds specifically to nerves which use the neurotransmitter acetylcholine. Once bound to the nerve terminal, the neuron takes up the toxin into a vesicle by receptor-mediated endocytosis [27]. As the vesicle moves farther into the cell, activating a portion of the toxin travels across the vesicle membrane into the cytoplasm of cell [26]. Once inside the cytoplasm, the toxin cleaves SNARE proteins, meaning that the acetylcholine vesicles can’t bind to the intracellular cell membrane, preventing the cell from releasing vesicles of neurotransmitter. This stops nerve signaling, leading to paralysis [26].
Botulinum toxin types A and B are used in medicine to treat various muscle spasms and diseases [24]. BTX is used to treat for muscle spasticity, muscle disorders like strabismus [28], hyperhidrosis [29], chronic headache [9, 24, 30], not to mention cosmetic use [31]. Binder WJ. reported that patients who had cosmetic injections around the face had relief from chronic headache[10]. This was initially thought to be an indirect effect of reduced muscle tension, but it is now known that the toxin inhibits release of peripheral nociceptive neurotransmitters, suppressing the central pain processing systems responsible for migraine headache [32]. FDA approved intramuscular botulinum toxin injections for prophylactic treatment of chronic migraine headache in 2010 [33].

The unusual side effects of GON blockade include transient post-injection dizziness, vaso-vagal syncopal attack, hair loss around the injection site and exaggerated headache [34]. The side effects of BoNT-A are not limited to direct paralysis and can also include flu-like symptoms, headaches, and allergic reactions [35]. Side effects from therapeutic use can be much more varied depending on the location of injection and the dose of toxin injected. In general, side effects from therapeutic use can be more serious than those that arise during cosmetic use. These can arise from paralysis of critical muscle groups and can include arrhythmia, heart attack, and in some cases seizures, respiratory arrest, and even death [35]. In our study, no adverse effects were observed for used drugs such as BoNT-A or local anesthetic agents.

A major limitation of this study is high dropout rate at 6 months VAS. Patients who do not feel that the treatment effect is sufficient may not have visited the outpatient clinic for treatment.
Therefore, 6 patients dropped out after 24 weeks in group BTX, and 16 patients dropped out in group BUP, and the only VAS score was evaluated after 24 weeks in 11 patients in group BUP. Therefore, the VAS score of 24 weeks after in group BUP was relatively low. However, the evaluation of patients' satisfaction was relatively accurate because there was no dropout in the face-to-face evaluation including telephone. Therefore, the patients' satisfaction and treatment effectiveness at 24 weeks after treatment could be better in group BTX.

Secondly, this study could not confirm the treatment efficacy and satisfaction of headache patients with specific causes. In future studies, the causes of each headache should be subdivided, and each treatment effect and satisfaction should be confirmed. Nevertheless, this study was to evaluate the safety and efficacy of GON block on the second cervical vertebra level under ultrasonography for the treatment of chronic occipital headache and to suggest the possibility of using botulinum toxin.

In conclusion, ultrasound guided GON block at the proximal was an effective and relatively safe treatment method and the patient satisfaction and treatment effect in group with botulinum toxin were higher than local anesthetics in long-term follow-up.
References


33. Lew MF. Review of the FDA-approved uses of botulinum toxins, including data suggesting


Table 1. Demographic Data of Two Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group BTX (N=27)</th>
<th>Group BUP (N=27)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.2 ± 11.2</td>
<td>55.2 ± 10.5</td>
<td>0.320</td>
</tr>
<tr>
<td>Gender</td>
<td>7/20</td>
<td>8/19</td>
<td>0.761</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160.2 ± 9.1</td>
<td>158.3 ± 7.3</td>
<td>0.394</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62.6 ± 11.2</td>
<td>59.9 ± 8.5</td>
<td>0.335</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.3 ± 3.2</td>
<td>23.9 ± 2.3</td>
<td>0.577</td>
</tr>
<tr>
<td>Affected site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>15 (55.56)</td>
<td>17 (62.97)</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>9 (33.33)</td>
<td>9 (33.33)</td>
<td>0.757</td>
</tr>
<tr>
<td>Both</td>
<td>3 (11.11)</td>
<td>1 (3.7)</td>
<td></td>
</tr>
</tbody>
</table>

Numerical quantitative data were presented by “mean ± SD” and tested by an independent t-test, and categorical data were presented by “frequency (%)” and tested by a chi-square test or a Fisher’s exact test. BMI: Body mass index.
Table 2. Anatomic Parameters of Group BUP and Group BTX Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group BTX (N=27)</th>
<th>Group BUP (N=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>NSD (mm)</td>
<td>21.2 ± 4.89</td>
<td>16.54 ± 3.91</td>
</tr>
<tr>
<td>NPD (mm)</td>
<td>13.38 ± 1.37</td>
<td>13.54 ± 1.53</td>
</tr>
<tr>
<td>Size of GON (mm²)</td>
<td>3.05 ± 0.25</td>
<td>3.07 ± 0.42</td>
</tr>
</tbody>
</table>

Numerical quantitative data were presented by “mean ± SD” and tested by an independent t-test.

NSD: Distance from the GON to midline (spinous process), NPD: Distance from the skin surface to the GON,
GON: Greater occipital nerve.
Figure 1. Consort-flow diagram of participants in the study.

Fig. 1. Consort-flow diagram of participants in the study.
Fig. 2. Ultrasound image of the greater occipital nerve (GON) of the left side away from the midline (spinous process) is seen. A is the distance from the GON to midline. B is the distance from the skin surface to the GON. OCI: Obliquus capitis inferior muscle.
Fig. 3. Comparison of VAS score between the two groups on each time course is seen.

Group BUP (n=27) defined as patients with ultrasound-guided greater occipital nerve (GON) block with bupivacaine and group BTX (n=27) as patients with ultrasound-guided GON block with botox A. One patient was not reached to obtain the VAS score at 8 weeks for group BUP and so dropped off.

* P < 0.05 compared with 4W, 8W, 24W on both groups. Pre: before greater occipital nerve block, 1W: 1 week after block, 4W: 4 weeks after block, 8W: 8 weeks after block, 24 W: 24 weeks after block.
Fig. 4. Comparison of Likert Scale between the two groups on each time course is seen.

Group BUP (n=27) defined as patients with ultrasound-guided greater occipital nerve (GON) block with bupivacaine and group BTX (n=27) as patients with ultrasound-guided GON block with botox A.

* P < 0.05 compared with 4W, 8W, 24W on both groups. 1W: 1 week after block, 4W: 4 weeks after block, 8W: 8 weeks after block, 24 W: 24 weeks after block. Likert scale: 1-excellent, 2-good, 3-fair, 4-poor, 5-no effect.