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Anatomical Regional Targeted (ART) BOTOX Injection Technique: A Novel Paradigm for Migraines and Chronic Headaches

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Summary: Migraine headaches are a debilitating disease that causes significant socioeconomic problems. One of the speculated etiologies of the generation of migraines is peripheral nerve irritation at different trigger points. The use of Onabotulinum toxin A (BOTOX), although initially a novel approach, has now been determined to be a valid treatment for chronic headaches and migraines as described in the Phase III Research Evaluating Migraine Prophylaxis Therapy trials that prompted the approval by the Food and Drug Administration for treatment of chronic migraines. The injection paradigm established by this trial was one of a broad injection pattern across large muscle groups that did not always correspond to the anatomical locations of nerves. The senior author developed the Anatomical Regional Targeted BOTOX injection paradigm as an alternative to the current injection model. This technique targets both the anatomical location of nerves known to have causal effects with migraines and the region where the pain localizes, to provide relief across a wide distribution of the peripheral nerve. This article serves as a guide to the Anatomical Regional Targeted injection technique, which, to our knowledge, is the first comprehensive BOTOX injection paradigm described in the literature for treatment of migraines that targets nerves and nerve areas rather than purely muscle groups. This technique is based on the most up-to-date anatomical and scientific studies and large-volume migraine surgery experience. *(Plast Reconstr Surg Glob Open 2016;4:e1194; doi: 10.1097/GOX.0000000000001194; Published online 27 December 2016.)*

Migraine headaches are a common and disabling condition that affects roughly 18% of females and 6% of males worldwide.[1] Often, these patients fail medical management and must look for more invasive treatment. One of these treatment options has been the injection of Onabotulinum toxin A (BOTOX), with growing evidence and Food and Drug Administration support for its use in the treatment of chronic migraines.[2–4] The landmark Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) trials[2,3,5] demonstrated that BOTOX was effective in treating chronic migraines. However, the PREEMPT injection paradigm is less targeted, with injection into a broad muscle group rather than a more customized approach corresponding with the peripheral nerves. It uses both fixed and "follow-the-pain" injection sites, with additional specific "follow-the-pain" sites considered depending on individual symptoms. The "fixed-site" injection technique implemented in the PREEMPT trial did not consider the patient's tender areas as a guide for an injection that corresponds to the anatomical

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location of the pain. Even the "follow-the-pain" approach described in the PREEMPT paradigm did not follow correct nerve anatomy as far as its surface topography and depth, nor did it correctly target the adjacent corresponding muscle.[6]

Based on the increased numbers of anatomical studies demonstrating the locations of muscles and nerves over the recent years in the plastic and reconstructive surgery literature,[7–14] we noticed that several of the injection sites advocated in the PREEMPT study were not being done in the most precise topographical locations. Since the initial work by Guyuron on migraine surgery[15] demonstrated that nerve compression can be involved in the genesis or worsening of migraines, the first generation of Guyuron-trained plastic surgeons has been injecting BOTOX for diagnostic and therapeutic purposes in anatomical locations that correspond to the topographical location and depth of these nerves.[15–20] Ironically, recent research in the neurology literature has shown that BOTOX not only works solely via muscle paralysis but also has a direct action on the nerve itself, preventing the genesis of migraines.[21,22] More recently, select neurologists have been injecting BOTOX in a more targeted and/or regional fashion but not in an anatomical fashion (Personal Communication: D. Friedman, 2014, 2015; B. Sorin, Plano Texas, North Texas Institute of Neurology & Headache, 2015; A. Lacy, Fort Worth, Tex., Cooks Children Hospital, 2016).

The quest to provide a better response rate to BOTOX in chronic migraine patients led the senior author (BA) to develop the "Anatomical," "Regional," and "Targeted" (ART) BOTOX injection paradigm for the treatment of both episodic and chronic migraine headaches. This technique stems from and expands upon the initial screening technique used preoperatively for surgical decompression,[15] and focuses on 3 components: "Anatomical," based on the surface anatomy of the corresponding nerves, the depth of the nerve, and the corresponding muscle around these nerves; "Regional," a directed focus on the region of where the pain starts (i.e., occipital, temporal, frontal); and "Targeted," based on the surface topography of the tender area, which at times may not fully correlate with the described and expected location due to anatomical variations.

The focal injection of BOTOX described by Guyuron, documented in migraine surgery publications, covers the zygomaticotemporal branch of the trigeminal nerve (ZTBTN), greater occipital nerve (GON), and corrugator muscle,[16,23] but only for screening purposes. The only other references to this type of injection based on the anatomy and region of the pain is a review article by the senior author (BA) in 2012[24] and a prospective trial by Guyuron that evaluated the response of forehead migraines to fixed corrugator injections.[19,20] Neither of these 2 articles included a comprehensive injection paradigm in all the necessary locations.

The ART injection approach adds focus to the delivery of BOTOX, thereby increasing its efficacy, decreasing complications, and minimizing oversaturation that could lead to BOTOX resistance.[25–27] The technique is based off the theory introduced by works from our neurology colleagues that BOTOX works directly on the nerves to decrease migraine pain[28,29] rather than an indirect effect by acting on the muscle alone. This technique has taken the initial Guyuron method[15] of BOTOX injection and added to it additional injection sites based on newer data regarding migraine etiology and nerve anatomy,[12–14,30] and the experience of the migraine BOTOX injection practice of the senior author,[20] to form the first comprehensive, nerve-specific treatment for migraines.

Providing convincing evidence that the ART injection technique is better than the current paradigm advocated by the PREEMPT trial[31] will require not only a large sample size with a standardized retrospective data review but also a robust prospective multicenter comparison trial similar in scope to the PREEMPT studies. The recent outcome of the senior author's (BA) retrospective study, and the forthcoming prospective multicenter randomized trials, is beyond the scope of this article and will be presented in the neurology literature by us for comparison with the PREEMPT technique. Thus, the focus of this article is solely to demonstrate the senior author's ART injection technique for both the plastic surgery and neurology community.

TECHNIQUE

All patients were seen by board-certified neurologists either before or after referral to our service. During the first visit, a diagnosis of chronic migraines (more than 15 headache days/mo or more than 8 migraine days/mo) is established along with documentation of failure of several classes of migraine medications. Based on these criteria, insurance approval for BOTOX injection in the plastic surgery office is almost always approved 2 to 3 weeks after the first visit.

After a detailed headache history is obtained, both the origin of pain and where the pain localizes to are determined, as the latter is often the only location initially mentioned unless the patient is specifically asked. The ZTBTN and supraorbital/supratrochlear nerve (SON/STN) injections are at fixed locations based on nerve and muscle anatomy. Injection variation in these areas based on a more specific "targeted" approach may increase complications of ptosis or diplopia. The variable site injections, based more on a targeted rather than "anatomical" approach, are the auriculotemporal (AT) nerve, GON, lesser occipital nerve (LON), tails of the GON/LON, and third occipital nerve (Table 1). Additionally, the ART technique targets both the primary and secondary trigger areas during the first injection visit because the goal of the injection is also to prevent the emergence of secondary "hidden" triggers[32] several weeks later. This differs from both the initial technique used by Guyuron of "chasing the second or third trigger every couple of weeks" to prescreen patients for surgery[5] and the "follow-the-pain" paradigm documented in the PREEMPT trials. The comprehensive ART technique is used as a treatment strategy alone and not necessarily a screening tool before surgery. For screening purposes before surgery, the author currently uses constellation of symptoms, nerve blocks, and region-specific ART injection when needed.

Table 1. Table Showing Regions, Patient Symptoms, and BOTOX Doses at Each Site and Corresponding Nerve That Is Targeted

	Anatomy	Regional	Targeted	Dosage (Unilateral)
GON	3 cm below and 1.5 cm lateral to the occipital protuberance[30]	GON pain at the base of the skull. Pain may radiate retro-orbitally but will always start in the occipital area	Point tenderness along the emergence of the nerve, within 0.5–1.5 cm lateral of anatomical site	25 units
LON	6.5 cm from midline and 5.3 cm below a transverse line connecting the external auditory canal[8]	Pain originating from mid to lower lateral sides of the neck	Point tenderness within 0.5 cm of the anatomical site and the posterior border of the sternocleidomastoid	7.5 units
TGON and TLON	Not well defined	Pain originating above and posterior to the GON	2–3 cm medial and superior to mastoid prominence	5–7.5 units
SON and STN	STN—deep and medial to the corrugator body; SON—superficial and lateral to the corrugator body	Pain originating above the brows extending above the forehead or originating at the orbital rim		12.5 units each corrugator/6.25–12.5 units to high forehead (unit)
ZTBTN	16.9 mm lateral and 6 mm cephalad to lateral orbital commissure[12]	Pain originates in the temporal region, lateral to the orbital rim	Low incidence of site-specific tenderness	12.5 units
AT (distal)	19 mm ant and 40 mm superior to anteriosuperior point of external auditory meatus[7]	Pain originating in the high temporal area[32]	Tenderness in the anatomical locations with 0.5-cm variation of the anatomical measurements is more reliable	2.5–5 units
AT (proximal)	13 mm anterior and 5 mm superior to anteriosuperior most point of external auditory meatus; 12 mm anterior and 17 mm superior to anteriosuperior point of external auditory meatus[7]	Pain along the border of the temporomandibular joint[32]	Tenderness above the temporomandibular joint in the soft tissue	2.5–5 units

TCON, Tail of Greater Occipital Nerve; TLON, Tail of Lesser Occipital Nerve.

FRONTAL SITES

For the SON/STN, the injection is based on the anatomy of the corrugator muscle.[14,28] This site is adjusted slightly when the patient is asked to frown at the brow, showcasing its topographical anatomy (Fig. 1). Digital occlusion of the supratrochlear and supraorbital vessels during injection with the nondominant thumb is important as this will decrease the rate of "microhematomas," which can lead to increased irritation around the nerves and potentially decreased response rate to BOTOX or increase in headaches.[33] We do not feel the need for topical anesthetics, but an ice pack is used to cool the skin immediately before injections, as it is important to minimize any irritation caused by needles in migraine patients. The medial injection should be deeper and the lateral injection more superficial, considering the anatomy of the corrugator (Fig. 2). The previous neurology paradigms, adopted from the PREEMPT trials, depicted the medial head of the corrugator in an incorrect higher position.[6] In addition, if the patient has tenderness on the inferior end of the orbital rim near the area of STN and SON emergence, BOTOX should not be injected over this area as there is a higher risk for lid ptosis due to proximity to the upper lid muscles, or even vertical diplopia in the event of leakage into the bony globe. Another method of injecting the corrugators is the lateral to medial approach with a single injection using a long needle, as described by Guyuron. However we feel that the point injection of the corrugators concentrates the BOTOX more around the SON and STN. (**See** video, Supplemental Digital Content 1, which demonstrates complete ART injection technique for frontal injection sites. This video is available in the "Related Videos" section of the Full-Text article on PRSGlobalOpen.com or available at ***http://links.lww.com/PRSGO/A345***.)

Compared to the PREEMPT model, our injection of the frontalis muscle is higher (only into the upper 1/2), which theoretically should provide for a lower rate of eyebrow ptosis.[34] The argument here is that frontalis injection is not targeting any specific compression areas or nerves. However, in our opinion, this is necessary not only to target the most distal aspects of the STN and SON nerves but also to relax the cephalic pull of the frontalis muscle. This would then decrease tension on the proximal STN and SON, which is potentially worsened by the superior pull of the frontalis muscle especially when it is compensating for eyelid ptosis.

TEMPORAL SITES

The ZTBTN is injected in an "anatomical" rather than "targeted" fashion because the tenderness reported by patients in this area is generally more diffuse rather than specific to the anatomical location of the nerve exit point from temporalis fascia. Because the anatomy of the nerve is very consistent in this area, an "anatomical" injection is sufficient. This point, described by Totonchi et al,[12] is generally 1.7 mm lateral and 6 mm superior to the lateral canthus. This injection, initially described by Guyuron et al,[16] is fanned out around the nerve into the temporalis

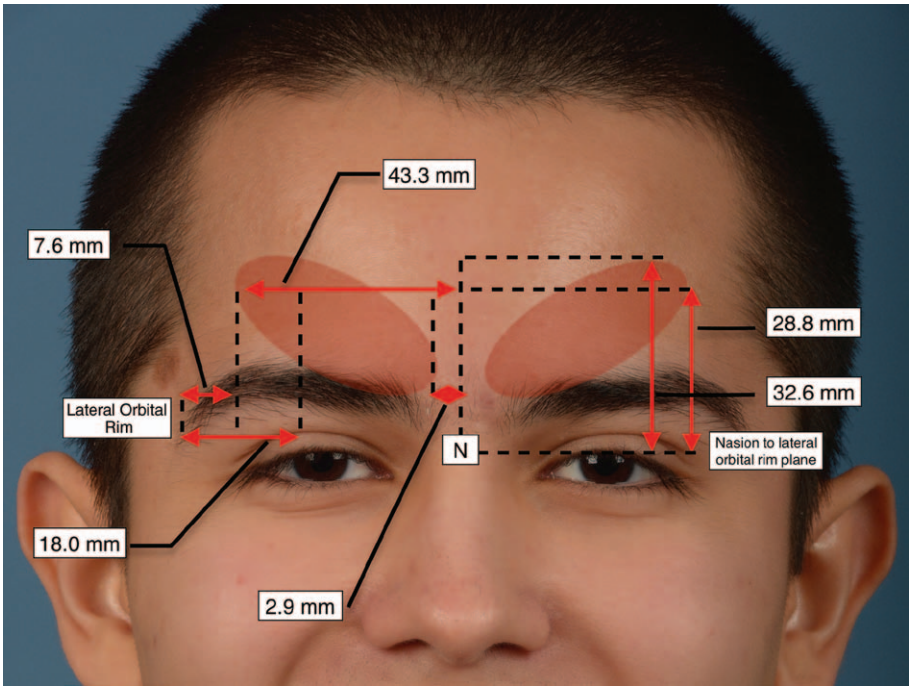


Fig. 1. Anatomical location of the corrugator.

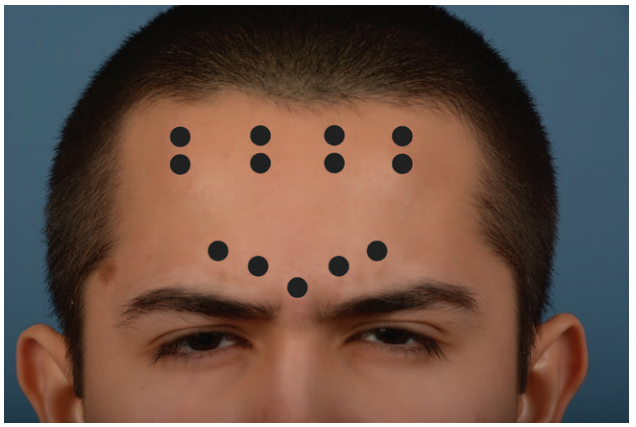


Fig. 2. Frontal injection sites. Image showing the injection sites as they correlate over the corrugator muscle where the SON and STN transverse. The patient is asked to frown to assist in determining these locations. The paired injection sites superiorly target the high frontalis, and the dose is adjusted here based on the length of the forehead from 12.5 to 25 units.

Video Graphic 1. Frontal injection technique. See video, Supplemental Digital Content 1, which demonstrates complete ART injection technique for frontal injection sites. This video is available in the "Related Videos" section of the Full-Text article on PRSGlobalOpen.com or available at ***http://links.lww.com/PRSGO/A345***.

muscle. We also inject a small amount of BOTOX into the space directly over the nerve exit point from the temporalis fascia to ensure that the superficial portion of the nerve that resides outside the temporalis is adequately exposed to BOTOX (Fig. 3). In our experience, a major drawback of the current neurologist injection paradigm is this nerve not being injected at the correct depth and location.

The AT nerve is injected in a more "targeted" fashion in several areas, based on tenderness throughout the areas of nerve distribution, which may or may not roughly correlate to the known anatomical areas of compression[7,9] (Video 2). (**See video, Supplemental Digital Content 2**, which demonstrates complete ART injection technique for temporal injection sites. This video is available in the "Related Videos" section of the Full-Text article on PRSGlobalOpen.com or available at ***http://links.lww.com/PRSGO/A346***.) The main compression point is where the anterior superficial temporal artery crosses the distal branch of the nerve (site 5A).[35] The second most common tender area, in our experience, is above constricting fibrous bands on the AT nerve directly superior to the temporomandibular joint (site 5B). Point tenderness here should not be confused with temporomandibular joint pain, which requires a different treatment. While recently described[36,37] to confirm site 5A compression by the artery, we do not rou-

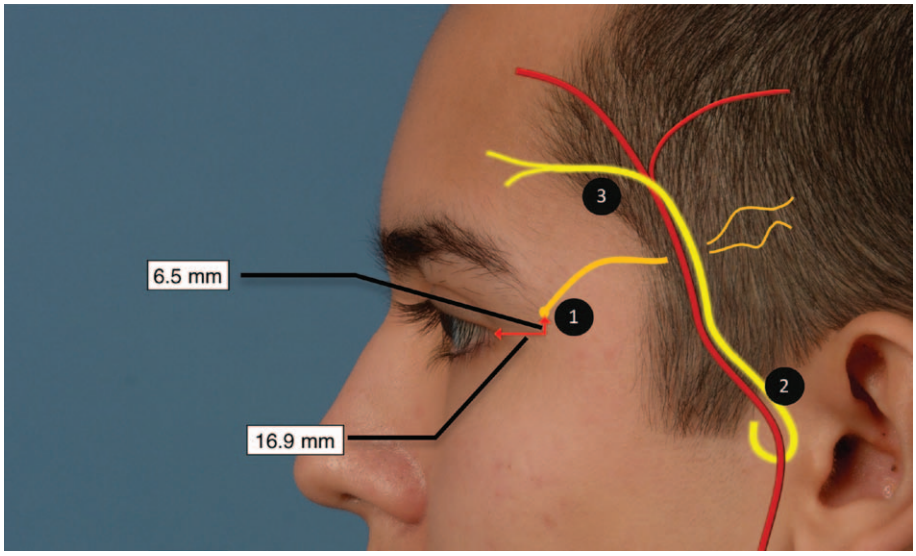
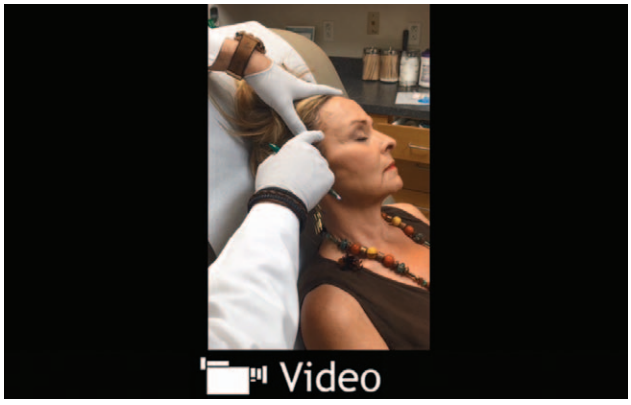


Fig. 3. Temporal injection sites. Image showing the relationship of the AT (bright yellow), ZTBTN (dark yellow), and the anterior and posterior branches of the superficial temporal artery (red) to the temporal injection sites. The ZTBTN is on a different fascial plane than the AT and superficial temporal artery laterally. 1, ZTBTN injection site, which is commonly 1.5 cm behind the emergence of this nerve from the deep temporal fascia; 2, proximal AT corresponding to the fascial compression bands; 3, distal AT corresponding to the anterior temporal artery crossing the AT nerve.

Video Graphic 2. Temporal Injection technique. See video, Supplemental Digital Content 2, which demonstrates complete ART injection technique for temporal injection sites. This video is available in the "Related Videos" section of the Full-Text article on PRSGlobalOpen.com or available at ***http://links.lww.com/PRSGO/A346***.



Video Graphic 3. Auriculotemporal injection technique. See video, Supplemental Digital Content 3, which demonstrates the author's evolved injection of the AT proximal and distal sites. This video is available in the "Related Videos" section of the Full-Text article on PRSGlobalOpen.com or available at ***http://links.lww.com/PRSGO/A347***.

tinely use Doppler to find this point when we inject BOTOX. Although the use of Doppler can be very helpful for intraoperative localization of the artery and academic exercises, we feel that the added injection time with an often apprehensive migraine patient adds no value to the routine use of Doppler. Both the distal and proximal injection sites are based on maximal point tenderness during the clinical examination rather than a strict anatomical location (Video 3). (**See video, Supplemental Digital Content 3**, which demonstrates the author's evolved injection of the AT proximal and distal sites. This video is available in the "Related Videos" section of the Full-Text article on PRSGlobalOpen.com or available at ***http://links.lww.com/PRSGO/A347***.)

As we described in a previous publication,[35] these areas can vary slightly and rely on point tenderness to target drug delivery more effectively.

OCCIPITAL SITES

The GON is injected in both an "anatomical" and "targeted" fashion, as the nerve exit point from the semispinalis capitis (a 1.5-cm diameter circle approximately 3 cm below and 1.5 cm lateral to the occipital protuberance) has been well described[30] and may correlate to the point of maximum tenderness. However, in our experience, the tender area is usually 0.5 to 1 cm lateral to this exit point, likely because of further irritation and compression by the nuchal line and

greater occipital vessels. When injecting this nerve, it is paramount to inject deep enough to pierce the trapezius fascia delivering the drug in the same space that the nerve resides. This injection is significantly deeper than the PREEMPT paradigm occipital injections and another major advantage to the ART technique. Instead of a 30-gauge needle, a longer and sturdier 27-gauge needle is used, which makes it easier to pierce the trapezius fascia. The LON is similarly injected in both an "anatomical" and "targeted" fashion, with injections modified to conform to the point of maximal tenderness commonly within 0.5 cm of the described anatomical landmark posterior to the sternocleidomastoid.[11] Additionally, there can be point tenderness in the distal "tail of the GON or LON" as they course over the mastoid and the superior/medial areas of the ear, where they can intertwine with the terminal branches of the occipital artery. (We have not had any issues injecting close to the vessels in the occipital area. In the case of a small amount of bleeding, immediate direct pressure is used for several minutes. This is in contrast to the corrugator area, where aggressive direct pressure should be avoided to prevent ptosis.) This injection is done in more of a "targeted" fashion, chasing the tender tail of the GON and LON. The third occipital nerve is injected far less commonly, also in an "anatomical"[8] and "targeted" fashion, depending on the severity of headache pain localizing from this area (Fig. 4). Recent studies show that the third occipital nerve is much less commonly involved in the pathogenesis of migraines.[38] Unlike the PREEMPT paradigm, there is no injection into the trapezius muscle lower on the neck where no real distinct nerve sites are located (Video 4). (**See video, Supplemental Digital Content 4**, which demonstrates the complete ART injection technique for occipital injection sites. This video is available in the "Related Videos" section of the Full-Text article on PRSGlobalOpen.com or available at ***http://links.lww.com/PRSGO/A349***.)

A majority of our patients receive the standard PREEMPT dose of 155 units of BOTOX, but in a more efficient way. In the select patients who only have a single trigger point or single "region" involved, we will use less than the standard dose and only target what is needed. However, we still adhere to the site-specific injection techniques listed above and do not simply "follow the pain" unless it corresponds with the above ART injection paradigm.

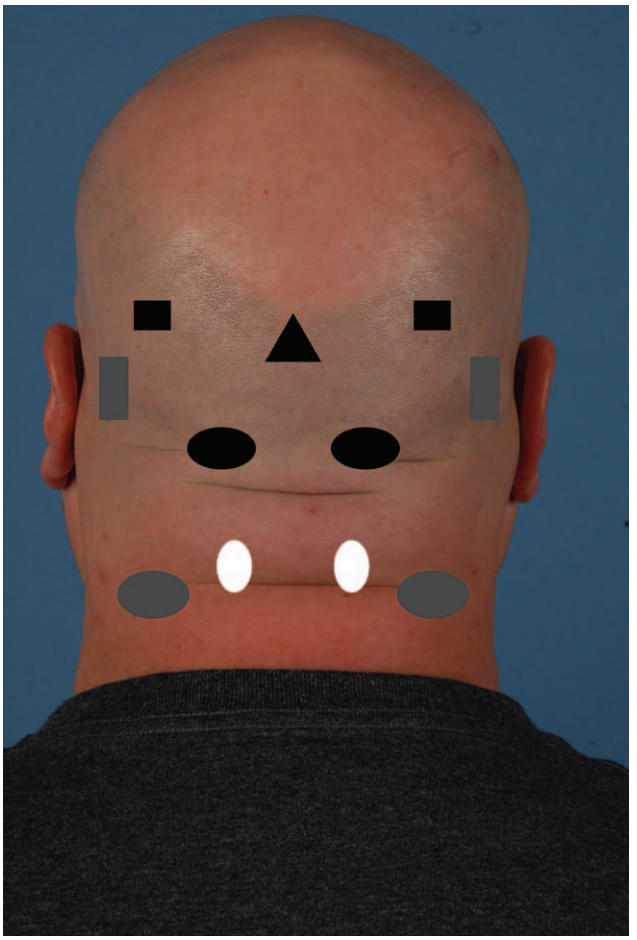


Fig. 4. Occipital injection sites. Image showing the occipital injection sites. Occipital protuberance (triangle), GON (black oval), tail of GON (black square), LON (gray oval), tail of LON (gray square), third occipital nerve (white circle). The third occipital nerve site is rarely injected as the patient usually does not have tenderness over this site.

CONCLUSIONS

The ART BOTOX injection technique is the first, to our knowledge, that describes a comprehensive migraine treatment strategy that targets BOTOX injections around the nerve and the various nerve regions, rather than an imprecise dispersed fashion throughout multiple muscle groups.[6,31] The ART injection technique is less of a "shotgun" approach than in the PREEMPT trials,[6] yet it is more comprehensive than the targeted approach initially described by Guyuron for screening purposes. The ART injection paradigm is not a screening tool, and both the surgeon and the patient should understand that the goal of this technique is a comprehensive treatment of the migraines with BOTOX.

By injecting closer to the nerves to target known anatomical sites of nerve irritation and focusing on regional sites of pain, the BOTOX injector can provide migraine patients with more pain relief, decreased complications from overinjection, potentially less BOTOX tolerance, overall increased patient satisfaction, and decreased attrition due to

Video Graphic 4. Occipital injection technique. See video, Supplemental Digital Content 4, which demonstrates the complete ART injection technique for occipital injection sites. This video is available in the "Related Videos" section of the Full-Text article on PRSGlobalOpen.com or available at ***http://links.lww.com/PRSGO/A349***.

complications and the potentially poorer response of diffuse injections. This method of injection may even prove useful in episodic migraines, which is currently thought to not be as responsive to the PREEMPT paradigm. Future prospective trials comparing this technique with the PREEMPT technique will definitively determine whether the senior authors' paradigm is validated for long-term use. Our current retrospective data, which is being considered for publication, may serve as a pilot guide to any future large prospective trials.

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PATIENT CONSENT

Patients provided written consent for the use of their images.

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