Headache
Series Editor: Paolo Martelletti

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Derya Uludüz
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Hayrunnisa Bolay *Editors*

Peripheral Interventional Management in Headache

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Headache

Series Editor

Paolo Martelletti
Roma, Italy

The purpose of this Series, endorsed by the European Headache Federation (EHF), is to describe in detail all aspects of headache disorders that are of importance in primary care and the hospital setting, including pathophysiology, diagnosis, management, comorbidities, and issues in particular patient groups. A key feature of the Series is its multidisciplinary approach, and it will have wide appeal to internists, rheumatologists, neurologists, pain doctors, general practitioners, primary care givers, and pediatricians. Readers will find that the Series assists not only in understanding, recognizing, and treating the primary headache disorders, but also in identifying the potentially dangerous underlying causes of secondary headache disorders and avoiding mismanagement and overuse of medications for acute headache, which are major risk factors for disease aggravation. Each volume is designed to meet the needs of both more experienced professionals and medical students, residents, and trainees.

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Peripheral Interventional Management in Headache

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Foreword

The history of the volumes of the Headache Book series endorsed by the European Headache Federation is enriched with a new volume and completes a diagnostic and therapeutic area, the interventional procedures, prerogative until today of pain physicians.

The scientific quality and the clinical approach of the volume are very important; their educational function is based on the clarity of exposition made possible by the effective competence either of the authors of the individual chapters and the publishers of the book.

The volume is enriched by video files that allow a real remote training.

This volume fills an operational gap that will place the headache experts in a full-range condition of action, rooting not only on drugs prescription but also on a clinical multimodality useful to complete the diagnostic and therapeutic paths necessary in the daily clinical activity in favor of patients with headache.

Rome, Italy — Paolo Martelletti

Preface

We aim to present the basic principles and practical guide for peripheral nerve interventions in headache disorders along with practical examples and illustrations to the clinicians. The invasive management of the headache has a substantial importance as a treatment option from the ancient times, and detailed illustrations of the peripheral targets and employed devices were even presented by Sabuncuoğlu in the fifteenth century. By receiving the torch of knowledge and wisdom from our ancestors, we committed ourselves to spread current scientific knowledge on pain management based on the principle that "alleviation of pain is the fundamental responsibility of a physician." Previous "practical interventional teaching course" experiences in the international meetings motivated us to take action. Following the necessary training and adhering to the basic rules, interventions were applicable in outpatient clinical settings as they are low cost, easy to perform, accessible, and efficient.

The book begins with a summary of the basic head and neck anatomy in relation to the headache mechanisms, the brief pharmacological properties of the drugs used in invasive methods. Peripheral nerve blocks, sphenopalatine ganglion block, botulinum toxin, dry needling, acupuncture, and ozone injections are the following chapters prepared by authors experienced in their fields.

The book is supported by a large number of recently created illustrations, facilitating the reader's understanding and providing opportunities for easier practice. Additionally, those interventions which are considered as "safe" methods in cases where systemic drugs cannot be used such as childhood, old age, and pregnancy are presented under separate headings. We believe that from a scientific standpoint, these practices will be viable options for every headache outpatient clinic, with a particularly strong potential of utility in regions with limited economic means.

With the hope and belief that the book will be a useful resource for clinicians and ultimately for the good for the patients…

Branding treatment of an acute migraine patient by Şerafettin Sabuncuoğlu in 1465.

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List of Videos

A number of videos demonstrating various techniques be found in the electronic supplementary material in the online version of the book. To access these videos, on http://springerlink.com enter the DOI number given on the bottom of the chapter opening page. Scroll down to the Supplementary Material tab and click on the respective videos link.

Video 4.1 Greater occipital nerve block (GON). Two ways to reach GON. Proximal approach is one approach injecting *approximately 1.5 cm lateral and 3 cm below the external occipital protuberence. Distal approach* is located *approximately 1/3 of the distance on a line from the external occipital protuberence to the center of the mastoid.* Performed by palpating the occipital artery approximately one-third between the occipital protuberance and mastoid process then infiltrating local anesthetic medial to the artery

Video 4.2 Ultrasound guided GON block. Palpating the occipital artery and injecting just medial to the occipital artery where GON is located

Video 5.1 Supraorbital and supratrochlear nerve block. Supratrochlear nerve is blocked by inserting needle above the eyebrow over its medial border. Supraorbital nerve runs approximately 2 cm lateral to the supratrochlear nerve

Video 5.2 Infraorbital nerve block. Aplication is done lateral from the 3rd canine teeth

Video 5.3 Sphenopalatin ganglion blockage (SPG)- Procedure A. Intranasal application using a cotton swab applicator. Patient lies in a supine position and medication given via nares with cotton applicator soaked in an anesthetic solution. The applicator is placed approximately 6 cm into each nares deep to the post middle tirbunate where SPG located for 10 minutes

Chapter 1
Introduction to Interventional Procedures; Timing and Patient Selection

Aynur Özge and Derya Uluduz

1.1 About Headache

Headache is a global problem and approximately 50% of the general population suffers from headaches. Headache diagnosis is made with an accurate examination and questioning according to the International Headache Society diagnostic criteria (ICHD-3) [1]. The median 1-year prevalence of primary headaches such as migraine and tension-type headache (TTH) in the Asia region is 9.1% and 16.2%, respectively. In Europe, the prevalence of TTH and migraine are 60% and 15%, respectively [2]. Primary headaches such as migraine, tension-type headache, and cluster headache can cause prolonged incapacitation and have a negative impact on quality of life. Headache has ranked among the top three diseases among the several hundred contributors to the global burden of disease [3].

1.2 Management

Headache management evolved beyond "taking two aspirins" with the development of the more effective migraine-specific treatments. Realistic determination of treatment goals in headache, introducing the temporal profile of treatment expectancy and sharing of this strategy with the patients, are among the important steps in the treatment. Treatment should include reduction of headache frequency, severity, and

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progression; reduction of migraine-related disability (loss of workforce or education); and correction of the deterioration in the patient's quality of life. It is also important to evaluate the comorbidities and variables that can lead to an increase in the frequency of pain. It is therefore essential to individualize the treatment, to carefully examine the comorbidities that can accompany the condition, and to evaluate the patient in detail. Multidisciplinary approach is also essential in headache treatment.

The main goals in long-term headache treatment are to reduce attack frequency and severity, reduce disability, improve quality of life, and educate the patient to manage the headaches. Various types of treatment options exist in headache management. Patients generally respond to medical treatment, lifestyle changes, and behavioral treatment methods, but the management might occasionally be challenging. Physicians have to deal with refractory patients who have failed acute or prophylactic treatments and need rescue therapies. Patients presenting to headache clinics generally suffer from chronic headaches and approximately 25–50% of these patients have medication overuse [4]. Patients with refractory headaches are probably the most intensely disabled group and their daily living activities are very much affected. Refractory headache patients may be difficult to treat and experience greater disability, creating a challenge for headache specialists. In recent years, interventional methods have come to the forefront in refractory headache patients who have not responded to medical treatments.

1.3 Interventional Techniques

Although local procedures, with the exception of botulinum toxin, have not been subject to blinded placebo-controlled trials, the use of interventional techniques in the management of refractory headaches of different types is a well-established practice among headache specialists [5, 6]. A wide variety of procedures have been described for a diversity of headache types including chronic migraine, cluster headache, cervicogenic headaches, chronic daily headaches, chronic tension-type headaches, and trigeminal and occipital neuralgia, among others. Interventional therapies can be feasible treatment options and should be considered in the refractory patients with a poor response to pharmacologic management. Patients with a late response to attack treatments, complicated migraine, refractory headache attacks in brainstem aura or hemiplegic migraine, and patients who have failed to respond to optimum medical treatment are good candidates for interventional procedures. These procedures are generally safe and effective. Relief with interventional procedures may engage secondary mechanisms and achieve long-term benefit decreasing systemic side effects from pharmacologic therapy.

Interventional treatments can also be utilized in patients that develop intolerable side effects from the pharmacological regimen, or those with significant comorbidities such as renal or hepatic failure in whose case the use of pharmacological treatment is not feasible. Headache treatment in pregnancy is also challenging because commonly used medications are frequently avoided. Interventional approaches such as peripheral nerve blocks can be performed safely during pregnancy for patients with debilitating headaches, as most patients have experienced rapid pain relief or attack frequency reduction with reassurance by its US Food and Drug Administration category B rating [7]. Interventional treatments can be also used for both short-term prophylaxis as well as the treatment of status migrainosus, where significant pain relief has been noted both immediately and after 24 h. Patients with medication overuse headache usually get worse once physicians stop their acute analgesic medications. Interventional treatments may help patients with medication overuse headache to stop analgesic overuse.

Tables 1.1, 1.2, and 1.3 referred to scientific-based suggestions of the main interventional procedures according to timing and potential side effects, respectively.

Interventional treatments should be performed in hospitals or treatment centers with sterile conditions and emergency medical care by highly specialized pain management physicians.

Table 1.1 Referred interventional procedures according to headache type

Headache type	Peripheral block	Botulinum toxin	Neuromodulation	RF	Other
Migraine	+	+	+	+	Acupuncture Ozone Trigger point inj
TTH	+	−	−	−	Trigger point Acupuncture Ozone
TAC	+	+	+	+	
MOH	+	+	+	+	Trigger point Acupuncture Ozone
Neuralgias	+	+	+	+	
Cervicogenic headache	+	−	−	+	Trigger point
Postdural puncture headache	+	−	+	+/−	Trigger point
Posttraumatic headache	+	−	+	+/−	Trigger point

RF radiofrequency thermocoagulation, *TAC* trigeminal autonomic cephalgia, *MOH* medication overuse headache

Table 1.2 WHEN to choose WHICH peripheral nerve block

Headache diagnosis	Peripheral nerve blocks
Primary headache disorders	
Migraine	GON, STN, SON, İON
Cluster headache	GON, SPG
Chronic daily headache	GON
Hemicrania continua	GON, SON
New daily persistent headache	GON
Secondary headache disorders	
Cervicogenic headache	GON, SON
Posttraumatic headache	GON
Postdural puncture headache	GON
Supraorbital neuralgia	SON
Auriculotemporal neuralgia	ATN
Trigeminal neuralgia	SPG

ATN auriculotemporal nerve, *LON* lesser occipital nerve, *SON* supraorbital nerve, *STN* supratrochlear nerve, *GON* great occipital nerve, *SPG* sphenopalatine ganglion

Table 1.3 Main side effects and considerations in peripheral interventional management

Main problem	Main side effects	What to do?
Local anesthesia allergy	Allergic reaction	Use steroids only
History of	Hypotension Hypertension	Anesthetic concentration is reduced. Limited number of nerve blockages
Pregnancy	Teratogenicity	Avoid steroids
Vasovagal attack	Vasovagal reaction	Apply in supine position
Syncope attack	Presyncope or syncope	Use bupivacaine, post-procedure rest
LAST	Local anesthetic systemic toxicity seizure, pulmonary arrest, arrhythmia—Very rare	Avoid intravascular injections
Anticoagulant therapy Anti-aggregant therapy	Hematoma	Pay attention to adjacent arteries (occipital, temporal), compression for 5–10 min
Cosmetic	Alopecia, cutaneous atrophy	Reduce steroid dose

The following figures show an algorithm of the interventional management procedures for migraine (Fig. 1.1) and neuralgias or cervicogenic headaches (Fig. 1.2).

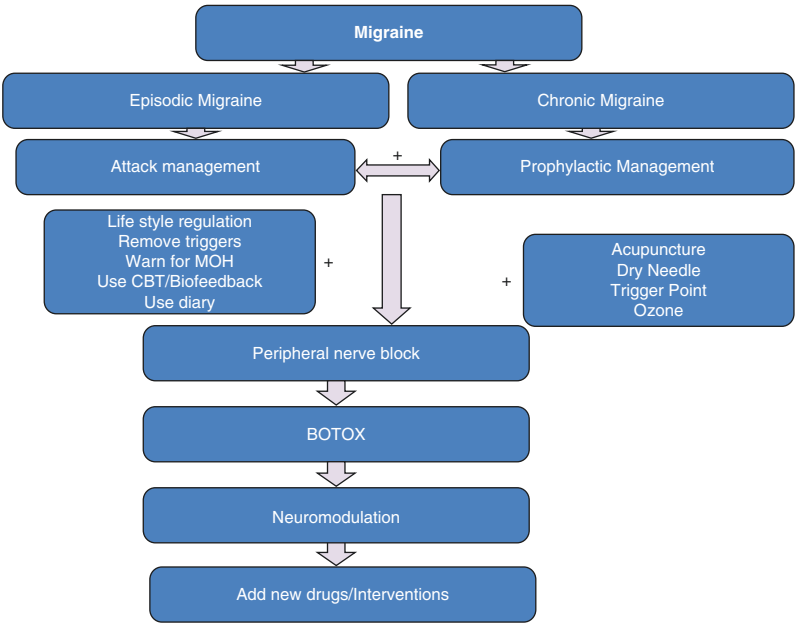

Fig. 1.1 Algorithm for interventional procedures in migraine. CBT Cognitive behavioral therapy

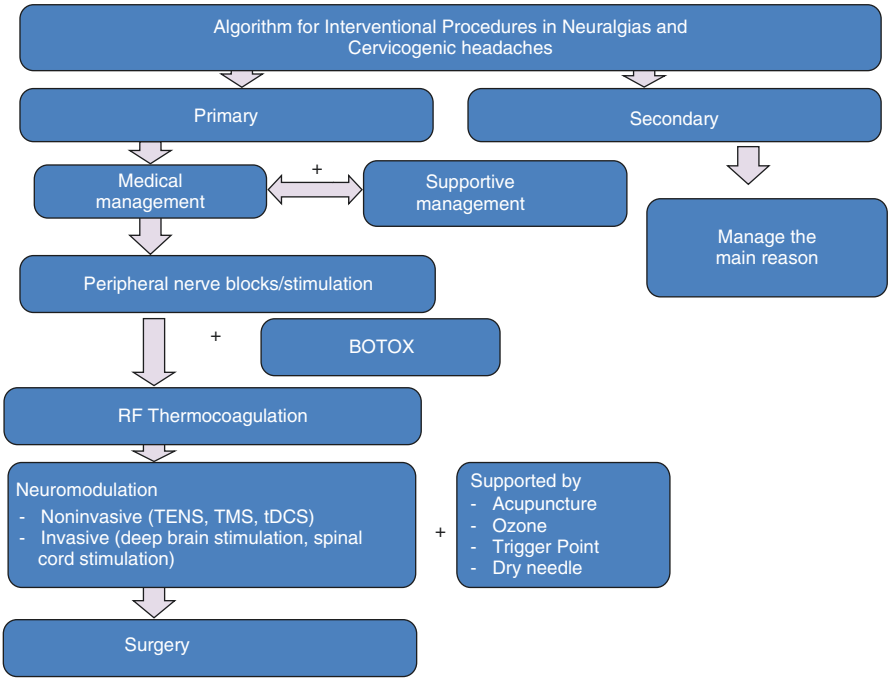

Fig. 1.2 Algorithm for interventional procedures in neuralgias and cervicogenic headaches. TENS transcutaneous electrical nerve stimulation, TMS transcutaneous magnetic stimulation, tDCS transcutaneous direct current stimulation. Note: Peripheral nerve blocks include SPG as well as other ganglion blocks

Conclusion

- Peripheral nerve blocks can be used for acute attack management, bridge therapy, or preventive treatment in various headache types including intractable headache disorders.
- The procedures are easy to apply in headache outpatient departments by trained physicians, and are low cost and effective.
- Interventional treatment of headaches deserves further attention so that expert physicians can acquire more evidence-based research and clinical practice data.
- Although definitive studies examining the usefulness of nerve blocks are limited, reports suggest that this area also deserves attention so that expert physicians can acquire more evidence-based research and clinical practice data.

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Chapter 2
Headache Anatomy and Mechanisms of Peripheral Nerve Interventions

Hayrunnisa Bolay and Omer Karadas

Introduction

Noxious signals transduced at nociceptors within the skin, scalp, tendon, fascia, muscle, mucous membranes, arteries and veins, meningeal layers, paranasal sinuses, joints, and bones are transmitted to central structures to be processed and modified and then perceived as head pain.

2.1 Transmission of Nociception from Peripheral Structures

Head and neck muscles, scalp, neck joints, temporomandibular joint, dental structures, paranasal sinuses, dura mater, cranial vessels, and venous sinuses are among the most important cranial structures for headaches [1, 2]. Nociceptive information from the anterior portion of the head, and the anterior and middle cranial fossa is transmitted to the brain through the trigeminal nerve, while information from the posterior portion of the head and neck are transmitted via the upper cervical nerves [3] (Fig. 2.1).

Nociceptive signals from peripheral structures such as the skin, scalp, muscles, cranium, joints, meninges and cranial vessels are detected and transduced by peripheral axons of the bipolar neurons, located in either the trigeminal ganglion or the upper cervical root ganglion. Pain and temperature sensation are then relayed

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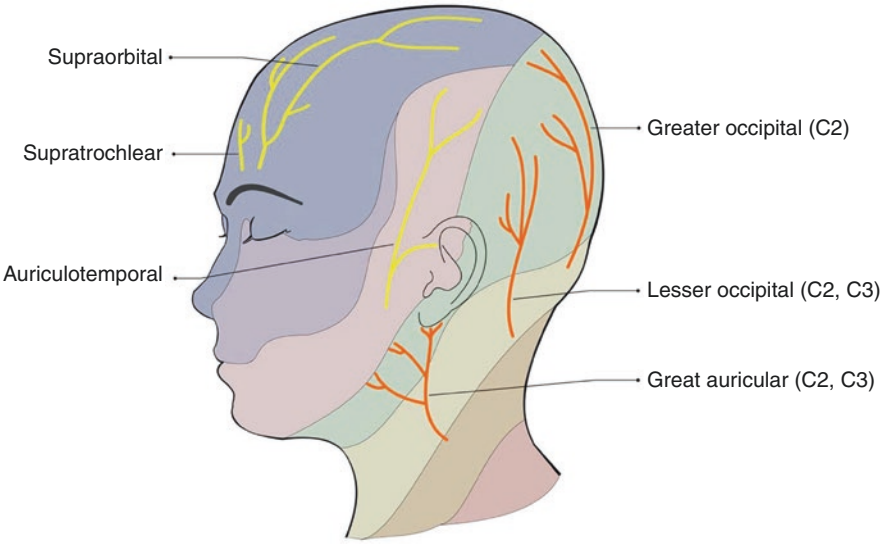

Fig. 2.1 Nociceptive information from the anterior portion of the head is transmitted to the brain through the trigeminal nerve, while information from the posterior portion of the head and neck is transmitted via the upper cervical nerves. The critical peripheral nerve targets for interventional approaches are shown

through centrally projecting fibers of bipolar neurons to the second-order neurons in the caudal brainstem or dorsal horn in the upper cervical medulla spinalis [1–4] (Fig. 2.2). The latter two structures constitute a functional unit called trigeminal spinal tractus or trigemino-cervical complex where the nociceptive information from the anterior and posterior part of the head and neck converge [1, 4]. In addition, the vagus nerve and spinal accessory nerve innervating the middle and lower portions of the trapezius muscle also join the trigeminal spinal tractus.

The trigeminal axons possess extensive branches and run through the skull in order to convey nociceptive inputs from the scalp, muscles, dura mater, or cranial vessels. Dura mater and blood vessels contain nerve fibers in the meninges while the arachnoid mater and pia mater are devoid of neural innervation, similar to brain parenchyma [4].

Activation of trigeminal nociceptors in one of the axonal branches outside the cranium could be reflected antidromically to other branches such as the periosteum or dura mater via the axonal reflex [5]. An extensive axonal branch within the intra- and extra-cerebral structures is one of the key features for referral pain. While the nociceptive information is ortodromically transmitted to the neuronal cell body in the trigeminal ganglia and further to second-order neurons in the trigeminal spinal tractus, the axonal reflex induces pain in the referral area. The convergence of trigeminal input onto the cervical dorsal horn neurons also provides another mechanism for reflecting pain outside the trigeminal receptive field.

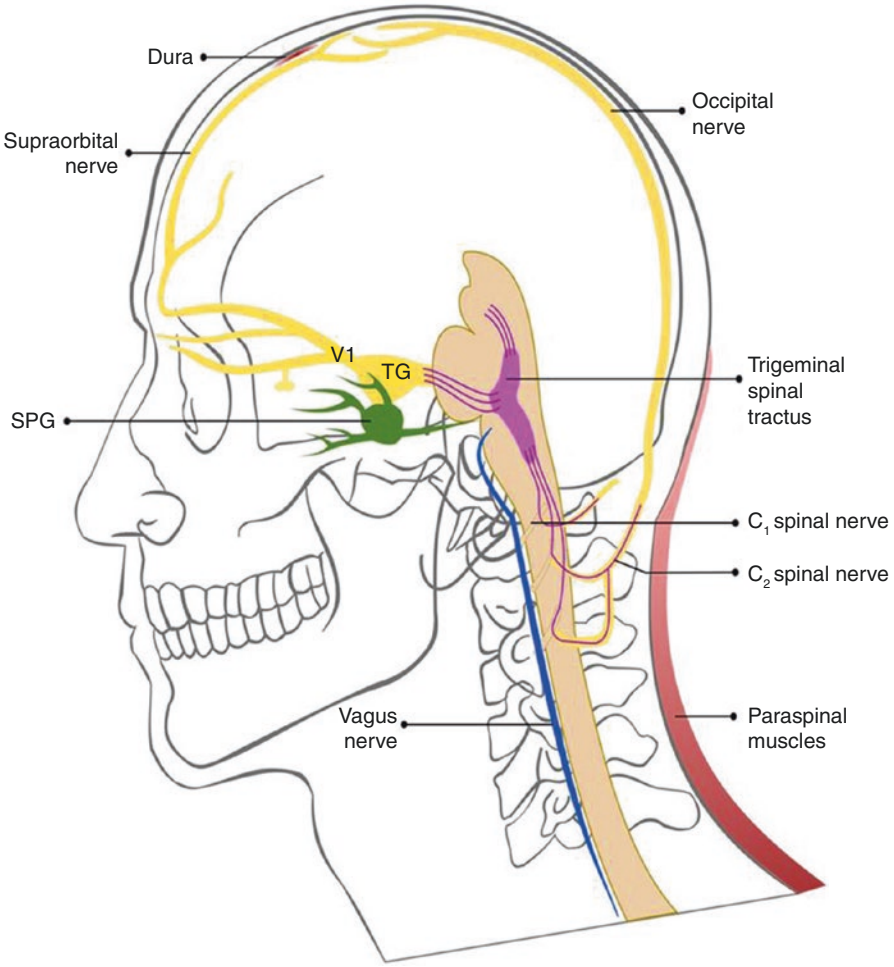

Fig. 2.2 Nociceptive signals from the skin, scalp, muscles, cranium, joints, cranial vessels, and meninges are detected by the peripheral axons of the bipolar neurons, located in either the trigeminal ganglion or the upper cervical root ganglion. Pain and temperature sensations are then relayed through centrally projecting fibers of bipolar neurons to the second-order neurons in the caudal brainstem or dorsal horn in the upper cervical medulla spinalis. The latter two structures constitute a functional unit called the trigeminal spinal tractus or trigemino-cervical complex where the nociceptive information from the anterior and posterior part of the head and neck converge. The convergence of trigeminal input onto cervical dorsal horn neurons provides another mechanism for reflecting pain outside the trigeminal receptive field

The ophthalmic, maxillary, and mandibular divisions of the trigeminal nerve all participate in the innervation of the dura mater. The ophthalmic branch (V1) innervates the majority of the anterior cranial fossa via the ethmoidal nerves, and the maxillary and mandibular divisions also have a role. The middle cranial fossa and dura mater are innervated predominantly by the nervous spinosus of the mandibular

Table 2.1 Innervation of essential pain-sensitive structures in the head and neck

Peripheral pain-sensitive structure	Sensory nerve	Receptive field	Rostro-caudal order in trigeminal spinal tractus
Lower jaw dental structures	Inferior alveolar, lingual, buccal, mental nerve, mandibular branch	V3	V3
Temporomandibular joint, masseter muscle	Auriculotemporal, masseteric, deep temporal nerves	V3	V3
Middle cranial fossa, dura mater	Nervus spinosus of the mandibular branch, middle meningeal nerve of the maxillary branch	V3, V2	V3
Middle meningeal artery and vein	Nervus spinosus of the mandibular branch, middle meningeal nerve of the maxillary branch	V3, V2	V3
Upper jaw, dental structures	Superior alveolar, palatine, infraorbital nerve, maxillary branch	V2	V2
Paranasal sinuses	Infraorbital nerve	V2	V2
Sphenopalatine ganglion	Pterygopalatine nerve, maxillary branch	V2	V2
Frontal sinuses	Supraorbital nerve	V1	V1
Periorbital area	Supraorbital nerve	V1	V1
Frontal muscle	Supraorbital nerve	V1	V1
Corrugator muscle	Supratrochlear nerve	V1	V1
Anterior fossa, dura mater	Ethmoidal nerves, ophthalmic branch, middle meningeal nerve of the maxillary branch	V1 > V2	V1
Tentorium	Nervus tentorii	V1	V1
Posterior fossa, infratentorial dura mater	C1, C2, meningeal branches of the vagus and hypoglossus nerve	C1, C2	C1
Posterior skin of the head, occipital muscles	GON	C2	C2
	LON	C2, C3	C2
	Great auricular nerve	C3	C3
Paraspinal and deep cervical muscles	Third occipital nerve	C3	C3

(V3) nerve [4–7]. The medial meningeal nerve of the maxillary branch also contributes to the innervation of the middle cranial fossa. The posterior fossa dura is innervated by the C1 and C2 cervical nerves and meningeal branches of the vagus and hypoglossal nerves [4–7] (Table 2.1).

2.2 Convergence of Peripheral Inputs on Second-Order Neurons

The spinal trigeminal nucleus extends from the neck to the pontine level and is also named the spinal trigeminal tractus. Upper cervical nerve root and accessory nerve root convergence in the trigeminal tractus provides the main scientific basis for

referred pain in the head, neck, and shoulder. There is a somototopic organization in the trigeminal spinal tractus where V1 is placed caudally and adjacent to C1, while V3 has the most rostral representation. Similar inverted somatotopy is found in the primary sensorimotor cortex.

The nociceptive information from the trigeminal receptive field and particularly from V1 significantly synapses with dorsal horn neurons of the C1 and C2 cervical nerves. Peripheral nociceptive inputs from the receptive fields of the three trigeminal nerve branches and the upper cervical nerves converge at the second-order neuronal level (Fig. 2.1). In addition, pain sensation from the upper cervical nerve receptive field converges on the trigeminal second-order neurons. The interference of noxious impulses transmitted either by the trigeminal nerve or upper cervical nerves is one of the key mechanisms to understand the occurrence of referred pain, muscle tenderness, and greater occipital nerve (GON) sensitivity in headache. The intensive convergence of afferent information from the trigeminal and upper cervical nerves leads to the formation of a functional complex for processing sensory information from the craniofacial structures.

The nociceptive neuron in the first cervical horn receives abundant afferents from craniofacial structures such as the forehead, cornea, dura mater, posterior part of the head, masseter muscle, and the temporomandibular joint [8]. Convergence of the cutaneous, musculoskeletal, and visceral inputs on C1 constitutes the central basis of peripheral nerve intervention in headache management.

A detailed examination of the nociceptive neurons at the C2 dorsal horn that receives convergent synaptic input from both the dura mater and greater occipital nerve (GON) has shown that the stimulation of nociceptive afferents in the dura mater induces immediate sensitization in the C2 nerve. In turn, GON stimulation dependent electrical activity in the C2 dorsal horn neurons was significantly increased upon simultaneous dural stimulation. The latter neurons also responded to mechanosensitive input from the deep suboccipitalparaspinal muscles (Fig. 2.3) [9].

Stimulation of GON yielded short-lasting pain lancinating to the ipsilateral ophthalmic branch of the trigeminal nerve and is associated with ipsilateral autonomic symptoms in humans. The upper cervical nociceptive projections converge on the trigeminal nociceptive tractus in humans [10].

2.3 Projections to the Thalamus

Second-order neurons in the trigeminal spinal tractus project to contralateral ventral posteromedial nucleus (VPM) of the thalamus via the trigeminal lemniscus or the ventral trigeminothalamic tractus. From the VPM of the thalamus, third-order neurons spread to the face area of the primary and secondary somatosensory cortex on the inferior portion of the postcentralgyrus.

From the thalamus, the discriminative feature of pain sensation is transmitted to the primary and secondary somatosensory cortex via the lateral pain pathway. Alterations in the pain intensity lead to changes mainly in the SI cortex while the

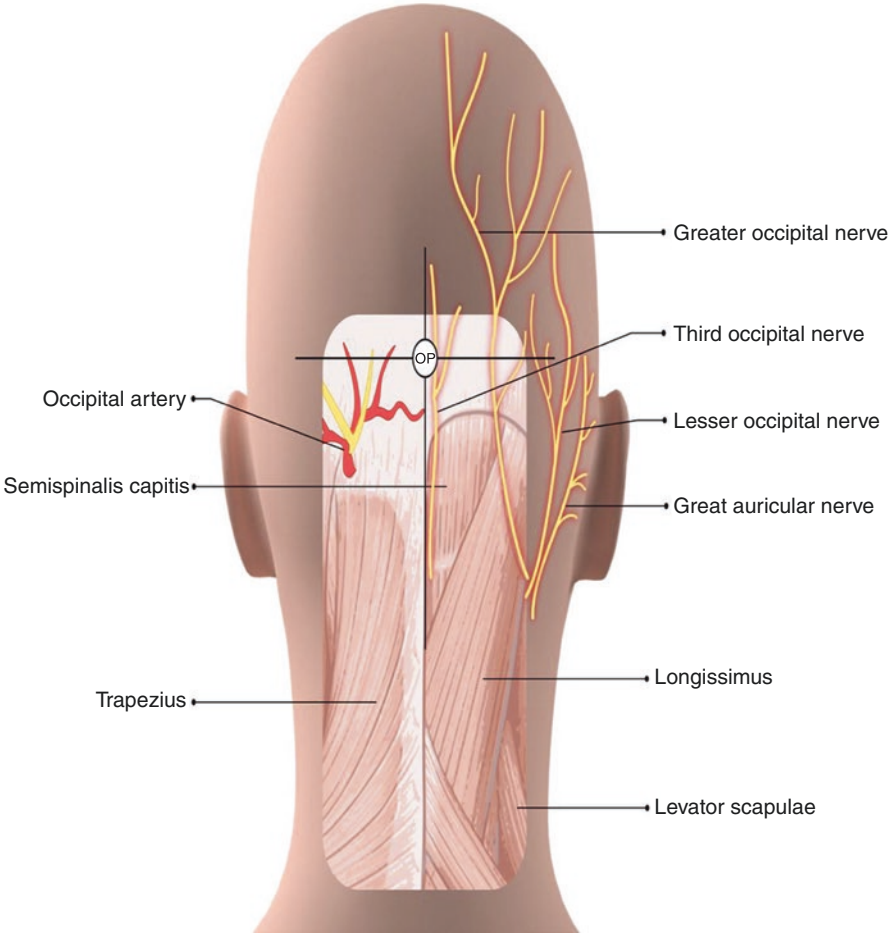

Fig. 2.3 The illustration of major peripheral nerves innervating the posterior part of the head and neck and their localizations in respect to the occipital artery and occipital and neck muscles

subjective scoring of unpleasant features of pain is associated with changes in the anterior cingulate cortex (ACC). Nociceptive stimulation of the ophthalmic branch of the trigeminal nerve, which transmits nociceptive information related with headache, also activates similar cerebral cortical regions such as the somatosensory cortex, the insula and the anterior cingulate cortex [1].

The medial pain pathway is involved in affective–emotional aspects of nociception and projects to the anterior cingulate cortex (ACC) through the parabrachial nucleus and amygdala. The insula and amygdala, as components of the medial nociceptive pathway, have been implicated in evaluative and affective processes. The anatomical connections between the trigeminal spinal tractus, parabrachial nucleus, amygdala, and ACC are implicated in emotional and autonomic functions during trigeminal nociception. The prefrontal cortex and orbitofrontal cortex are also

involved in the evaluation of affective experiences, contributing to the emotional aspects and cognitive processes of pain perception [1].

2.4 Projections to the Brainstem and Hypothalamus

The spinal trigeminal tractus extensively projects to other subcortical brainstem areas such as the superior salivatory nucleus (for parasympathetic outflow to cranial structures), lateral periaquaductal graymatter (PAG), parabrachial nuclei, the hypothalamus, cerebellum, and rostral ventrolateral medullary reticular formation (to participate in viscero-sympathetic reflexes).

The parabrachial nucleus is an important projection site for trigeminal nociceptive information. Many of the neurons in the lateral parabrachial area project to both the ventromedial hypothalamus and the central nuclei of the amygdala. Trigeminal afferent fibers from V1/cornea preferentially synapse with neurons projecting to the parabrachial nucleus in the trigeminal spinal nucleus. PBN has reciprocal connections with the forebrain areas and insular cortex and receives input from the amygdala. The amygdala is a critical relay station in the trigemino-parabrachialamygdaloid nociceptive transmission. The amygdala projects to the insular cortex and mediodorsal thalamic nucleus. The trigeminal projections to the parabrachial nucleus are related with autonomic-emotional responses to pain [1].

A substantial fraction of trigeminal spinal tractus neurons directly project to the hypothalamus such as the paraventricular nucleus, lateral hypothalamic area, and the A11 nucleus. Hypothalamic projections are mainly involved in the processing of meningeal and cutaneous inputs from the ophthalmic branch of the trigeminal nerve. The transmission and perception of trigeminal pain are subject to modulation by the hypothalamus, and descending axons from those hypothalamic areas to the trigeminal spinal tractus exist.

2.5 Sphenopalatine Ganglion

Trigeminal spinal tractus neurons project to the ipsilateral superior salivatory nucleus in the brainstem and provide the afferent arm of the trigemino-parasympathetic reflex. The efferent parasympathetic fibers originate from the superior salivatory nucleus and travel with the facial nerve and synapse at the sphenopalatine ganglion (SPG). Through the sphenopalatine ganglion (SPG) the parasympathetic efferents project to various cranial structures including the intra-cerebral and extra-cerebral arteries, lacrimal glands, conjunctiva, and nasal mucosa. The sphenopalatine/pterygopalatine ganglion (SPG), located in the pterygopalatine fossa, is mainly an extracranial parasympathetic ganglion, though sympathetic fibers and sensory fibers from the maxillary branch also cross the ganglion. Trigeminal nerve activation, even through spreading depolarization waves in the cerebral cortex, could initiate

the trigemino-parasympathetic reflex and increase meningeal blood flow [11]. Pharmacological blockade of SPG is employed for effective treatment of cluster or migraine attacks, probably via the trigeminal nociceptive system. However, long-term benefit of SPG stimulation may arise from hypothalamic modulation since the superior salivatory nucleus receives afferents from the hypothalamus [1].

2.6 The Vagus Nerve and Parasympathetic Efferents

The vagus nerve has regulatory roles in heart rate, breathing, and digestion as it is the major parasympathetic branch of the autonomic nervous system. It has afferent projections to nucleus tractus solitarius in the brainstem, which acts in the regulation of physiology, chemistry, plasticity, and behavior of the brain. It also has a role in central and peripheral anti-inflammatory pathways mediated by acetylcholine and/or norepinephrine [12].

Vagus nerve stimulation affects the locus coeruleus, dorsal raphe nucleus, PAG, ventral posteromedial nucleus, and cingulate cortex, and this reflects the role of norepinephrine, serotonin, and central sensitization that are responsible in the pathophysiology of headache disorders [12].

Vagus nerve stimulation results in inhibitory modulation of headache transmission by influencing the activity in the trigeminal spinal nucleus and its projections to the thalamus and the cortex. Cortical spreading depression waves can be inhibited by vagal nerve stimulation.

Recent studies imply that the sympathetic and parasympathetic tone of the body is lateralized to one hemisphere where the insular cortex, amygdala, and lateral hypothalamus participate. The left hemisphere, and particularly the insula, is proposed to mediate parasympathetic function while the right hemisphere affects sympathetic function [13]. It is plausible to suggest that unilateral headache and aura symptoms may induce autonomic asymmetry in migraine.

2.7 Antinociceptive Projections

The transmission of nociceptive information to the second-order trigeminal neuron is controlled by the inhibitory pathway descending from the PAG, and the rostral ventromedial medulla (RVM). The PAG is located in the mesencephalon and plays a central role in nociception by exerting an inhibitory action on pain transmission. The PAG receives projections from the pain matrix such as the anterior cingulate cortex, the insular cortex primary somatosensory cortex, and the prefrontal cortex. In addition to cerebral cortical structures, the hypothalamus, amygdala, and parabrachial nucleus also contribute to the descending modulation of nociceptive activity. Stimulation of the PAG or the RVM suppresses nociceptive responses [1, 14].

Supraspinal opioid receptors play a key role in descending inhibitory controls relaying through the PAG and the RVM. Projections from serotoninergic RVM cells play a role in antinociceptive influence upon stimulation of the RVM or the PAG. Noradrenergic neuronal cell groups in the locus coeruleus (or A6), A5, and A7 also exert an antinociceptive influence through spinal α2-adrenoceptors. The hypothalamic paraventricular nucleus and central amygdala send projections to the locus coeruleus.

The hypothalamic paraventricular nucleus sends axons to the trigeminal spinal tractus and the superior salivatory nucleus, which gives rise to parasympathetic outflow to cephalic vasculature. The hypothalamic paraventricular nucleus and/or arcuate nucleus are involved in stress-induced analgesia. Analgesia induced by opioids or placebo is mediated by the functional connectivity between the PAG and the rostral part of the anterior cingulate cortex that has abundant opiate receptors [15, 16].

Direct projections from the amygdala to the PAG –the RVM system provides input for emotional modulation of pain. In accordance, opioid injection into the amygdala exerts an antinociceptive effect. The parabrachial nucleus sends descending projections to the trigeminocervical complex.

Descending projections from the cerebral cortex to the trigeminal spinal tractus modulate headache. Cortical projections originating from the primary somatosensory cortex inhibit trigeminal nociception [1, 14].

The insular cortex is the key player in the pain matrix with interoceptive and homeostatic functions. Lesions of the insula are associated with increased tolerance of pain. The insular cortex sends direct projections to the trigeminal spinal tractus. Trigeminal-mediated nociception could also be indirectly modulated by the insula through PAG, PBN, and RVM.

The dorsolateral prefrontal cortex (DLPFC) and orbitofrontal cortex (OFC) are operational in pain modulation by attention and expectation. The affective component of nociception is inversely correlated with the activation of DLPFC and ACC–PAG and high-frequency repetitive transcranial magnetic stimulation (TMS) application over DLPFC is associated with amelioration of pain in chronic migraine patients [1].

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Chapter 3
Pharmacology of Interventional Headache Management

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Interventional procedures such as peripheral nerve blocks, trigger point injections, and sphenopalatine ganglion blocks are used in the treatment of headache disorders and provide rapid pain relief. Local anesthetics, corticosteroids, and botulinum toxin are the drugs widely used in the interventional management of headache disorders.

3.1 Local Anesthetics

Local anesthetics (LAs) are used to preferentially block sensory nerves for the interventional treatment of headache. Local anesthetics are also used in trigger point injections and sphenopalatine ganglion block.

3.1.1 Mechanism of Action

During the resting state of the neuronal membrane, voltage-gated sodium channels (Navs) are impermeable to Na+. Invading action potentials depolarize the membrane and start Na+ influx through the opened Navs. After a while, they become impermeable to Na+ even if the depolarization continues. LAs are found in two forms within the solutions: Ionized and nonionized. Only the nonionized fraction (lipophilic fraction) of LAs can cross the myelin sheath and the nerve membrane,

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and *lipophilicity* therefore correlates well with potency. Once within the neuron, the ionized fraction binds to the inactivation gate located in the inner pore of the channels. LAs preferentially bind to channels when they are in the inactivated state and prolong the duration of inactivation, which consequently prevents the firing of neurons and propagation of the action potentials [1].

LAs sequentially block sensory information and this is known as a differential block. Nerve fibers display different susceptibility to LA actions. LAs preferentially block smaller diameter nerve fibers before the others. But if the axon is myelinated, it is likely to be blocked first even if the diameters are similar as in type B fibers being blocked before type C fibers. The firing frequency and duration of action potentials also increase the nerve fibers' susceptibility to local anesthetic actions. As a result, LAs sequentially block sympathetic conduction, temperature, pain, and touch, finally ending in a somatic motor block. Peripheral nerve blocks result in prolonged analgesia that endures beyond their anesthetic effect, and central pain modulation is suggested as the mechanism underlying this prolonged effect. The allodynia that is seen in the dermatomes beyond the distribution of the injected nerve may be reduced after a sensory nerve block. It seems that the effect of a peripheral nerve block is much more than just local anesthesia. In trigger point injections, the local anesthetics disrupt the trigger points by their chemical effects and cause the relaxation and extension of the muscle fibers.

3.1.2 Recommended Doses

The most widely used local anesthetics for peripheral nerve block in headache management are bupivacaine and lidocaine but prilocaine is also reported in the literature. A wide range of doses for local anesthetics is reported for peripheral nerve blocks for headache management. The reported doses per peripheral nerve block are 3–5 ml 1% lidocaine, 0.5–5 ml 2% lidocaine, 3 ml 0.25% bupivacaine, 4–6 ml 0.375% bupivacaine, 0.5–4.5 ml 0.5% bupivacaine, and 5 ml 1% prilocaine. Various local anesthetics and doses have been reported for trigger point injections for the interventional management of headache disorders. The most common local anesthetics used for trigger point injections in headache disorders are lidocaine (0.5–2%) and bupivacaine (0.25–5%), but mepivacaine (3%) and ropivacaine (10 mg) are also mentioned in the literature. Robbins et al. have recommended 1% lidocaine or 0.5% of bupivacaine (2–4 ml per each trigger point) for trigger point injections in headache disorders [2]. The reported dose ranges used for intranasal sphenopalatine ganglion block in cluster headache and chronic migraine are 2–10% lidocaine, 0.25–1% bupivacaine, 2% mepivacaine, 0.2% ropivacaine, and 5–10% cocaine. In our practice, we use 0.25% bupivacaine for peripheral nerve blocks (2–3 ml for greater occipital nerve and lesser occipital nerve blocks; 1–2 ml for supraorbital and supratrochlear nerve blocks). We use a cotton-tipped applicator soaked in 10% lidocaine or 0.5% bupivacaine for intranasal sphenopalatine ganglion block and 0.5% lidocaine or a mixture of 0.5% lidocaine and 0.167% bupivacaine for trigger point injections. Lidocaine and bupivacaine *can be diluted* with sterile saline. The

recommended dose limits for local anesthetics per treatment are 300 mg for lidocaine and 175 mg for bupivacaine. Dose limits for local anesthetics based on body weight are 4.5 mg/kg for lidocaine and 2 mg/kg for bupivacaine [3, 4] and these maximum doses equal 16 ml of 2% lidocaine and 28 ml of 0.5% bupivacaine for a 70 kg adult patient.

3.1.3 Side Effects

LA systemic toxicity is always a potential risk and can even end up with fatality. Systemic toxicity primarily involves the cardiovascular system and central nervous system, may occur with all LAs, and is independent of the route of administration (Table 3.1). Allergic reactions to LAs are rare events and mostly in the form of allergic dermatitis or asthmatic attack. One must be extra careful to distinguish allergic reactions from the adverse effects and the effects of coadministered vasoconstrictors. The esters of PABA are more likely to cause allergies than amide-type local anesthetics. Finally, even though prilocaine has the lowest risk of systemic toxicity among the amide LAs, it may cause methemoglobinemia because of accumulation of its metabolite, o-toluidine (Table 3.2).

Table 3.1 Local anesthetics commonly used in headache disorders

Generic name	Potency (Procaine = 1)	Onset (min)	Duration of analgesia (hours)	Maximum dose (mg/kg)[a]	Maximum dose with adrenaline (mg/kg)[a]
Lidocaine 2%	4	10–20	3–8	4.5	7
Mepivacaine 1.5%	2	10–20	3–10	5	7
Ropivacaine 0.2%	16	15–30	5–16	3	3.5
Ropivacaine 0.5%	16	15–30	5–24	3	3.5
Bupivacaine 0.5%	16	15–30	6–30	2	3

[a]These recommendations do not completely rule out systemic toxicity since it may occur with any dose

Table 3.2 Systemic adverse effects of local anesthetics

CVS adverse effects	CNS adverse effects
Tachycardia and hypertension (initial sympathetic activation) Hypotension Cardiac arrhythmias Cardiovascular arrest	Circumoral and tongue numbness Metallic taste Sedation Dizziness Visual and auditory disturbances Restlessness Nystagmus Muscular twitching Tonic–clonic convulsions Coma Respiratory depression

CVS cardiovascular system, *CNS* central nervous system

3.2 Corticosteroids

Peripheral nerve blocks consist of local anesthetic injection with or without steroids around peripheral nerve branches. The duration of analgesia obtained with a single injection nerve block is increased by adding steroids to local anesthetics.

3.2.1 Mechanism of Action

Corticosteroids show their effects in interventional headache management via their anti-inflammatory and weak membrane stabilizer properties and by inhibiting unmyelinated C-fiber transmission. They are commonly used in the management of headache and other pain mainly because of their anti-inflammatory properties. The inhibition of cytokine and chemokine synthesis is particularly significant among the anti-inflammatory properties of glucocorticoids. Steroids provide prolonged pain relief by inhibiting the secretion of pro-inflammatory cytokines and the formation of prostaglandins.

Glucocorticoid receptor (GR) is an intracellular receptor that acts as a ligand-inducible transcription factor. Glucocorticoids exert their functions by binding to their glucocorticoid receptors, which then bind to glucocorticoid response elements in DNA to repress transcription. However, some of the genes that are deactivated by glucocorticoids have negative glucocorticoid response elements in their promoter sequences. A negative glucocorticoid response element blocks the binding of the transcription complex to DNA and results in blockade of mRNA production. The inhibitory effect of glucocorticoids is due to protein–protein interactions between activated GR and nuclear transcription factors such as activator protein-1 (AP1) and nuclear factor kappa B (NF-κB).

Glucocorticoids act on various targets via various pathways to exert their anti-inflammatory effects. They inhibit the production of prostaglandins by three different mechanisms. Three mechanisms of the glucocorticoid-induced inhibition of prostaglandin production are the induction and activation of annexin I, the induction of MAPK phosphatase 1, and the suppression of transcription of cyclooxygenase 2 [5]. Moreover, glucocorticoids decrease the stability of mRNA for genes for inflammatory proteins such as vascular endothelial growth factor and cyclooxygenase 2. Glucocorticoids suppress the expression of genes that code for some receptors of inflammatory mediators such as tachykinin receptors (NK1 and NK2 receptors) and bradykinin receptors (B1 and B2 receptors) and also repress the transcription of the genes for inducible nitric oxide synthase.

Glucocorticoids also exert their anti-inflammatory actions through induction of anti-inflammatory gene transcription. They upregulate anti-inflammatory proteins such as lipocortin 1, serum leukoprotease inhibitor (SLPI), interleukin 10, and the interleukin 1 receptor antagonist. The GR also increases transcription by binding to coactivator factors such as CREB binding protein (CBP), which in return induces activation of RNA polymerase II, and results in the formation of messenger RNA.

Steroids were also shown to inhibit the transmission of pain and attenuate heat and mechanical sensitivity. Locally applied corticosteroids mainly target thin unmyelinated C fibers that carry nociceptive information and block their transmission. When a depot corticosteroid is locally applied, this inhibitory effect is observed within 30–60 min and remains constant until the drug is removed [6]. The nerve recovers completely within 60 min after the removal of the corticosteroid. Direct membrane action rather than anti-inflammatory properties is the mechanism underlying this inhibition of transmission in unmyelinated C fibers. Steroids also have direct effects on the electrical properties of nerve cells. It has been shown previously that local application of corticosteroids suppresses ectopic neural discharges and produces nerve conduction changes in experimental neuromas when there is no evident inflammation and degenerative or regenerative changes. Steroids can cause membrane hyperpolarization via the γ-amino butyric acid (GABA) A receptor anion channel and can result in decreased neuronal excitation, local anesthesia, and membrane stabilization.

3.2.2 Recommended Doses

Methylprednisolone, triamcinolone, dexamethasone, and betamethasone are used in peripheral nerve blocks (Table 3.3). The reported dosages used in peripheral nerve blocks for headache management are 40–80 mg for methylprednisolone, 20–40 mg for triamcinolone, 4 mg for dexamethasone, and 2–12 mg for betamethasone. None of the studies in the literature clearly provides a dosage with optimum benefit. The only study where a comparison between doses was made was a case study using methylprednisolone [7]. Methylprednisolone 40 mg was reported to provide no relief whereas pain relief was noted with doses of 50–60 mg. However, the patient reported an increase in the headache with a higher dose (80 mg). For headache

Table 3.3 Comparison of commonly used corticosteroids, duration of action, plasma half-lives, elative potencies, and equivalent doses

Corticosteroid	Activity	Plasma half-life (min)	Glucocorticoid activity (relative potency[a])	Mineralocorticoid activity (relative potency[a])	Equivalent dose (mg)
Hydrocortisone	Short-acting	90	1	1	20
Methylprednisolone	Intermediate-acting	180	5	0.5	4
Triamcinolone	Intermediate-acting	300	5	0	4
Dexamethasone	Long-acting	100–300	30	0	0.75
Betamethasone	Long-acting	100–300	25	0	0.75

[a]Relative to hydrocortisone

disorders, it is not recommended to use corticosteroids in trigger point injections based on the available literature since a clear biological rationale is lacking.

3.2.3 Side Effects

The well-known side effects of local steroid injections are the occurrence of alopecia and atrophy in the skin and subcutaneous tissue at the injection site.

3.3 Botulinum Toxin

Botulinum toxin (BoNT) is used in the interventional management of chronic migraine. BoNT can also be used in trigger point injections.

3.3.1 Mechanism of Action

BoNTs are highly lethal toxins, produced by several bacteria of the Clostridium genus. They have seven isoforms, designated as types A–G. BoNT proteins are composed of a heavy chain (H-chain) and a light chain (L-chain). The L-chain is zinc-dependent endopeptidase (matrix metalloproteinase) and responsible for both the neurotoxic action and its specificity. The L-chain works only when it is in the cytoplasm and halts neurotransmitter release. Both L and H-chains cannot passively penetrate into the presynaptic site. The H-chain overcomes this barrier by promoting endocytosis of BoNTs. The C-terminus of the H-chain is required for binding to the presynaptic membrane and consequently for BoNT endocytosis. The N-terminus of the H-chain is responsible for translocation of the L-chain.

The underlying mechanism of BoNT neurotoxicity is its ability to block neurotransmission at the neuromuscular junction (NMJ) or neuroeffector junctions by preventing acetylcholine release. This is achieved in four steps [8]: (1) attachment of BoNTs to the nerve terminals; (2) internalization of BoNTs via endocytosis; (3) translocation of BoNTs into the cytosol from the vesicles; (4) cleavage of some release machinery proteins by the L-chain. BoNTs exclusively bind to terminals of the peripheral nerves, and chiefly to the cholinergic nerves of skeletal muscles and parasympathetic system. BoNTs attach to the neuron by binding to polysialogangliosides and either to the luminal domain of synaptotagmin (stg) or synaptic vesicle transmembrane protein (SV2) depending on the serotype. This dual binding significantly improves the specificity of BoNTs to the presynaptic site since these vesicle proteins (stg and SV2) are only exposed to the extracellular environment in active nerve terminals. The entry of BoNTs to the terminal is highly related to the synaptic turnover rate, and activity increases

their entry. When the endocytosis is completed, the vacuolar proton pump acidifies the inside of the newly formed vesicles. Acidification triggers conformational alterations of both chains, and the H-chain then invades the vesicular membrane, forming a channel on it in the final stage. The translocation process is accomplished by the passage of the L-chain through this channel into the cytoplasm.

Neurotransmission in the NMJ and neuroeffector junctions is accomplished by the fusion of vesicles to the active zone membrane. The fusion of two lipid bilayers is an energetically uphill reaction. This energy barrier is overwhelmed by the specialized proteins known as SNARE (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptors) proteins that are located on the vesicles and cell membrane and in the cytoplasm. The vesicular SNARE protein, synaptobrevin (VAMP) and the membrane SNARE proteins, SNAP-25 and syntaxin-1, normally form a complex so that the vesicles dock to the membrane. After their priming, this metastable complex is stabilized by complexins and the vesicles become ready to be released via exocytosis. The invasion of the nerve terminal by the action potential/s results in intracellular calcium increase in the close vicinity of the presynaptic release sites. The calcium signal is detected by synaptotagmin-1, which triggers vesicle exocytosis by removing the complexin protein from the core-complex and permitting fusion with the strong pull of membranes to each other by means of the SNARE complex.

BoNTs specifically cleave one of the SNARE proteins and render this protein useless. BoNTA/E and BoNTB/D/F/G are specific for SNAP-25, synaptobrevin and syntaxin, respectively. BoNTC can cleave both SNAP25 and syntaxin.

A widely accepted pathophysiological model for BoNT use in chronic migraine is not available. A suggested mechanism for the efficacy of BoNT in chronic pain is the inhibition of peripheral sensitization and indirect reduction in the central sensitization [9]. BoNT inhibits the release of neuropeptides associated with pain such as substance P [10] or calcitonin gene-related peptide (GCRP) at the nociceptive nerve endings [11]. BoNT also blocks the release of glutamate and prevents the expression of Fos, a product of the immediate early gene, c-fos. Animal studies suggest that there is a site for BoNT in the central nervous system [12]. The mechanism of the central antinociceptive action of BoNT is still obscure.

3.3.2 BoNT Preparations

Currently, all commercial formulations contain only BoNTA or BoNTB, as they have a longer duration of action and higher specificity and potency. Various formulations are available worldwide: onabotulinum toxin A contains preservative-free, lyophilized BoNTA powder (50 or 100 units), human albumin, and sodium chloride. Abobotulinum toxin A contains lyophilized BoNTA (300 or 500 units/vial), serum albumin, and lactose. Incobotulinum toxin A contains lyophilized BoNTA (50 or 100 units/vial), human albumin, and sucrose. Rimabotulinum toxin B is supplied in

liquid form (BoNTB, 5000 units/ml), human serum albumin, sodium succinate, and sodium chloride. The two other approved BoNT formulations are Chinese botulinum toxin A (CBTX-A) and Neuronox (BoNTA, a formulation in Korea and Southeast Asia). New formulations are also under development such as topical BoNTA (gel form), extended duration BoNTA (Daxibotulinum toxin A), and Botulinum toxin E formulation with faster onset and shorter duration.

The various BoNT formulations are not biosimilar or bioequivalent, and each has a different composition, quantity of active molecules, components, dosage, and potency. Hence, there is no confident way of making dose conversions among the BoNTA formulations, yet. According to some systematic reviews and clinical trials, it is suggested that the dose ratio is approximately 2.5–3:1 for abobotulinum toxin A:onabotulinum toxin A and around 1:1 for incobotulinum toxin A:onabotulinum toxin A. However, more studies are necessary to determine the accurate dose conversion ratios.

3.3.3 Efficacy

In medical practice, pharmacological denervation of BoNT appears in 1–3 days, and peaks at around 1–4 weeks, and gradually weakens after 3–4 months. However, the duration of action and the degree of blockade significantly vary depending on the formulation, dose, site of injection, and the number of previous injections.

3.3.4 Immunogenicity

BoNTs are in complexes with nontoxic accessory proteins, which can act as adjuvants and lead to neutralizing antibody formation and reduced treatment efficacy. However, the incidence appears to be rare [13].

3.3.5 Side Effects

In general, BoNT injection is a safe procedure with few side effects, which are usually mild and transient. The most common side effects are swelling or bruising at the injection site, mild headache, or flu-like symptoms. The spread and diffusion of the BoNTs to nontargeted areas may cause a spectrum of conditions from mild symptoms like double vision, ptosis, and limb weakness to rare but life-threatening conditions such as dysphagia, respiratory muscle weakness, and breathing difficulties. As lower doses are less likely to cause side effects, gradual increment based on the patient's response is advisable.

3.3.6 Contraindications

Absolute contraindications for BoNT injection are as follows: (1) infection at the site of injection; (2) known hypersensitivity to BoNT formulations or its components; and (3) abobotulinum toxin A should not be used in patients who are allergic to cow's milk protein.

Relative contraindications are neuromuscular disorders such as myasthenia gravis, myopathies, Eaton–Lambert syndrome or amyotrophic lateral sclerosis. Since simultaneous use of two agents with NMJ blocking capabilities may potentiate BoNT effects, BoNTs should be used with caution in patients taking drugs such as aminoglycosides and non-depolarizing neuromuscular blockers, succinylcholine, quinidine, and magnesium sulfate.

Because of the maternal–infant transmission risk, BoNTs (pregnancy category C) should be avoided during pregnancy and lactation.

3.3.7 Recommended Doses

It is essential to follow the PREEMPT [14] onabotulinum toxin A injection protocols of fixed-site/fixed-dose or follow-the-pain for maximum efficacy in chronic migraine. In the PREEMPT fixed-site/fixed-dose injection paradigm, a total of 155 U of onabotulinum toxin A is injected to 31 points across seven specific head and neck muscles (4 × 5 U to the frontalis muscle, 1 × 5 U to the procerus, 2 × 5 U to the corrugator, 4 × 5 U to the temporalis muscle on each side, 3 × 5 U to the occipitalis muscle on each side, 4 × 5 U to the cervical paraspinal muscles, and 3 × 5 U to the trapezius muscle on each side). In the follow-the-pain paradigm, an additional 40 U is injected to eight more points, two in the temporalis muscle, two in the occipitalis muscle, and four in the trapezius muscle. The patients should be carefully evaluated before treatment to minimize side effects. A wide range of doses for BoNT is reported for trigger point injections. In the literature, the onabotulinum toxin A dosage per each trigger point ranged from 5 to 50 U, whereas the dosage of abobotulinum toxin A varied from 25 to 400 U. Only one study compared three doses (10 U, 25 U, and 50 U per each trigger point) of onabotulinum toxin A and it was shown that the effect of onabotulinum toxin A was not dose-dependent [15].

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Chapter 4
Greater Occipital Nerve and Lesser Occipital Nerve Blocks

Ugur Uygunoglu and Aksel Siva

Introduction

The greater occipital nerve (GON) is the medial branch of the second cervical dorsal ramus, but it may also receive some fibers from the third cervical nerve. It courses between the inferior capitis oblique and semispinalis capitis muscles, entering the scalp between the semispinalis capitis and trapezius muscles. The GON provides sensation to the medial portion of the posterior scalp, with radiation ventrally up to the vertex. The occipital artery usually lies just lateral to the GON, and is the most useful landmark for locating the nerve (Fig. 4.1) [1, 2].

The GON is the most common nerve targeted for blockage, either alone or in combination with other peripheral nerves such as the lesser occipital nerve (LON) and branches of the trigeminal nerve (supraorbital, supratrochlear, and auriculotemporal nerves). The landmark of the GON is defined as the medial third of a hypothetical line drawn between the mastoid process and the occipital protuberance. In clinical practice, physicians may estimate the location of the GON as a thumb's breadth lateral to the external occipital protuberance (2 cm laterally) and approximately at the base of the thumbnail (2 cm inferior) [3].

The LON originates from the superficial branches of the cervical plexus and contains fibers from ventral rami of C_2 and C_3. It supplies the lateral part of the occiput. The location of the nerve can be estimated as the lateral third of a hypothetical line drawn between the mastoid process and occipital protuberance (Fig. 4.2). The LON block is usually performed together with the GON block in patients with headache located predominantly in the lateral portion of the occipital region [1, 2].

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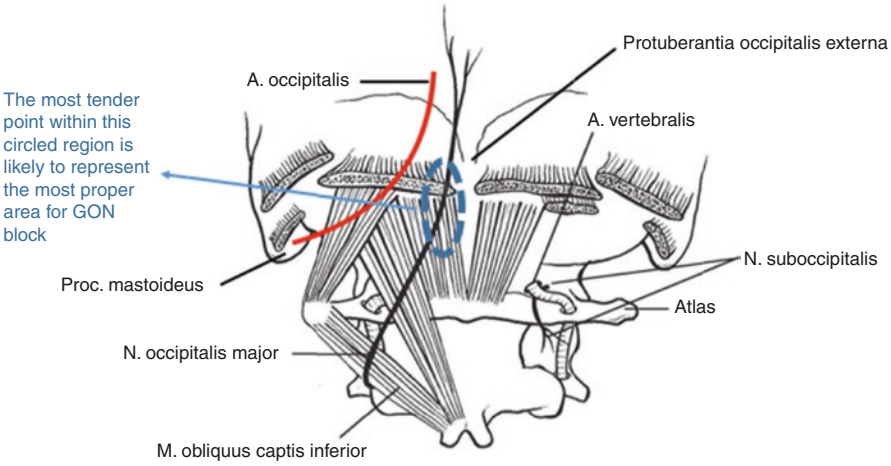

Fig. 4.1 Anatomy of the great occipital nerve (GON). (Reprinted from Temel Nöronanatomi (p. 234) by Mehmet Yıldırım, 2016. İstanbul, Nobel Tıp Kitabevi, Copyright:2016. Reprinted with permission)

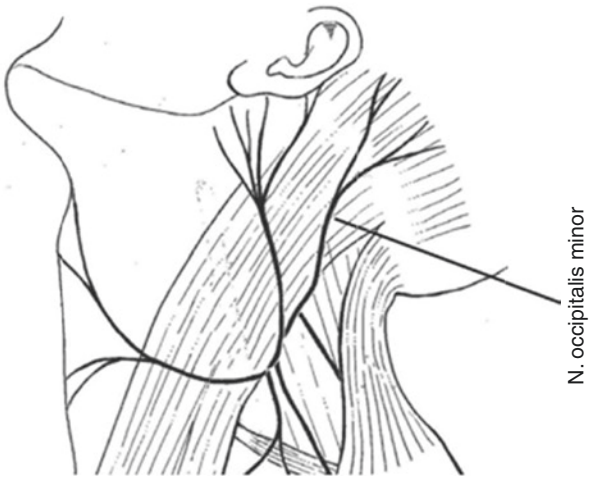

Fig. 4.2 Anatomy of the lesser occipital nerve (LON). (Reprinted from Temel Nöronanatomi (p. 234) by Mehmet Yıldırım, 2016. İstanbul, Nobel Tıp Kitabevi, Copyright: 2016. Reprinted with permission)

The injection site for GON and LON block differs among studies. While the aforementioned hypothetical line has been used in some studies, the nerve block was performed in the area of maximal tenderness, along the superior nuchal line in others. The American Headache Society (AHS) suggests the following injection sites: one-third of the distance between the external occipital protuberance and the mastoid process for the GON block and two-thirds of the distance between the same points for the LON block [4]. In terms of increasing the efficacy of the injections, Palamar et al. have suggested using ultrasonography to detect the exact location of the GON, but there is no published data showing the superiority of ultrasonography guidance so far [5].

Although PNB is commonly used to treat acute and chronic primary headache disorders and even some types of secondary headaches, the exact mechanism of PNB is still unclear [6]. Given that the response duration of PNBs exceeds the half-life of local anesthetics, the mechanism of action would seem to be related to changes in brain nociceptive pathways rather than to a peripheral mechanism. In addition, when considering that the trigeminal nucleus caudalis (TNC) neurons receive convergent input from both occipital and trigeminal afferents, the GON block may reduce the input to the TNC and thereby diminish central sensitization [7].

In terms of PNB mechanism, Young et al. have shown that allodynia that is related to sensitization of pain neurons improved faster than the headache when the patients were evaluated 5 minutes after the GON block. They suggested that the descending inhibition hypothesis might have been related to this response rate, and that the GON block presumably affected the central mechanism reducing input into the trigeminocervical complex [8].

4.1 GON and LON Blocks for the Treatment of Various Headache Types

In a survey conducted by Blumenfeld et al. on American Headache Society member physicians and aimed toward identifying the indications for occipital nerve block, the responses included occipital nerve/notch tenderness (94.5%), occipital headache (78.2%), prior injection response (61.8%), neck pain or trigger point tenderness (43.6% each), frontal headache (32.7%), supraorbital or infraorbital notch tenderness (30.9%), temporal headache (27.3%), and neck muscle spasm (23.6%) [4].

In terms of headache types, chronic cluster headache and chronic migraine were the most frequent headache types for the indication of nerve block which is similar to our clinical practice [4]. Below are the headache types that we use GON and LON block for in our practice. Although we have some anecdotal cases regarding a positive response to GON block in tension-type headache, data showing the efficacy of nerve blocks in tension-type headache is scarce.

4.1.1 Cluster Headache

Transitional therapies, also called bridge therapies, including GON block and steroids are commonly used to treat bouts of cluster headache. Following the two randomized control trials demonstrating the efficacy of GON block in cluster headache, this form of treatment was accepted as the only class A evidence treatment for maintenance and transitional prophylactic therapy in cluster headache [9]. A study evaluating 83 patients with chronic cluster headache treated with GON block showed that

~60% of patients obtained a ≥50% reduction in the frequency and/or severity of the attacks for a median duration of 21 days [10]. The results of that study are in line with those of other studies showing a good response to GON block in cluster headache [11, 12]. However, the main difference between that study and others is that the GON block was repeated every 3 months for a maximum of four injections in the former whereas it was performed only once in the others. The repetitive injections resulted in significant remission periods over the long term. Another interesting finding of that study was that the GON block was repeated in accordance with the patients' requests in the nine patients who did not respond to the first block but only two had a good response to the second block, and neither had a response to the third block. In our clinical practice, we follow the same procedures as stated in the aforementioned literature for chronic cluster headache [10].

4.1.2 Migraine

Given that the approved medications in chronic migraine are effective only after a lag period, GON blocks may be an alternative treatment option, serving as transitional therapy with rapid efficacy. Although GON blocks are inexpensive, relatively easy to administer, and have been used for decades in various types of headache disorders, there have only been four randomized controlled trials of their use in migraine so far, and only one focused on the long-term treatment of chronic migraine with a GON block [13–16]. Cuadrado et al. reported that the GON block significantly reduced the number of moderate to severe headaches, as well as the total number of headaches, within 1 week of intervention [16]. To the best of our knowledge, their study was the first to support the use of GON block as an adjunctive or transitional treatment in chronic migraine. Dilli et al. concluded that, compared to placebo, GON block did not reduce the frequency of moderate to severe migraine days in patients with episodic or chronic migraine. However, one of the main issues of their study was that the GON block was administered only once [14]. By contrast, Inan et al. reported superior efficacy of a GON block versus placebo in 84 patients when the GON block was administered once a week for 4 weeks, with treatment continuing monthly for 2 months. The authors found significant decreases in the severity, duration, and monthly frequency of migraine in the 72 patients who completed the study [15]. Although many headache specialists and patients have provided evidence of the substantial clinical efficacy of GON block in chronic migraine, the lack of adequate randomized placebo-controlled studies and the inconsistency among studies have discouraged clinicians from performing the GON block more often in these patients. However, only 44.8% of chronic migraine patients use preventive medications regularly [17]. Thus, it is our belief that the GON block should be performed in patients with chronic migraine and frequent episodic migraine (≥4 per month) at least once as transition therapy and even prophylactically, to decrease the dose of medications associated with poor compliance because of their side effects.

4.1.3 Occipital Neuralgia

Occipital neuralgia is defined as "unilateral or bilateral paroxysmal, shooting or stabbing pain in the posterior part of the scalp, in the distribution(s) of the greater, lesser and/or third occipital nerves, sometimes accompanied by diminished sensation or dysesthesia in the affected area and commonly associated with tenderness over the involved nerve(s)" [18]. This is the only headache type in which the response to GON and LON blocks is among the diagnostic criteria. Recently, Kissoon et al. showed the association between occipital neuralgia and $C_{2–3}$ spinal cord lesions in patients with idiopathic inflammatory demyelinating disease. This finding should encourage clinicians to perform magnetic resonance imaging of the cervical spine in patients presenting with occipital neuralgia [19].

4.1.4 Postdural Puncture Headache

GON block with dexamethasone may also play a role in the management of patients presenting with postdural puncture headache that does not respond to conservative management. Given that epidural patch treatment includes complications such as back pain, paresthesia, radiculitis, temporary cranial nerve palsies, cauda equina syndrome, epidural abscess, and late arachnoiditis, the GON block may be effective in patients with postdural headache, although it only offers symptomatic management and does not address the dural leak [20].

4.2 Treatment Intervals and the Drugs

The treatment intervals and drugs used for GON block remain a matter of debate. The response duration to PNB varies substantially (from hours to years) among patients, regardless of the headache type. Clinical observations of the difference in response duration have led to questions regarding the frequency of PNB administration in patients who do and do not complain of headache. Lidocaine and bupivacaine are the most common local anesthetics used in PNB because they are less likely to cause an allergic reaction than other LAs. However, no study has compared the efficacy of various LAs in GON block. The volume of LA typically ranges from 0.1 to 10 mL, and injections are generally administered with a 25–30-gauge and 0.5–1.5-inch needle. The needle is inserted until it just touches bone. After needle insertion and before the infiltration of the LA, aspiration should be done to ascertain that the needle is not inside the occipital artery [21]. The expert consensus recommendations of the AHS include the use of lidocaine 1–2% and/or bupivacaine 0.25–0.5%. If a combination of the two drugs is used, the recommended volume ratio (lidocaine/bupivacaine) is 1:1–1:3. The choice of steroid is at the clinician's discretion but those

most commonly used are triamcinolone (40 mg), methylprednisolone (40–80 mg), and betamethasone (16 mg). The volume ratio of LA to corticosteroids is generally 2:1–3:1 [4]. However, despite the recommendations of the AHS, most clinicians choose an anesthetic and a treatment interval based on their own experience.

4.3 Outcome

Since the tenderness is due to the central sensitization in chronic forms of headaches, tenderness in the pericranial nerves should be examined in every patient by palpation. As tenderness over the GON is a good predictive factor of outcome [12], clinicians should palpate the GON to improve patient selection before deciding on the use of the GON block and providing patients with more detailed information about the potential response to this procedure.

4.4 Side Effects

The most frequent side effects of GON block include pain at the injection site and numbness. Lightheadedness and syncope may also occur, as well as local hematoma, local infection, and nausea. Skin atrophy, hyperpigmentation or hypopigmentation of the skin, and local alopecia have also been reported when GON block is used in conjunction with steroids [21]. However, PNB is safe and well-tolerated compared to other treatments and their side effects.

4.5 Contraindications

The contraindications of GON block are infection and malformation (e.g., hemangioma) at the injection site, and allergy to anesthetics and/or corticosteroids. Furthermore, nerve block should not be performed in patients taking anticoagulants, in those with diseases that increase bleeding time (e.g., idiopathic thrombocytopenic purpura), or in those with arrhythmia or liver failure [21].

In addition to PNB, trigger point injections (TPI) may be administered to patients having tenderness in the neck and shoulder. The most commonly used local anesthetics for TPIs are lidocaine and bupivacaine, in volumes ranging from 0.1 to 5 mL. The most frequent side effects are pain at the injection site and bleeding [6].

4.6 Personal Comments

In our clinical practice, we prefer PNB and TPI as either rescue or transition treatment and simultaneously with the initiation of preventive treatment in naïve headache patients. If the patient is already on prophylactic medication but without

benefit, we perform PNB (mainly GON) and then follow the patient for at least 3 months to assess its efficacy. At the end of the third month, we continue PNB treatment every 3 months if the patient shows at least a 30% response and discontinue it otherwise. For GON block, we tend to use lidocaine 2% (2 mL) with 80 mg methylprednisolone for each side. Our (as yet unpublished) experience has shown that headache patients with cluster headache and medication-overuse headache are likely to obtain the greatest benefit from these procedures as rescue therapy. In chronic migraine, we perform GON block at least once, and consider botulinum toxin treatment if we do not obtain sufficient benefit after the procedure. We also use GON block as prophylaxis in pregnancy, as most medications cannot be used due to the side effects. We perform GON and LON block bilaterally except in cluster headache, where the nerve block is applied to the side of the pain. If the pain is refractory to GON and LON block, other cranial PNBs are offered in addition to GON and LON if tenderness is palpated in the corresponding areas of the nerves. The patient is monitored for bleeding after the procedure. The patient is monitored for at least 2 hour in our outpatient clinic after the first injection and is not allowed to drive a car after the procedure for 4 hour. If the procedure has been performed previously on the same patient, he or she is monitored for 30 minutes and then discharged after the blood pressure and heart rate are checked.

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Chapter 5
The Role of Other Peripheral Nerve Blocks

Ömer Karadaş and Hakan Levent Gul

Introduction

Peripheral nerve blocks have been used for both acute and preventive treatment of headaches for decades and are safe and effective therapeutic options for many patients with headache disorders [1–3]. They can cause long-lasting (several weeks to months) pain relief [4]. This long-lasting effect is thought to be due to central pain modulation [5]. Nerve blocks may be an option for patients who have failed to obtain relief with their home medications or who do not want to use drugs. Blocks may also be used to treat patients who need relief between onabotulinum toxin A injections. Nerve blocks can be used for the acute treatment of medication overuse headache. Nerve blocks are safe and can be appropriate for children and pregnant patients and also in patients who must avoid using many drugs (with kidney-liver diseases) [6, 7]. In pregnancy, lidocaine is considered a category B drug.

Greater occipital nerve block is the most common peripheral nerve block procedure. However, we will discuss other peripheral nerve blocks excluding greater occipital and lesser occipital nerve blocks in this chapter.

Sphenopalatine ganglion blocks in addition to supratrochlear, auriculotemporal, supraorbital, infraorbital, and mental nerve blocks and cervical root blocks or their various combinations can be used in patients with headache disorders. Local anesthetics are employed for these nerve blocks (Table 5.1).

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Table 5.1 Main peripheral nerve block procedures and preferred headache disorders

Nerve block	Indication
Auriculotemporal	Auriculotemporal neuralgia
Supratrochlear	Chronic headaches (TTH, migraine)
Supraorbital	Chronic headaches (TTH, migraine), Infraorbital neuralgia
Infraorbital	Chronic headaches (TTH, migraine), Infraorbital neuralgia
Mental	Fascial pain, chronic headaches (TTH, migraine), mental nerve neuralgia
Sphenopalatine	Cluster headaches, migraine, other trigeminal autonomic Cephalalgias, Orofacial pain syndromes
Cervical root	Various kinds of headaches, neck and spine pain, cervicogenic headaches, C3 neuralgia, TTH, occipital neuralgia

5.1 Nerve Blocks

5.1.1 Auriculotemporal Nerve Block

The auriculotemporal nerve is a branch of the trigeminal nerve's mandibular division. It plays a role in providing sensation over the ear and temporalis muscle.(A,B) The auriculotemporal nerve passes behind the temporomandibular joint and superior to the parotid gland's surface, and then ascends close to the superficial temporal artery, passed over the posterior portion of the zygoma and ends as superficial temporal branches.

The block can be performed by injecting 2–3 cc bupivacaine or lidocaine superior to the posterior portion of the zygoma and anterior to the ear (palpate the temporal artery anterior to the tragus and inject 2 mm anteriorly at a depth of 4–6 mm; perform negative aspiration before injection). An alternative technique is as follows: insert the needle at the posterior margin of the mandibular ramus inferior to the tragus and inject at a depth of 20 mm (Fig. 5.1) [6, 12].

This block can be performed for auriculotemporal neuralgia, a condition characterized by unilateral lancinating pain in the temporal and auricular areas. Potential side effects are Frey's syndrome or abnormal gustatory sweating as a result of auriculotemporal nerve injury.

5.1.2 Supratrochlear Nerve Block

The supratrochlear nerve is the largest branch of the ophthalmic division of the trigeminal nerve. It is located medial to the supraorbital nerve. The supratrochlear nerve passes medial to the trochlea in the orbital roof, ascends onto the forehead through the frontal notch, and follows the supratrochlear artery close to the bone, spreading to the upper eyelid and the skin over the forehead.

The block can be done by inserting the needle above the eyebrow over its medial border and injecting 1–2 cc bupivacaine or lidocaine (use a 30-gauge,

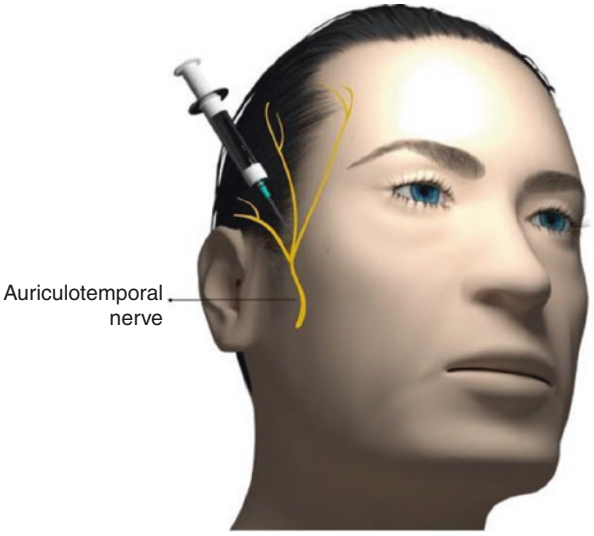

Fig. 5.1 Auriculotemporal nerve block

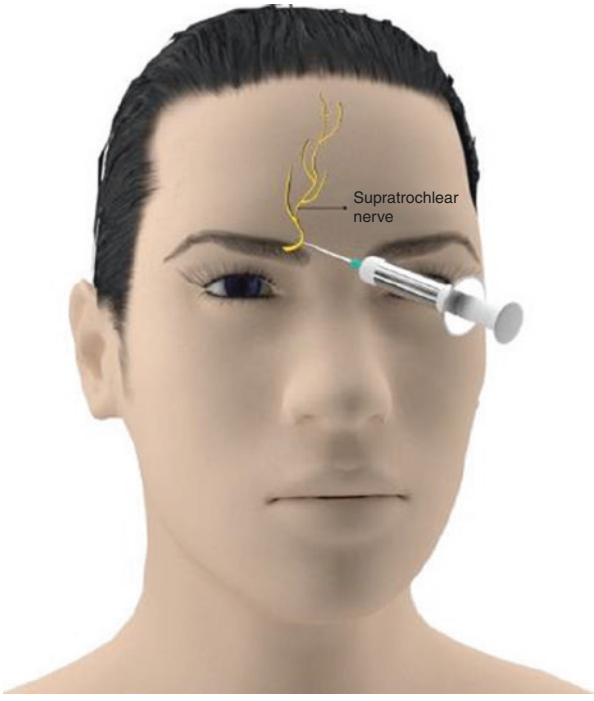

Fig. 5.2 Supratrochlear nerve block

0.5-inch needle; insert it at the medial aspect of the corrugator muscle, a finger-breadth lateral to the procerus and at a depth of 3–4 mm; perform negative aspiration before injection). Alternatively, identify the supraorbital ridge by palpation, and then insert the needle lateral to the ridge and inject medially and subcutaneously (Fig. 5.2) [6–12].

The supratrochlear nerve block can be performed for the management of chronic headaches like tension-type headache and migraine. The nerve is also blocked during regional anesthesia in cosmetic surgery procedures like hair restoration.

5.1.3 Supraorbital Nerve Block

The supraorbital nerve is the larger of the 2 terminal branches of the frontal nerve. It passes through the supraorbital notch (foramen) and spreads to the upper eyelid and conjunctiva, and ascends to the forehead close to the supraorbital artery and then spreads to the scalp up to the lambdoid suture with the medial and lateral branches. The supraorbital notch, the pupil, the infraorbital foramen, and the mental foramen are all on an imaginary line.

The block can be performed by inserting the needle to the corrugator muscle, at the mid-pupillary line, at a depth of 3–4 mm (perform negative aspiration before the injection). An alternative technique is detecting the supraorbital notch with palpation at the superior margin of the orbit at the mid-pupillary line, and then inserting the needle medially while avoiding entering the foramen (Fig. 5.3) [6, 12].

The supraorbital nerve block can be performed for the management of chronic headaches like tension-type headache and migraine. It can also be used in the management of supraorbital neuralgia, which is a rare type of neuralgia characterized by persistent pain over the supraorbital region and forehead. Patients generally feel

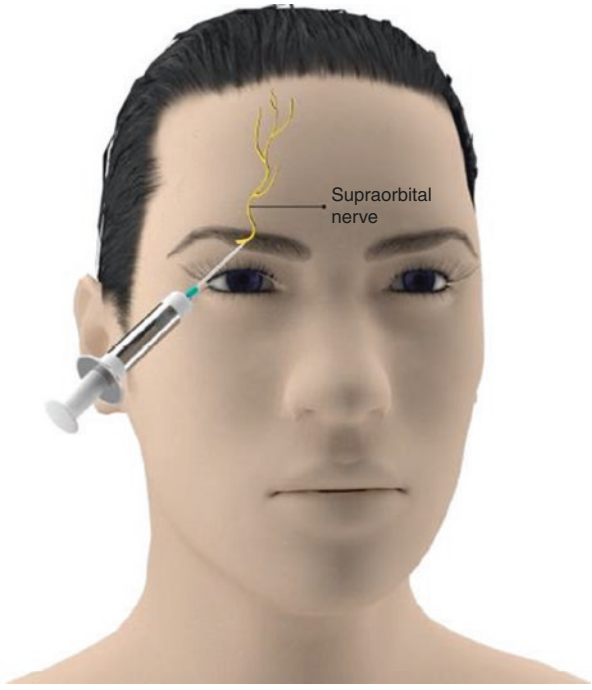

Fig. 5.3 Supraorbital nerve block

shock-like paresthesias in the distribution of the nerve. Supraorbital neuralgia is also named goggle headache or swimmer's headache.

5.1.4 Infraorbital Nerve Block

The maxillary nerve enters the face through the infraorbital canal and ends as the infraorbital nerve. It receives sensory branches from the upper lip, the side of the nose, and the lower eyelid.

Intraoral block: palpate the infraorbital foramen and while keeping the palpating finger over the infraorbital rim retract the cheek. Introduce the needle into the mucosa for 1.5–2.5 cm, and inject 2–3 cc bupivacaine or lidocaine (perform negative aspiration before the injection).

Extraoral block: palpate the infraorbital foramen and keep the palpating finger over the infraorbital rim. Insert the needle through the skin, the subcutaneous tissue and the quadratus labii superioris muscle, and inject 2–3 cc bupivacaine or lidocaine (perform negative aspiration before the injection) (Fig. 5.4) [6–12].

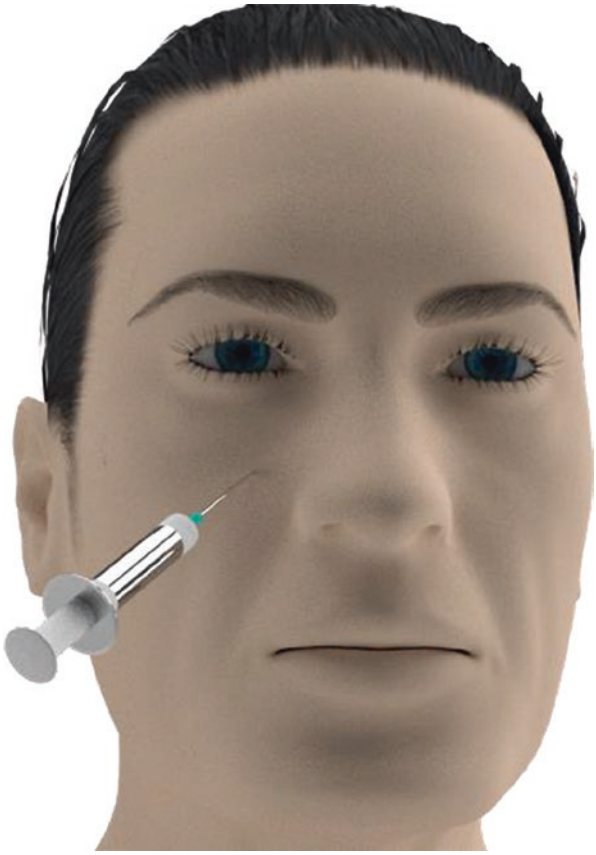

Fig. 5.4 Infraorbital nerve block

Infraorbital nerve block can be performed for the management of facial pain and chronic headaches such as tension-type headache and migraine. It is frequently used in dental practice. Infraorbital neuralgia is an indication of a block that usually happens due to trauma, plastic surgery, shingles, or other viral infections. Symptoms of infraorbital neuralgia are sharp, shooting, sensitivity, and tingling pain.

5.1.5 Mental Nerve Block

The mental nerve is a branch of the mandibular nerve. It continues as the inferior alveolar nerve and exits via the mental foramen. It then divides into 3 branches below the depressor anguli oris muscle. It spreads to the skin of the chin and mucous membrane of the lower lip.

The mental foramen is palpable between the 2 lower premolar teeth in adults.

Intraoral block: palpate the mental foramen and retract the cheek. Introduce the needle into the mucosa for 1.5–2.5 cm and inject 2–3 cc bupivacaine or lidocaine (perform negative aspiration before the injection).

Extraoral block: palpate the mental foramen. Insert the needle through the skin and subcutaneous tissue and inject 2–3 cc bupivacaine or lidocaine (perform negative aspiration before the injection) (Fig. 5.5) [6, 12].

Mental nerve block can be performed for the management of facial pain and chronic headaches like tension-type headache and migraine and is often used in

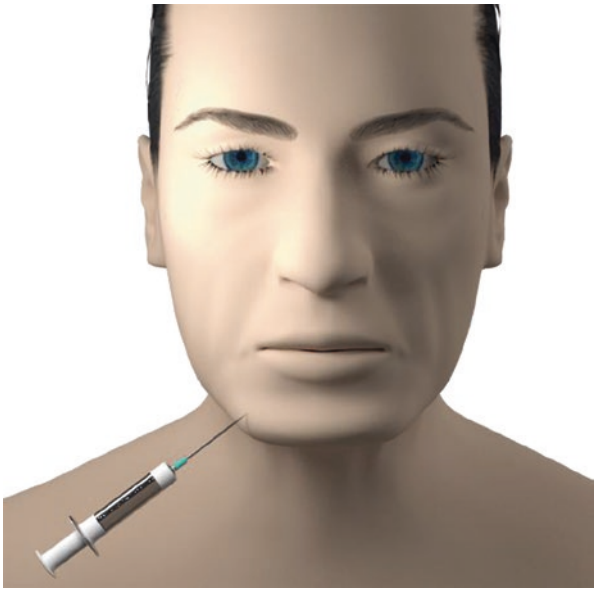

Fig. 5.5 Mental nerve block

dental practice. Mental nerve neuralgia is a painful disorder of the mental nerve. It can be due to dental procedures and can be treated with a block.

5.1.6 Sphenopalatine Ganglion Block

The sphenopalatine ganglion (pterygopalatine ganglion) is a collection of nerve cells closely associated with the trigeminal nerve, and is a complex region of cell bodies and fibers. It contains autonomic and sensory nerves and is superficially located and triangularly shaped, and is less than 5 mm in size. It is covered by 1–1.5 mm of connective tissue and mucous membrane and can be blocked by topical or injection methods.

The block can be done transcutaneously, by intraoral injection or by topical application to the overlying mucosa in the lateral wall of the nasal cavity (lateral/infrazygomatic, transoral, and transnasal approaches).

The transnasal method is the easiest and simplest approach. The patient is first instructed to lie back with the head tilted back. Then, a small applicator or catheter is inserted through the nostril to the very back of the nasal cavity. A cotton swab applied an anesthetic agent (4% lidocaine) or catheter drips are administered to the back of the nasal cavity, and is absorbed through the bone and into the sphenopalatine ganglion, and is kept there for 30 minutes with dripping.

The inhalation of the anesthetic is also effective for a sphenopalatine ganglion block, in which case the anesthetic is administered without the use of an applicator. For this procedure, the patient is placed on their back with the nose pointed upward toward the ceiling. A 2% viscous lidocaine solution is usually administered into the nasal passageway and the patient is instructed to quickly inhale.

The intraoral approach is another method that can be used to perform a sphenopalatine ganglion block. Palpate the patient's gum line to locate the proper area for needle insertion. Once the correct location is identified, a small dental needle is inserted and a local anesthetic is injected.

The infrazygomatic method is less commonly used. The patient is first placed in the supine position with a pillow under the head. Sterilize the face on the appropriate side and then numb the skin with a local anesthetic to ensure patient comfort throughout the entire procedure. The pterygopalatine fossa (appearing as a "V" or an "inverted vase") is identified using fluoroscopy and a real-time X-ray device will allow visualization of the needle the entire way up the skull so that it can be properly placed inside the pterygopalatine fossa and reach the sphenopalatine ganglion. Once the needle is properly positioned, a small amount of anesthetic (2 ml lidocaine, marcaine) is injected into the fossa (Fig. 5.6) [6, 12].

Sphenopalatine ganglion block can be performed for the management of cluster headaches, migraine, and other trigeminal autonomic cephalgias and also for intractable orofascial pain syndromes such as persistent idiopathic facial pain.

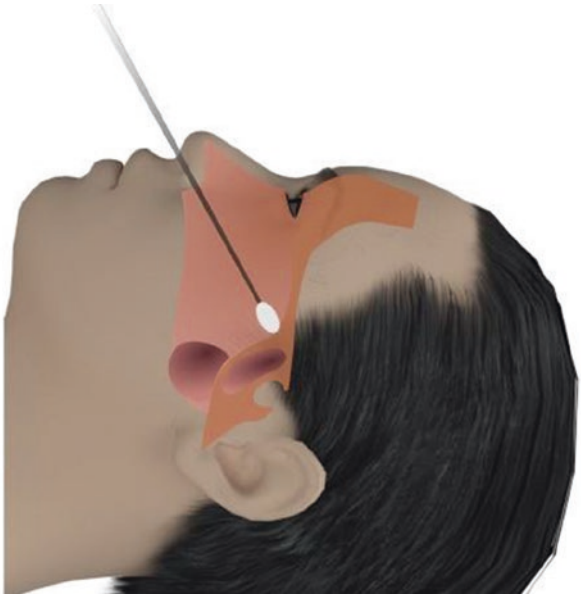

Fig. 5.6 Sphenopalatine ganglion block

5.1.7 Cervical Root Block

The second and third cervical root blocks are effective in some headaches [6, 14, 15].

The positions of the transverse processes have to be noted for this procedure. C2 is approximately 1.5 cm below the mastoid process and C3 is a further 1.5 cm below C2. Angle the needle slightly in the caudal direction. Inject 2 ml 1% lidocaine or 2 ml 0.25% bupivacaine at each point (perform negative aspiration before the injections) [6, 13–15].

A C2-C3 root block can be performed for various kinds of headache, neck and spine pain, cervicogenic headaches, C3 neuralgia, tension-type headache, and occipital neuralgia.

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Chapter 6
OnabotulinumtoxinA for Refractory Headache

Abigail L. Chua, Sait Ashina, and Richard Lipton

Introduction

The term refractory headache is commonly used to describe a "persistent headache that is difficult to treat or fails to respond to standard headache treatments" [1]. While headache specialists have long recognized this subset, there is no universally accepted definition. This lack of a concise definition complicates referral to appropriate specialists and headache care centers, the development of evidence-based care plans, and choosing patients for clinical trials [2]. It is also important to note that the term "refractory headache" does not clearly specify the headache type. The International Classification of Headache Disorders 3rd edition [3] lists four groups of primary headache disorders (migraine, tension-type headache (TTH), trigeminal autonomic cephalalgias (TACs), and other) and multiple secondary types (such as medication overuse headache) that could all be labeled as "refractory" in some circumstances. Treatments for these headache disorders vary but generally include acute therapies meant to relieve or abort the symptoms of a headache attack and preventive medications which are used to decrease the frequency, severity, or duration of headache attacks. Refractory headaches fail to respond to standard headache treatments. Chronic migraine (CM) is likely the most common subtype of these headaches. For

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refractory chronic migraine, escalation of care is needed, and patients are often transitioned to more procedurally based therapies such as onabotulinumtoxinA.

In this chapter, the pharmacological properties, efficacy, and tolerability of onabotulinumtoxinA will be reviewed, with special focus on its potential role in the treatment of refractory headaches. In addition, practical topics such as dosage and administration will be discussed.

6.1 OnabotulinumtoxinA

OnabotulinumtoxinA (BOTOX®) is derived from the gram-positive anaerobic bacteria *Clostridium botulinum*, and is commonly known for its use in treating facial wrinkles such as "frown lines" and "crow's feet" [4]. It is also used in the treatment of other medical conditions such as strabismus, blepharospasm, cervical dystonia, hyperhidrosis, spasticity in stroke, and overactive bladder. In 2010, onabotulinumtoxinA was approved for the preventive treatment of CM in both North America and much of Europe [5]. To date, it remains the only treatment specifically approved for the prevention of chronic migraine. Chronic migraine is characterized as headaches occurring ≥15 days per month for more than 3 months, with at least eight of those headaches linked to migraine [3]. OnabotulinumtoxinA has been assessed in small, mostly open-label trials for other disorders such as nummular headache, cluster headache, and other TACs; its use remains off-label for headache disorders other than chronic migraine.

6.2 Migraine and Its Subtypes

Migraine is a common, disabling neurological disorder that affects approximately one billion people worldwide. Defining characteristics include a moderate to severe headache that worsens with routine physical activity, and is accompanied by symptoms such as nausea, vomiting, photophobia, and phonophobia [3] in various combinations. Migraine is categorized into episodic or chronic subtypes based primarily on whether headache days occur <15 days per month (episodic migraine) or ≥15 days per month (chronic migraine). Chronic migraine is known to develop from episodic migraine at a rate of approximately 3% per year, and is associated with significant psychosocial and economic burden [6]. Common risks factors for chronification of migraine include obesity, depression, stressful life effects, ineffective acute treatment, and comorbid pain disorders [6, 7].

6.3 Mechanism of Action of OnabotulinumtoxinA in Chronic Migraine

Botulinum neurotoxins (BoNTs) are proteolytic enzymes that cause temporary paralysis by disrupting vesicle fusion in the presynaptic terminal and preventing neurotransmitter release at the neuromuscular junction and from sensory neurons

[4]. While serotypes A, B, E, and F of botulinum toxin are known to cause the clinical syndrome of botulism in humans, neurotoxins BoNT/A and BoNT/B also have medicinal applications. Each toxin serotype cleaves specific protein complexes called soluble NSF-attachment protein receptors (SNARE), which include syntaxin, VAMP2 (also known as synaptobrevin), and SNAP-25. SNARE proteins form *trans*-SNARE complexes that are anchored onto plasma membranes of neuronal cells. These proteins mediate the fusion of vesicles with the postsynaptic membrane, leading to neurotransmitter release. BoNTs are composed of a heavy chain and a light chain held together by a disulfide bond, with the heavy chain containing the translocation (N-terminus) and binding (C-terminus) domains of the protein. When BoNTs are injected into tissue, the heavy chain C-terminus binds to extracellular transporters such as ganglioside receptor (GT1b) and synaptic vesicle glycoprotein 2 (SV2) [4]. The neurotoxin is then internalized and undergoes a conformational change that allows the light chain of BoNT to enter the cytosol of the neuronal cell. In the case of BoNT/A specifically, internalization of the light chain leads to the cleavage of the SNARE protein SNAP-25 (synaptosomal-associated protein of molecular weight 25 kDa). Cleavage of SNAP-25 results in damage to the *trans*-SNARE complex, preventing the fusion of synaptic vesicles. This results in failure of neurotransmission and ultimately leads to paralysis of the affected cells.

Application of onabotulinumtoxinA into muscle results in transient chemical denervation and muscle relaxation. While its exact mechanism of action in the treatment of chronic migraine is not known, there are several prevailing theories (see Table 6.1). OnabotulinumtoxinA impairs the release of inflammatory neuropeptides such as substance P and calcitonin gene-related peptide (CGRP) [4]. Injection of onabotulinumtoxinA into regions innervated by the trigeminal nerve is thought to inhibit the release of these pain-mediating neuropeptides from peripheral nerve terminals, which in turn blocks the development of peripheral and central sensitization (phenomena that occur in CM pathophysiology) [8]. OnabotulinumtoxinA may also exert a neuromodulatory effect on cell surface receptors such as TRPV1 (transient receptor potential cation channel vanilloid subfamily member 1) and mechanosensitive ions channels such as TRPA1 (transient receptor potential cation channel ankyrin subfamily member 1) by preventing their integration onto nociceptive nerve terminals via cleavage of SNAP-25. This in turn results in the inhibition of peripheral sensitization and indirect inhibition of central sensitization. An alternate hypothesis suggests that retrograde transport of onabotulinumtoxinA into peripheral nociceptive neurons, followed

Table 6.1 Proposed MOA of onabotulinumtoxinA on chronic migraine (CM) (Refs. [4, 8])

OnabotulinumtoxinA Action	Effect on CM pathophysiology
Block peripheral release of inflammatory neuropeptides such as CGRP and substance P	Inhibition of peripheral and central sensitization
Neuromodulation of TRPV1 and TRPA1	Inhibition of peripheral and central sensitization
Retrograde transport and transcytosis of onabotulinumtoxinA into peripheral nociceptive neurons	Directly affects central pain processing

by transcytosis into second-order neurons, can have a direct effect on central pain-processing. In vivo studies in rats have challenged the notion of onabotulinumtoxinA transcytosis [8].

6.4 Therapeutic Application, Efficacy, and Tolerability of OnabotulinumtoxinA

The potential for onabotulinumtoxinA in the treatment of migraine was discovered serendipitously. In the early 1990s, a plastic surgeon noted that patients receiving cosmetic onabotulinumtoxinA reported improvements in their migraine symptoms [4]. This discovery ultimately led to the successful execution of two pivotal phase III multicenter studies evaluating the effects of onabotulinumtoxinA in chronic migraine. The PREEMPT (*P*hase III *R*esearch *E*valuating *M*igraine *P*rophylaxis *T*herapy) 1 and 2 trials both included an initial 24-week randomized, double-blind, placebo-controlled phase, followed by a 32-week open-label phase [9–10]. Patients were recruited from North American sites in PREEMPT 1 and North American and European sites in PREEMPT 2. Eligible participants ranged in age from 18 to 65 years of age and met ICHD-2 diagnostic criteria for CM. The studies randomized a total of 1384 participants to receive either onabotulinumtoxinA ($n = 688$) or placebo ($n = 696$). Patients were mostly Caucasian (90%) women (86%), with a mean age of 41 years.

In the 28-day baseline screening period, participants completed a daily telephonic diary; eligible participants were then treated. During the treatment phase, patients were randomized to receive two cycles of injections given 12 weeks apart. Active treatment included at least 31 injections of onabotulinumtoxinA 155 Units (U) or placebo. Three rounds of onabotulinumtoxinA injections were administered during the 32-week open-label extension phase. Investigators were given the liberty of adding up to eight additional injections into the temporalis, occipitalis, and trapezius muscles using a "follow the pain" pattern. These injection paradigms (155 U into 31 sites or 195 U into 39 sites) are now termed the "PREEMPT protocol" (see Fig. 6.1)**.**

Primary endpoints for the trials included mean change of monthly frequency of headache episodes from baseline to week 24 (PREEMPT 1) and mean change from baseline to week 24 in the monthly frequency of headache days (PREEMPT 2). OnabotulinumtoxinA showed statistically significant improvement versus placebo in the primary endpoint for PREEMPT 2 but not PREEMPT 1. However, pooled data from both trials did show a significant mean decrease in the monthly frequency of headache days from baseline to week 24 in the onabotulinumtoxinA group compared to placebo (−8.4 days for onabotulinumtoxinA versus −6.6 days for placebo, $P < 0.001$, 95% CI -2.52 to 1.13) [11]. In addition, significant reductions in frequency of migraine days, days with moderate to severe headache, total

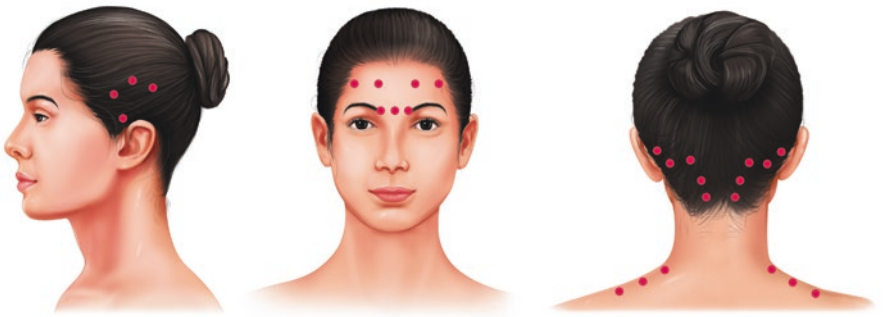

Fig. 6.1 PREEMPT protocol for Botox Administration (Refs. [9, 10, 15]). ©Leizl Chua

hours of headache on headache days, migraine episodes, headache-day severity, and headache impact (as measured by the Headache Impact Test (HIT-6) and the Migraine Specific Quality of Life Questionnaire (MSQ) were seen in those who received onabotulinumtoxinA versus placebo. Data from the 32-week open-label phase of both trials indicated that, at week 56, participants who had received all five onabotulinumtoxinA cycles had statistically better results than those who received three cycles of onabotulinumtoxinA after two injection cycles of placebo.

Most adverse events (AE) in the PREEMPT 1 and 2 trials were mild to moderate in severity, and the proportion of participants who discontinued due to AE were low (3.8% in the onabotulinumtoxinA group versus 1.2% in the placebo group). The most common AE in the treatment group included neck pain (6.7% in double-blind phase, 4.6% in open-label phase), muscle weakness (5.5%, 3.9%), ptosis (3.3%, 2.5%), injection site pain (3.2%, 2.0%), and musculoskeletal pain (2.2%, 1.1%) [8]. Only one serious AE (hospitalization due to migraine) was reported in the onabotulinumtoxinA treated group.

6.5 OnabotulinumtoxinA for Refractory Migraine

Refractory migraine (RM) is a clinically relevant subset of migraine that lacks a formal definition. In 2009, the Refractory Headache Special Interest Section (RHSIS) of the American Headache Society (AHS) conducted a survey of 151 members of AHS in an attempt to formulate standard diagnostic criteria for RM [2]. Their proposed criteria suggest that a diagnosis of refractory migraine or refractory chronic migraine can be made in individuals that have a history of migraine or chronic migraine who continue to have significant headache-related disability despite 1) making positive lifestyle changes and avoiding migraine attack triggers, 2) having had an adequate trial of at least 2 classes of preventive treatments

(anticonvulsants, tricyclic antidepressants, or antihypertensives such as beta blockers or calcium channel blockers), and 3) completing an adequate trial of both triptans and dihydroergotamine, as well as NSAIDS or combination analgesics [2]. An adequate trial was defined as a minimum of 2 months of use at therapeutic or tolerable doses.

Studies evaluating the use of onabotulinumtoxinA in RM can be challenging given the lack of clear diagnostic guidelines and clear definitions of this headache. Oterino et al. conducted an open-label trial using the proposed RHSIS criteria to evaluate patients attending their refractory headache clinic in Spain [12]. Authors investigated 35 participants, (32 of which were women) aged 24–68 years of age, all of whom met criteria for CM with or without analgesic overuse and showed inadequate response to beta-blockers, topiramate, flunarizine, valproic acid, and amitriptyline. The mean headache days per month prior to onabotulinumtoxinA treatment was 24.7, with severe, disabling headaches totaling 8.2 per month. Frequent oral triptan use (average of 22 tablets per month) was seen in 29 patients, and 6 participants were using subcutaneous sumatriptan 4.5 times per month. Treatment consisted of 100 U of onabotulinumtoxinA (5 U per injection) injected into ten muscle sites bilaterally: one into the corrugator, two into the frontalis, three into the temporalis, two into the suboccipitalis, one into the semispinalis, and one into the splenius. An additional 40 injection sites were added if adequate response was not seen with the initial 100 U dose. Treatments were given every 3 months, and the total number of treatments ranged from 2 to 16 (median number of treatment was 4). A 50% reduction in headaches days per month was seen in nine patients, with two experiencing a 75% reduction in headaches days per month. The frequency of severe headache days was reduced by 46% (average of 3.8 days per month). In addition, oral triptan consumption was decreased from 22 to 11 tablets per month, subcutaneous sumatriptan was reduced to 1.5 per month (down from 4.5 per month), and the need for emergency services due to headache was reduced from 3 to 0.4 (approximately 87% reduction). AE were mild and included four cases of cervical pain and two cases of eyebrow asymmetry. This open-label study suggests the use of onabotulinumtoxinA for the treatment of RM. However, randomized placebo-controlled trails investigating the role of onabotulinumtoxinA in the treatment of RF are warranted.

6.6 OnabotulinumtoxinA for Cluster Headache

Considered “one of the most painful syndromes known to man” [13], cluster headache (CH) is a trigeminal autonomic cephalalgia (TAC) that affects approximately 0.3% of the population, with men affected 3 times more often than women. Approximately 15–20% of those with cluster headache have a chronic form of the condition. Chronic CH attacks occur without a remission period, or with remission periods lasting less than 3 months, for at least 1 year [3]. Common treatments of CH consist of acute treatments such as high-flow oxygen, sumatriptan, and ergotamine

and preventive treatments such as verapamil, lithium, topiramate, and valproic acid. Between 10% and 20% of those with CH develop resistance to conventional preventive therapies and go on to have refractory cluster headache [13]. Refractory chronic CH is defined by the European Headache Federation as a condition in which at least three severe cluster attacks occur per week, despite a trial of at least three adequate preventive treatments [13].

Research into the pathophysiology of CH has revealed some similarities to the pathophysiology of migraine. For example, dysfunction in the posterior hypothalamus causes secondary activation of the trigemino-autonomic brainstem pathways, leading to neurogenic inflammation of meningeal vessels, similar to that seen in migraine [14]. Also similar to migraine, plasma levels of CGRP are shown to be elevated during CH attacks, as well as interictally in patients with episodic CH. Given these similarities, and onabotulinumtoxinA's known ability to inhibit CGRP release from peripheral nerve terminals, onabotulinumtoxinA as CH preventive therapy has been tried. Reports include small case studies and open-label trials.

Twelve patients fulfilling ICHD-2 criteria for episodic ($n = 3$) and chronic ($n = 9$) CH were enrolled in an open, nonrandomized, single-center study conducted in Germany [14]. Participants were all men, with an average age of 42 years, and mean disease duration of 6 years. Current prophylactic treatments of the participants, which included verapamil, methysergide, lithium, topiramate, and valproate, were not changed, and usual acute treatments were allowed. OnabotulinumtoxinA was administered into the temporalis (10 U), frontalis (10 U), splenius capitis (10 U), and trapezius (20 U) muscles ipsilateral to the patient's headache site. Those who showed a positive response (at least a 50% reduction in pain intensity and/or attack frequency) to the initial administration received another treatment 3–10 months later. Patients with episodic CH did not show improvement after onabotulinumtoxinA treatment, while one patient with chronic CH had a total cessation of attacks for 3 months. Two others with chronic CH had an improvement in attack frequency and severity for 10 weeks. Improved response to acute treatment with oxygen was also seen in the study. A fourth patient, who had no improvement in CH attacks, experienced an improvement in a concomitant occipital pain that was ipsilateral to his CH site. Randomized placebo-controlled trials of onabotulinumtoxinA in chronic CH and refractory CH with well-defined injection paradigms are needed to support the use of onabotulinumtoxinA in these conditions.

6.7 OnabotulinumtoxinA for Medication Overuse Headache

Medication overuse headache is defined as a headache occurring on ≥15 days per month in a patient with a pre-existing headache disorder [3]. It occurs in susceptible individuals who regularly overuse one or more acute headache treatments for >3 months. MOH usually (but not always) resolves after the overused treatment is stopped. Successful cessation of acute treatment overuse usually requires an

effective preventive treatment strategy. However, in many instances, medication overuse is a result of insufficient benefit from preventive treatments, thus making the treatment of MOH challenging.

The PREEMPT trials included patients who reported using acute medication at least twice weekly (65% of the 1384 patients enrolled). Pooled analysis of PREEMPT 1 and 2 trials showed significant improvement in headache days on week 24 and at each 4-week interval thereafter in a subgroup of patients with medication overuse. Significant improvement over placebo was also seen in headache severity, triptan use, HIT-6 sore, and MSQ [4].

An open label, nonrandomized study of 44 patients with refractory CM and acute medication overuse was conducted to assess the efficacy of onabotulinumtoxinA in this patient population. Participants were men and women aged 18–80 years, with a diagnosis of refractory CM (defined in this study as use of 3 classes of prophylactic drugs with temporary or no effect) [5]. Only 36% of participants were taking preventive treatments at the time of the study, while 73% were using approximately 31.33 ± 29.64 doses of acute treatments per month. For this study, participants were not asked to stop or alter their preventive or acute treatment use. OnabotulinumtoxinA was administered every 3 months for 36 months using the PREEMPT injection protocol [15]. Variables used to assess efficacy included frequency of migraine days, frequency of moderate to severe headache days, total cumulative headache hours, and frequency of acute medication use. MIDAS and HIT-6 score were also assessed. Significant improvement in all variables was seen at completion of the study. More than half of participants had a more than 50% reduction in headache days, and a reduction of 25% in acute treatment overuse was observed. Adverse effects were reported by 6 patients and included ptosis, neck pain, and blurred vision. These studies suggest that onabotulinumtoxinA may be effective and result in improvement of headache in patients with refractory CM and medication overuse.

6.8 Administration of OnabotulinumtoxinA for Chronic Migraine

Reconstitution or preparation of onabotulinumtoxinA (BOTOX®) should be done using 0.9% preservative-free normal saline. In the PREEMPT trials, each 100 U vial of onabotulinumtoxinA was diluted with 2 mL of preservative-free normal saline, resulting in a final concentration of 5 U per 0.1 mL [15]. Reconstituted BOTOX® should be used immediately or kept in its original container and refrigerated at 2–8 °C for no more than 24 h.

Administration of onabotulinumtoxinA for CM is based on the PREEMPT protocol [15]. The recommended dose is 155–195 U administered intramuscularly as 0.1 ml (5 U) injections [8]. The total number of injections can vary from 31 to 39, and should be administered bilaterally into the appropriate muscles, except for the procerus, which is only injected once. See Fig. 6.1 and Table 6.2 for detailed information on injection sites.

Table 6.2 OnabotulinumtoxinA administration for CM based on PREEMPT injection protocol (Adapted from reference [15])

Injection site	Total dose (in Units)	Divided into number of sites (5 U per site, 0.1 mL = 5 U)
Procerus	5	1
Corrugators	10	2[a]
Frontalis	20	4[a]
Temporalis	40	8[a]
Occipitalis	30	6[a]
Cervical Paraspinal	20	4[a]
Trapezius	30	6[a]
Total dose: 155[b]		

[a]Indicates site number should be divided in half to distribute dose bilaterally
[b]195 U can be given if 50 U divided into 10 temporalis sites, 40 U divided into 8 occipital sites, and 50 U divided into 10 trapezius sites

Conclusions

RH disorders can be challenging to treat and may require therapy beyond oral medications. OnabotulinumtoxinA has proven efficacy for prevention of CM. Small, open-label studies have demonstrated a potential role of onabotulinumtoxinA in the treatment of RH headaches. While there is still insufficient evidence to warrant the use of onabotulinumtoxinA in RH disorders, developing standardized diagnostic criteria for RH, and conducting larger trials should offer more insight.

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Chapter 7
The Role of Interventional Procedures in Childhood and Adolescent Headaches-Peripheral Neuromodulation

Ishaq Abu-Arafeh and Vincenzo Guidetti

Introduction

Studies on the pathophysiology of migraine, over the past 20–30 years, have increased our understanding of the origin of migraine attacks, the pain network in the brain and the interaction of different neurotransmitters in different areas of the brain. Migraine attacks may consist of several phases occurring in succession with premonitory symptoms, the aura, the headache, the post-monitory symptoms and finally the resolution. Some of these phases can be brief, mild, or absent in some attacks and in some patients.

Early symptoms of migraine attacks such as premonitory symptoms and the aura were shown to take origin at a central location in the brain. However, the starting point of the headache phase is still debatable. Some researchers believe of a central origin of head pain and others believe the headache phase begins with the activation of peripheral nociceptors. There is some evidence to suggest that the origin of the input that causes the headache in migraine attacks is an abnormal peripheral sensitisation with possible role of cerebral, dural, or extracranial perivascular nociceptors [1].

Regardless of the origin of the onset of migraine attack, central as in migraine aura or peripheral with nociceptors stimulation, the trigeminocervical complex plays a pivotal role in the pathogenesis of migraine involving several neurotransmitters including calcitonin-gene related peptide (CGRP), substance P (SP), gamma-aminobuteric acid (GABA) and others.

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Activation of different points on the brain pain network and in particular the periaqueductal grey matter can modulate trigeminal and peripheral nociception [2, 3].Therefore, stimulation of accessible cranial and peripheral cervical nerves may have the potential to influence the course of the head pain, neuralgias and primary headache disorders.

In some patients, the management of chronic headache can be difficult, and the response to conventional treatment can be inadequate. Many children and adolescents with chronic headache that occurs on at least 15 days per month for at least three consecutive months find acute treatment with painkillers ineffective and preventative treatment with migraine prophylaxis and pain-modulating agents unhelpful. Some children may also suffer from added problems such as medication overuse headache and psychiatric co-morbidities such as anxiety, depression, mood swings and school refusal. The interaction between the primary headache, the co-morbidities and the overuse of medications may play an important part in the chronification of the primary headache disorders and the resistance to treatment. Therefore, several treatment modalities have been developed including cranial and peripheral nerve stimulation and nerve block and transcranial magnetic stimulation with variable success in different types of primary headache disorders and neuralgias in adult patients and to a lesser extent in children and adolescents. Patients with chronic migraine with or without medication overuse and those with trigeminal autonomic cephalalgias (mainly chronic cluster headache) were the main candidates for such treatments.

The indications for use of neuromodulation in adult patients are mainly related to the refractory nature of the headache disorders, the failure to respond to conventional treatment and in some patients due to intolerable side effects of medications. Neuro-modulation may also be a good alternative to systemic medication in patients with certain cardiovascular co-morbidities, pregnant ladies or breast-feeding mothers. In paediatric age group, treatment failure is the main indication for use of neuromodulation.

Headache disorders that have been reported to respond to treatment with peripheral nerve block or stimulation in adults are chronic cluster headache, hemicranias continua, migraine, chronic post-traumatic headache, cervicogenic headache and neuralgias. In children, the experience with nerve block is still in its early stages, and there is only limited published data on their use.

7.1 Greater Occipital Nerve Block

The greater occipital nerve (GON) arises as the medial branch of the posterior division of the second cervical nerve (C2). GON carries sensory signals from a large part of the scalp extending from the back of the neck to the vertex on the medial side. GON block is the most commonly undertaken procedure in the treatment of chronic headache disorders. Other nerves that may also be treated are the lesser occipital nerve (LON), supra trochlear (STN) and supraorbital (SO) branch of the ophthalmic branch of the trigeminal nerve.

A consensus statement on the use of peripheral nerve block reviewed the evidence for the procedures and showed that the treatment of patients with migraine, chronic daily headache, cervicogenic headache, post-traumatic headache and cranial neuralgias is mainly derived from case reports and open observational studies. Two double-blind placebo-controlled trials were cited for the evidence in relation to cluster headache [4].

Two large open observational retrospective studies reported on results of GON block in 205 children and adolescents (46 from the USA and 159 from the UK). Chronic migraine was the most common indication for the treatment in 75% of patients with significant benefit in two-thirds of the patients. Other patients had trigeminal autonomic cephalalgias and other types of headache with slightly lower but comparable response rates [5, 6].

7.1.1 Selection of Patients

Candidate for treatment with GON block are those with chronic migraine and trigeminal autonomic cephalalgias (TACs) who are most likely to benefit from the treatment. Children and adolescents should have tried and failed to respond to conventional acute and preventative treatment when in appropriate doses to age and weight for an adequate duration of time. Patients should also have made accurate recording of their symptoms on appropriate headache diaries. A full explanation of the GON block procedure and the medications to be used are given to children and their parents/guardians and been given adequate time to ask questions and understand the procedure. It should be explained to children and their parents/guardians that the treatment is unlicensed in most countries and they understand that the effects are transient. A mechanism to report adverse events should be in place.

7.1.2 Contraindications for GON Block

GON block is usually safe and free from major adverse reactions; however, treatment should not be given if the patient had previous allergic reaction to local anaesthesia. Treatment should be avoided in presence of scalp infection until treated and fully resolved. Children with bleeding disorders should be assessed, and treatment be given if deemed safe.

7.1.3 GON Block Procedure

The procedure can be done at an outpatient setting and no special preparation is needed other than making sure the child understands the procedure and agreeing to the injection. One side is usually treated at a time although occasionally bilateral

injection may be needed. The choice of the injection side depends on the side most often affected and the presence of an area of tenderness and allodynia.

Anatomical bony landmarks are usually used to determine the optimum injection site in order to allow maximum infiltration of the nerve. The optimal site is at a point located at one third the distance, on an imaginary line, from the occipital tubercle in the middle and the mastoid process on the side. Palpation of the nerve before injection may identify areas of tenderness and confirm the location.

The injection consists of a combination of steroid (methylprednisolone) and a local anaesthetic (lidocaine), but a lidocaine without steroids can also be given. The treatment is given using a fine needle (French Gauge 27–30). The plunger of the syringe should be pulled before injecting to make sure of the position of the needle is not inside a blood vessel in order to avoid accidental intravascular injection and systemic effect. The injection volume is between 1 and 2 ml and should infiltrate the area well.

7.1.4 Response to Treatment

A successful response to GON block is often noted soon after the injection and can be tested by assessing pain sensation on the scalp area innervated by the GON away from the injection site. If pain sensation is reduced, the effect may last several days and up to 4 weeks.

In a large retrospective study of 159 adolescents in the UK, the improvement in headache following GON block was defined as at least one third reduction in frequency or severity of the headache or patients' report of improvement. Sixty-eight percent of the 85 patients with chronic migraine, 59% of the 13 with new daily persistent headache (NPDH) and in 4 of the 6 patients with trigeminal autonomic cephalalgias reported improvement in their headaches after GON block. The improvement lasted for a mean of 9 weeks ±4 and minimum of 3 weeks [5].

Potential adverse events are relatively rare, but pain at injection site, infection and local or systemic allergic reactions are occasional events [6].

7.2 Greater Occipital Nerve Stimulation

Electrical peripheral nerve stimulation has been used for a long time in the treatment of pain. It can be delivered as non-invasive transcutaneous electrical impulses for accessible peripheral nerves, but invasive implantable devices may be needed for other indications including GON stimulation in the treatment of chronic migraine. The procedure has been shown to provide some relief in adult patients, but we are not aware of any similar reports in children and adolescents [6].

A meta-analysis of the published literature identified three randomised controlled trials that are amenable to analysis. Meta-analysis showed reduction of an

average of 2.59 migraine days per month in the active treatment group compared to the sham treatment group. The results need to be taken with caution as controlled trials in interventional therapies can always be difficult to assess ensure blinding despite the use of sham treatment [7].

GON stimulation is therefore a potential treatment option for children, but lack of strong evidence and the invasive nature of the treatment may make it less suitable for young children. Further research is still needed.

7.3 Trigeminal Nerve Stimulation: Supraorbital Branch

Non-invasive transcutaneous electrical stimulation of the supraorbital branch (V1) of the trigeminal nerve may provide pain relief in people with headache disorders. Evidence of its mechanism of action may be derived from positron emission tomography (PET) and functional MRI imaging showing transient metabolic and perfusion changes in the frontal lobe, particularly at the anterior cingulate cortex which may play a role in the pathogenesis of migraine and other central nervous system disorders [8].

An open clinical trial in adults with migraine showed 57% reduction in pain intensity following an hour of external electrical stimulation of trigeminal nerve [9]. In a double-blind sham-controlled trial using "cephaly" for the prevention of migraine, a significant reduction in migraine days and 26% therapeutic gain were achieved when the device was used for 20 minutes per day for 3 months. No adverse effects are associated with this treatment [10].

The role of the trigeminal nerve stimulation in cluster headache is in need of further evaluation. Similarly, studies are needed in children and adolescents in order to assess the role of trigeminal nerve stimulation in the management of chronic migraine.

7.4 Transcranial Magnetic Stimulation

Magnetic stimulation is a technique that induces an electrical current in the exposed tissue. Magnetic stimulation has been known for the past 30 years and been investigated as a diagnostic and a therapeutic tool. Transcranial magnetic stimulation (TMS) induces neuronal membrane depolarisation and an action potential which triggers an electrical current and conduction through the brain. Magnetic stimulation of the brain can influence cortical activities and may interrupt cortical spreading depression and abort the migraine aura [11].

The therapeutic value of TMS in the management of patients 18–68 years of age was assessed in a large multicentre randomised double-blind sham-controlled trial. The trial showed that early treatment of migraine with aura by TMS resulted in a significant increase in freedom from pain at 2 hours compared with sham stimula-

tion, and absence of pain was sustained 24 and 48 hours after treatment. TMS was safe and with no significant adverse effects [12].

In an open study, patient with migraine without aura were also shown to respond to treatment with TMS but to a lesser extent. No adverse effects were reported [12]. The ESPOUSE study is an open observational trial of TCS in for the prevention of mingraine in patients with migraine with and without aura. Ninety-five patients between 18 and 65 years of age were recruited and resulted in reduction of migraine days and improvement in quality of life as measured by the HIT-6 score [13].

A small observational study on children and adolescents 8–17 years of age suggested that TMS device is acceptable and the treatment is feasible, but the numbers were not large enough to draw any conclusions on efficacy [14]. Trials in children and adolescents are still needed before TMS can be recommended for children and young people.

Conclusion

Experience from research in adult patients suggest that nerve block, nerve stimulation and transcranial magnetic stimulation are safe and have the potential to offer relief from headache in children and adolescents with intractable headache disorders. Further research in children and adolescents is required to establish the efficacy of these treatment modalities.

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Chapter 8
Interventional Headache Management in The Elderly

Osman Özgür Yalın and Seden Demirci

Case

A 68-year-old woman with a 40-year history of migraine without aura unresponsive to multiple treatment was referred to the headache outpatient department. The frequency of headache had increased in recent years. She described the headache as throbbing and with associated photophobia, phonophobia, nausea, and lacrimation. The headache frequency was 20 days/month, and duration was 8–10 hours, involving mostly the left side of her head and sometimes bilateral. The intensity of pain was high (VAS:9), and her symptoms generally got worse with effort. She had a history of gastric bleeding and coronary artery disease. For acute treatment, acetylsalicylic acid and acetaminophen were ineffective. She was taking ibuprofen and triptans; drugs had been partially beneficial at first but had become ineffective later on. She had increased ibuprofen to two tablets per day and triptans to at least 3 days per week. She had no response to preventive agents including topiramate, propranolol, and valproate. Amitriptyline was effective in decreasing the frequency and severity of headache, but she could not continue to use amitriptyline due to excessive somnolence during the daytime. Neurological examination and neuroimaging were unremarkable. She had chronic migraine with medication overuse. The drugs were planned to be discontinued. As the migraine was refractory to various medical treatments, and considering the presence of adverse events and comorbid conditions, it was decided to proceed with a greater occipital nerve (GON) block. She underwent administration of GON blocks with lidocaine. After the GON block, her pain intensity and severity were dramatically decreased. Injections continued monthly for 3 months.

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Introduction

Headache is one of the most prevalent complaints in neurology practice in the elderly population. Tension-type headache, migraine, chronic daily headache, and cluster headache are the most commonly reported primary headache disorders in the elderly. It is known that 10.5% of the general population start to suffer from chronic headache (CH) after the age of 50 with some phenotypic differences. In CH men with onset after the age of 50, the average duration of active periods was 60 versus 39 days for those with onset before 50. CH onset after the age of 50 is not rare, but the late onset represents a negative prognostic factor because it requires more attention to clinical-based and management strategies, particularly in women [1–4]. Although primary headache disorders are more common than secondary ones, secondary headaches become more frequent with increasing age. Hershey et al. reported that patients older 65 years had secondary headache disorders nearly ten times more frequently than the other age groups and also that 15% of elderly patients had potentially serious and treatable secondary headache disorders, emphasizing the need to exclude these secondary causes [5]. Although most of the headache disorders' prevalence decreases with age, chronic headache disorders such as chronic tension-type headache and chronic migraine still have a significant prevalence in the elderly [6].

Headache characteristics differ between the young and elderly patients. Headache becomes more atypical in elderly adults, making it a challenge to define the patients. Sensory sensitivities including phonophobia and photophobia as well as nausea and vomiting frequency decrease; however, autonomic symptoms including rhinorrhea and bilateral tearing can increase with advancing age. Associated neck pain has also been noted in elderly patients [2, 7]. Blood vessels may become less compliant due to the arteriosclerotic aging process; hence, they neither constrict nor dilate as much as before in response to migraine attacks. Hormonal fluctuations, which can trigger migraine attacks in young females, do not occur after the menopause. The neurotransmitter-level changes with age may also decrease the prevalence of migraine [1].

Careful consideration of the diagnosis of headache is important in the elderly, and assessment of the general headache features, current medications, and comorbid medical conditions including hypertension, diabetes mellitus, cardiac diseases, and gastrointestinal tract diseases is essential for providing the correct treatment. Polypharmacy, medication overuse, and altered pharmacokinetics from impaired liver and renal functions are other concerns in the elderly [7].

The main goals of the treatment for all headache disorders are to reduce headache frequency, severity, and duration with its accompanying symptoms and to optimize the ability of patient to function in a normal manner. The first approach is to avoid potential triggers, recommending regular meals and avoidance of skipping meals, together with adequate hydration and regular sleep. The elderly group is especially sensitive to dehydration, and the clinician should ensure adequate hydration. Sleep problems are especially common in the elderly population, and good sleep habits and sleep hygiene should be ensured. As a result, the neurologist first

has to act like a general practitioner and evaluate the patient's general health including psychiatric and cognitive conditions. Secondly, a decision should be made regarding the prophylactic treatments available for headaches as pharmacotherapy or interventional management. Patients aged ≥65 years have also been rarely included in clinical studies of headache disorders, and the ability to generalize evidence-based treatments to the geriatric population is therefore limited [6].

Headache medications including Nonsteroidal antiinflammatory drugs (NSAIDs), dihydroergotamine, or triptans are frequently avoided and/or contraindicated in the elderly due to the risk of coronary artery disease, stroke, kidney injury, and gastrointestinal complications. Likewise, some effective prophylactic agents including tricyclic antidepressants; antiepileptics such as valproate, topiramate, and gabapentin; and beta blockers are used cautiously in the elderly due to their cholinergic and cardiac side effects, sedative properties, as well as the risk of cognitive impairment and osteopenia [6]. Moreover, older adults take more medications for coexisting conditions and have higher number of administrations per day, and there is an important decrease in compliance with treatment. Additionally, owing to the reduction of cognitive functions, managing polypharmacotherapy for older individuals is also more difficult, and they may occasionally take drugs at improper doses and at the wrong time [1]. Taking these risks into account and considering safer but still effective treatment for headache would be ideal for the geriatric population. Interventional methods are not related to drug interactions or any major adverse effects in this population. They may hence be a safer alternative treatment for the management of headache [6]. The two main methods of botulinum toxin treatment and peripheral nerve block treatment will be discussed below in this chapter.

8.1 Botulinum Toxin (BonT) Treatment

Botulinum toxin (BonT) is an attractive treatment modality in older patients. Its indications as a non-oral prophylactic agent have expanded in neurology practice. Clinically, BonT has been used to treat several different headache types including tension-type headache, cervicogenic headache, migraine, and chronic daily headache. Clinical studies have shown good efficacy and safety for several headache types.

The advantages of BonT injections are no need to use daily drugs, no drug–drug interactions, long duration of action, and relatively rare adverse events. There are limited data on BonT treatment for headache disorders in the elderly population. The standard methods and dosage of BonT for headache disorders will be discussed in another chapter of this book.

BonT A is effective and commonly used in older patients for preventive treatment of chronic migraine. It significantly decreases the frequency and severity of chronic migraine headache and related disability and improves the quality of life [8]. Benefit from BonT A treatment was also demonstrated in patients with or without medication overuse [9]. For Chronic tension type headache (CTTH), studies on

the role of BonT A treatment have produced various results [10]. Karadas et al. found that the severity and frequency of CTTH declined with 50 units of BonT A in the second month after the injection, and improvement was maintained at the fourth month after the injection [11]. BonT can also be used successfully for cervicogenic headache, myofascial syndromes, and fibromyalgia.

BonT A injection for trigeminal neuralgia, which is the most common neuralgic syndrome in the elderly, was reported to be effective in case series. A small number of case reports have also suggested benefit from BonT A treatment in elderly patients with hypnic headache. Dialysis headache has been reported to be treated with BonT providing the advantage of avoiding drug interactions or systemic side effects in elderly patients [12].

BonT injections are usually well tolerated in the elderly. There are no additional absolute contraindications for this population. In some patients who have age-related ptosis, the ptosis may worsen with BonT injections in the lower third of the frontal muscles. Thus, the dose and location of the injections should be modified according to the baseline ptosis of the patient. Neck weakness in the area of the cervical paraspinal muscles and swallowing difficulty are potential complications of the injections; these complications are more common in the elderly group due to the fact that elderly patients have baseline neck weakness and, frequently, diffuse muscle atrophy. Slightly adjusting the injection location to an area closer to the skull base can avoid neck weakness. Moreover, if the patients have thin neck muscles, low dosages should be used. In modification of the PREEMPT protocol, the standard protocol includs 31 points, and 5 units for each point is recommended. Neck injections could be decreased to half dosage to avoid this possible side effect. BonT should be avoided in older adults with neuromuscular disorders, in particular myasthenia gravis [13]. Antiaggregants and anticoagulants are commonly used drugs in the elderly population. Although caution is needed for the injections in these groups of patients, discontinuing the antiaggregant or anticoagulant drugs is not mandatory. Checking the prothrombin time and applying proper pressure on the injection points are recommended.

In conclusion, BonT treatment is an effective, safe, and well-tolerated treatment option in elderly patients. The long-lasting effect, lack of drug–drug interactions, and the relatively rare adverse events make it an appropriate alternative treatment for elderly patients.

8.2 Peripheral Nerve Blocks

Peripheral nerve blocks (PNB) have been used in the management of craniofacial neuralgias and various types of headaches for several decades, and the relevant experience continues to increase. It is technically easy to perform in the outpatient setting and provides quick improvement in the headaches and related symptoms in many patients [14].

In clinical practice, the most commonly used location for nerve blocks in headaches is the greater occipital nerve (GON). Other commonly performed local anes-

thetic procedures are blocks of the lesser occipital nerve, several branches of the trigeminal nerve, supra orbital nerve, supra trochlear nerve, and the auriculotemporal nerve. Local anesthetic agents with or without steroids have been used to perform the nerve block. Lidocaine and bupivacaine are the most commonly used local anesthetic agents as they are amides and are less allergenic compared to ester categories. Steroids such as triamcinolone diacetate and methylprednisolone can be added if an inflammatory component of pain is suspected. PNB frequently has long-lasting analgesic effects, provides headache relief for weeks to months in some patients, and has long-lasting pharmacokinetic features according to the anesthetic used.

PNB can be considered in older adults who fail to respond to other treatments or who have contraindications to several acute and prophylactic therapies [10]. GON block has been used effectively for the treatment of migraine, chronic migraine, cluster headache, cervicogenic headache, occipital neuralgia, and posttraumatic headache. There are several placebo-controlled studies showing positive results in the treatment of these headache disorders [6, 14, 15]. In elderly patients with cluster headache who have contraindications to using systemic corticosteroids, occipital nerve block appears to be a good option. Treatment procedures of cervicogenic headache, which is more frequent in geriatric patients owing to the fact that cervical disc degeneration becomes more common with age, may involve occipital nerve blocks or facet injections. For Tension type headache (TTH), administration of PNB may be efficient, but the current data are limited and variable [10]. PNB may also be a useful treatment option for hemicrania continua and indomethacin intolerance [15].

PNB is usually safe, effective, and well tolerated with very few and infrequent contraindications for elderly patients [14]. A strong knowledge of the anatomy of various nerves is crucial to ensure good results and to avoid adverse events. PNB could be used in similar indications for elderly patients, but the evidence for headache disorders specifically in these patients is scarce in the literature [6]. It has advantages regarding drug interactions and side effects related to pharmacological treatment. Adverse events are transient and mostly mild. Minimizing the number of injections in elderly patients and using a diluted mixture have been recommended for preventing local infections that may arise from impairment of the skin barrier [15]. For the elderly population, steroids should be used carefully especially in patients with diabetes mellitus, glaucoma, and immunosuppressive conditions. This treatment might change the blood pressure in the elderly, and hypotension, bradycardia, and vasovagal syncope are important side effects of PNB in these patients. To avoid hypotension, it has been recommended to reduce the anesthetic concentration (avoid lidocaine 5%). The procedure should be performed in the decubitus position if possible. In case of vasovagal syncope, block administration should be stopped, and the patient should be placed in the Trendelenburg position. The resting time should be longer than usual. Fluid replacement and atropine could be considered at a dose of 0.4–0.5 mg intravenously or subcutaneously if necessary. A temporary and mostly negligible increase in arterial blood pressure may also develop in elderly patients. To avoid hypertension, limiting the number of nerves to be blocked

in a single session and restricting PNB to unilateral GON injections are recommended. The compression time should be increased to 5–10 minutes in patients taking antiplatelet or anticoagulant medications [14].

In conclusion, PNB as a minimal invasive and effective option might be a safer alternative to pharmacotherapy considering the inherent challenges related to headache management in the elderly patient.

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Chapter 9
International Headache Management in Pregnancy and Lactation

Necdet Karlı and Nevra Öksüz

Introduction

Headache is one of the most prevalent complaints in a woman's reproductive period and in pregnancy and puerperium. Primary headaches including migraine, tension-type headache (TTH), and trigeminal autonomic cephalalgias (TACs) account for most of these headaches [1]. As there are also very serious secondary headaches associated with pregnancy, these need to be excluded first. The point to be considered is whether the patient has previously had headache or it is a new headache that has occurred for the first time. In the presence of a known primary headache, it should be questioned in detail whether it is different from the typical headache or has the same features as the previous headaches [2]. If a diagnostic test is necessary to exclude secondary headaches, all imaging modalities may be used. Neuroimaging risks for both mother and the fetus are associated with the threshold of exposure to ionizing radiation and magnetic fields. Both magnetic resonance imaging (MRI) and computed tomography (CT) can be used and have minimal risk. In contrast to the lactation period, contrast agents are not recommended for imaging during pregnancy because of the serious side effects [3].

Pregnancy and lactation are difficult physiological conditions for all medical disorders. The difficulty is bidirectional: the impact of the disorder on pregnancy and lactation and vice versa. Treatment is limited with the effects and side effects of the medication on the fetus, mother, the course of pregnancy, labor, and lactation. The same problems exist for headache disorders as well. Migraine and all other headache disorders, whether primary or secondary, and particularly when

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they are chronic or resistant to treatment, are an important problem both for the mother and the fetus. On the other hand, the changes in hormonal situation and lifestyle might have a great impact on the course of headaches, particularly migraine. Medications used for the treatment of primary headaches are not specific to these headache disorders. Antiepileptics (valproic acid, topiramate), antidepressants (tricyclics), beta-blockers (propranolol, metoprolol), and calcium channel blockers (verapamil) are used along with some other kinds of agents which are not specific for these headache disorders. Headache treatment can therefore become much more problematic [4].

Migraine improvement is typical for most pregnant women, but the prognosis for women who have migraine with aura or chronic migraine is less predictable. Migraine is now also an established risk factor for the development of preeclampsia. Recent data indicate the hazards of compounds containing butalbital and possibly a better safety profile for triptans than previously believed during pregnancy. An important percentage of migraineurs suffer from worsening of their migraine during pregnancy. In those whose migraine improves during pregnancy, the migraine recurs within a short time after delivery. Episodic tension-type headache (TTH) generally does not cause a major concern. However, a very small percentage of TTH sufferers may need treatment both during pregnancy and lactation. Trigeminal autonomic cephalgias (TACs) and other primary headache disorders are mostly infrequent. Non-specific medications are used to treat TACs. Therefore, difficulties similar to those in migraine treatment also exist in TAC treatment during pregnancy and lactation. Although the number of studies is limited, peripheral nerve blocks and non-invasive neurostimulation devices are procedural and emerging therapies that have promising safety profiles for pregnant women with headache disorders. Interventional treatment is relatively safe, thanks to the local anesthetics we use. On the other hand, local injection is generally accepted to be safer than systematic usage of drugs. These two factors make us feel safer when treating pregnant and nursing woman. Even though there is very limited data and few studies in pregnancy and lactation, interventional methods including botulinum toxin injections, peripheral nerve blocks, trigger point injections, and neurostimulation methods could be a wise treatment option [4, 5].

Primary Headache Disorders

9.1 Migraine and Tension-Type Headache

As pregnancy progresses, the frequency and intensity of migraine tend to improve. Less is known about tension-type headache (TTH). Although there are only a few studies that have evaluated TTH in pregnancy, it is thought that TTH improves in pregnancy but not as much as migraine.

9.1.1 Peripheral Nerve Blocks (PNBs)

PNBs have long been used in the management of various types of headaches by many clinicians. PNB is a simple, safe, and commonly used method that is effective without any serious side effects. PNBs are considered safe during pregnancy as the risk to the fetus is low because of the peripheral location and lack of central effect [6].

The most common sites for PNBs in migraine are the great occipital nerve (GON) and lesser occipital nerve (LON). Blockage of supraorbital, infraorbital, supratrochlear, and auriculotemporal nerves is also beneficial for pain in the area of distribution of these nerves. These procedures are often performed by the injection of local anesthetics with or without steroids. Although there are many studies showing the efficacy of GON blocks in migraine patients, no standard protocol has yet been established. Lidocaine or bupivacaine is usually preferred as local anesthetics at a volume of 0.1 to 10 ml, because of their amide structure (less allergenic compared to ester categories). Lidocaine is recommended over bupivacaine because of its FDA category. Methylprednisolone, dexamethasone, and triamcinolone can be used as corticosteroids at a volume of 0.1 to 2 ml. Steroids, which may not offer additional therapeutic benefits, should be avoided given the risk of accelerating fetal lung development. The agents that can be used in PNBs and TPIs during pregnancy and lactation are shown in the table below (Table 9.1).

PNBs have been found to be ineffective when studied in tension-type headache treatment. TPIs are therefore commonly recommended in tension-type headache.

Headache intensity increases in the postpartum period when compared with pregnancy. Similar to the pregnancy period, PNBs may provide another treatment option for lactating mothers. Lidocaine passes into breast milk in small amounts. In contrast to the presence of many studies on the use of PNBs in non-pregnant women, there are only a few studies in pregnant women.

Table 9.1 Agents used in interventional management

Agent	FDA pregnancy category	Lactation category	Advice of AAP
Lidocaine	B	L2	Compatible
Prilocaine	B	Not known	Not known
Bupivacaine	C	L2	Not known
Methylprednisolone	C	L2 (except for long term high dosage)	Compatible
Triamcinolone	C	L3 (not reported via milk)	Not known
Dexamethasone	C	L3 (avoid high doses)	Not known
Betamethasone	C	L3 (none reported)	Not known
Botulinum toxin	C	Not known	Not known

AAP American Academy of Pediatrics

9.1.2 Trigger Point Injections (TPIs)

TPIs have long been performed to treat headache disorders. However, the underlying pathophysiological mechanisms of TPIs have not been understood well, and their efficacy, safety, and methodology have not been studied in pregnancy yet despite the widespread use. TPIs are used for many types of headaches including episodic and chronic primary and secondary disorders with the presence of active trigger points. Similar to PNBs, lidocaine and bupivacaine can be used as local anesthetics, and methylprednisolone, dexamethasone, and triamcinolone are used as corticosteroids. Although a variety of agents, doses, and volumes of these agents have been used for different types of headache disorders by clinicians, the use of local anesthetics predominates and is consistent with our clinical experience. The most common sites for TPIs are the posterior cervical paraspinal, sternocleidomastoid, temporalis, and trapezius muscles. TPI procedures are mostly performed for chronic tension-type headache (CTTH) at a rate of 81.5%, chronic migraine (CM) at a rate of 67.7%, status migrainosus at a rate of 56.8%, and episodic tension-type headache at a rate of 41%. However, a reduction of headache intensity and allodynia was seen when GON block was added to TPI therapy in a study including episodic and chronic migraine patients.

Restrictions for both TPIs and PNBs are similar and include the inability to cooperate, local trauma, infection, allergic reaction to injection, and pregnancy. Although pregnancy is accepted as a restriction, half of the clinicians use TPIs during pregnancy but also state they would avoid injections in the first trimester [7, 8].

The management of migraine and TTH is similar. However, PNBs, and particularly GON blocks, are most commonly used in migraine as an interventional method. Conversely, TPIs are preferred in TTH. Some non-pharmacological therapies like stress management and biofeedback can be used for both conditions but are more efficacious in TTH.

Botulinum toxin A (BonT-A) treatment is widely used in cosmetic applications, spasticity, pain, and headache. BonT-A has an FDA indication for chronic migraine. The effect of BonT-A administration in pregnancy is completely unknown, and it is not recommended, given the lack of well-controlled human studies during pregnancy. Although BonT-A treatment has an FDA indication for chronic migraine, it has been used in CTTH patients with myofascial trigger points [8].

Currently, we do not have adequate information on BonT-A applications in pregnancy. There are a few reports of physicians knowingly or unknowingly injecting BonT-A to pregnant women. One reported medically terminated pregnancy, and one had a spontaneous abortion. The other 17 of 19 pregnancies completed their pregnancy periods without any complication and any fetal malformation [9].

We do not recommend injections to pregnant women until more data are available. It is also unknown if BonT-A passes into breast milk, so it would be important for nursing mothers not to receive injections until further information is gathered. The number of studies on interventional management in pregnancy and lactation is limited. Table 9.2 summarizes such studies.

Table 9.2 Interventional studies in pregnancy and lactation

First author, year, reference number	Study design	Number of participants, (number in treatment group)	Intervention	Number of PNBs	Results
Govindappagari et al. (2014) [4]	Retrospective review	13 pregnant women with migraine	PNBs (GON, auriculotemporal, supraorbital, and supratrochlear)	27 times in 13 pregnant women (single injection = 6, multiple injections = 7)	Significant reduction of mean pain score = 3.0 (±2.1 standard deviation) with no serious adverse events
Govindappagari et al. (2014) [5]	Retrospective review	11 pregnant women with headache (9 with migraine, 2 with high attack frequency headache)	PNBs (GON, auriculotemporal, supraorbital, and supratrochlear)	24 times in 11 pregnant women	In migraineurs, the average pain score before and after the procedure were 8.3 and 4.7. In high attack frequency headache, the average pain score before and after were 3.5 and 0.8
Morgan JC et al. (2006) [8]	Retrospective study	16 pregnant women (19 pregnancies) with cervical dystonia ($n = 9$), strabismus ($n = 2$), limb dystonia ($n = 1$), oromandibular dystonia ($n = 1$), spasmodic dysphonia ($n = 1$)	Botulinum toxin A	12 were injected during the first trimester, 1 during the second, 1 during the third, and 1 had more than 1 injection during three separate pregnancies	The study was not on migraine, but as a result, one pregnancy was terminated medically, and one experienced spontaneous abortion. The other 17 pregnancies went to full term
Yalın OÖ et al. (2018) [15]	Case report	1 SUNCT	Infra- and supraorbital nerve blocks	1 injection for both nerves (infra- and supraorbital)	Headache completely diminished after the first injection, and no recurrence was observed for 1 year
Kent S et al. (2016) [18]	Case series	3 cases of postdural puncture headache	Transnasal sphenopalatine ganglion block	1 injection	All three patients had significant pain relief without need for an epidural blood patch

GON great occipital nerve

9.1.3 Neurostimulation Methods

These methods are increasingly used to treat headache disorders. There are several non-invasive and invasive stimulation devices available, and there are multiple targets for neurostimulation in headache. Neurostimulation devices could be used during pregnancy in theory, but the safety of such devices in this period has not been proven yet [10].

9.2 Trigeminal Autonomic Cephalalgias (TACs)

9.2.1 Cluster Headache

Cluster headache (CH) is a strictly unilateral, severe, debilitating headache associated with autonomic features and lasting 15–180 min. It is the most frequent TAC and can be very debilitating. Treatment of CH is complicated during pregnancy and lactation due to the aforementioned problems. Greater occipital nerve block (GONB) and sphenopalatine ganglion (SPG) block are the most widely used interventional treatments in TACs and CH. There are no studies on the interventional treatment of TACs during pregnancy and lactation, and there is therefore always a question of safety and efficacy.

9.2.1.1 Greater Occipital Nerve Block

Greater occipital nerve block has been shown to be an effective treatment method in cluster headache. The efficacy varies between 60% and 80% (partial to full remission) according to the drugs used for the block, the technique, the number of blocks, and the severity and type (episodic vs. chronic) of cluster headache. The effect lasts 3–70 days. The second and third injections might increase the efficacy. There is no consensus on the composition of drugs to use for the block. However, the amount and the ingredients of the medication used are somewhat similar among the practitioners. Various amounts of corticosteroids and local anesthetic agents have been used in different ratios. The widely used corticosteroids are betamethasone, methylprednisolone, dexamethasone, and triamcinolone, and the commonly preferred local anesthetics are xylocaine, lignocaine, lidocaine, prilocaine, and bupivacaine. It has been reported that addition of corticosteroids to local anesthetics has shown significant efficacy [11]. Betamethasone and dexamethasone should be avoided due to their effect of accelerating fetal lung development [6]. One should also be very cautious when using any kind of corticosteroids during pregnancy. Side effects include local bleeding, edema, bruising, local pain, alopecia (due to corticosteroids), cutaneous atrophy (due to corticosteroids), and syncope. These are all minor side effects, mostly due to the injection itself.

9.2.1.2 Sphenopalatine Ganglion Block (SPGB)

Various techniques are used for SPGB with various efficacy rates. However, the simplest way for SPGB is the transnasal approach. Lately, intranasal catheters have been developed for easy delivery of medicaments. The traditional way is with a cotton-tipped swab. Various local anesthetics are used for SPGB as in GONB. The most widely used one is lidocaine. In our center, we use SPGB for drug-resistant episodic and chronic CH. The author prefers lidocaine 10% for cotton swab and 2–3 ml lidocaine 10% for direct injection through the catheter.

9.2.1.3 Trigger Point Injection

Trigger point injection (TPI) is beneficial when accompanied by drug treatment or other interventional treatments in chronic tension-type headache and cluster headache. The safety profile of TPI in pregnant and nursing patients is similar to nerve blocks as mentioned before. There is one study reporting a beneficial effect of TPI in episodic and chronic CH besides preventive therapy [12]. Injections can be repeated according to the pain response. A fixed schedule is not recommended because of the variable response to TPI among patients and different headache types. In our headache center, we prefer lidocaine for TPI in pregnant patients. We use a total of 2–4 ml of 2% lidocaine per muscle and 0.5 cc per injection site.

9.2.2 Paroxysmal Hemicrania

Paroxysmal hemicrania (PH) is a severe headache which is very similar to CH. It lasts 2–30 min and is shorter than CH with a higher frequency. It is an indomethacin-responsive headache disorder. Indomethacin is an FDA category C prior to 30-week gestation and FDA category D starting at 30-week gestation. It should therefore be avoided during pregnancy. Studies on interventional treatment in PH are very limited in number in the non-pregnant population and are not available in pregnancy and lactation. Antonaci et al. reported a negative outcome in chronic PH with lidocaine GONB [13]. Despite the lack of evidence, many practitioners use GONB in PH.

9.2.3 Hemicrania Continua

Hemicrania continua (HC) is another indomethacin-responsive headache that is strictly unilateral, severe, associated with autonomic symptoms, and present for more than 3 months. Besides GONB, supratrochlear nerve (STN), supraorbital nerve (SON), and lesser occipital nerve (LON) blocks have been reported to be effective in HC [14]. There is no data on pregnancy and lactation yet.

9.2.4 *Short-Lasting Unilateral Neuralgiform Headache (SUNCT and SUNA)*

These are extremely rare headaches, and GONB appears to be effective in SUNCT and SUNA. Its effectiveness seems to be lower than in any other TAC [15].

9.3 Secondary Headache Disorders

Interventional treatment modalities are also used in secondary headaches. Cervicogenic headache, post-lumbar puncture headache, medication overuse headache (MOH), and head and face neuralgias may all benefit from interventional therapies. GONB is the most preferred procedure in secondary headaches, particularly cervicogenic headache.

9.3.1 *Cervicogenic Headache*

Cervicogenic headache (CEH) is caused by the cervical spine and its bony, disc, and soft tissue components. It is a side-locked headache that can sometimes be associated with nausea/vomiting, photophobia, and phonophobia and is mostly worsened by certain head and neck postures. According to the existing literature, pregnancy does not have an influence on CEH [16]. There are no data on the treatment of CEH during pregnancy and lactation. GONB, GONB with LONB, and C2/C3 nerve blocks have been effective in CEH in a number of studies [16]. Lidocaine and corticosteroids have been proven to be effective in the treatment of cervicogenic headache when injected together. GONB and LONB can be performed together using the same methodology as described before. Betamethasone and dexamethasone should be avoided because of early fetal lung development. Other corticosteroids should also be used cautiously during pregnancy.

9.3.2 *Medication Overuse Headache*

There are limited data about the efficacy of interventional therapies in medication overuse headache (MOH). GONB has been proven to be effective for triptan overuse headache [17]. Although all symptomatic medications should be stopped during pregnancy, in real-life practice, we encounter some pregnant MOH patients. Besides discontinuation of the symptomatic drug, GONB can be used as an adjunctive treatment to relieve the pain for the first few days.

9.3.3 Headaches Attributed to Abnormal CSF Pressure: Postdural Puncture Headache

Lumbar puncture (LP) is used for diagnosis and treatment in a number of diseases and might result in postdural puncture headache (PDPH). Epidural anesthesia for cesarean section and labor are other common reasons of PDPH. If conservative treatments fail, epidural blood patch (BP) and GONB are effective treatments in relieving PDPH. Transnasal SPGB is an alternative and safer way to relieve PDPH when compared to BP [18].

9.3.4 Intracranial Hypo- and Hypertension

Intracranial hypotension might be caused by dural puncture, trauma, or spontaneous leakage of CSF. If conservative treatments fail, BP is the treatment of choice. Idiopathic intracranial hypertension (IIH) does not pose any obstetric risk in pregnant women (Evans). In case of idiopathic intracranial hypertension, LP may be needed to lower the intracranial pressure. LP is a safe method and can be performed any time during pregnancy. After diagnosing IIH and failure of the conservative treatments, LP is performed, and a total of 30–50 ml of CSF is collected in order to lower the intracranial pressure [19].

9.3.5 Painful Lesions of the Cranial Nerves and Other Facial Pain

Previously described GONB, LONB, and SPGB should be considered cautiously in pregnant women suffering from occipital and trigeminal and other types of neuralgias.

Conclusions

PNBs and TPIs seem to be effective and safe, particularly for migraine and TOCs, during pregnancy and lactation. However, adequate data are still lacking. The drug of choice and dosages vary between headache centers and physicians. One should avoid headache treatment as much as possible during pregnancy and lactation unless it is a must. We believe that PNBs and TPIs should be considered alone or in combination when treatment is needed.

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Chapter 10
Efficacy of Trigger Point Injections and Dry Needling

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Introduction

Myofascial pain is a regional musculoskeletal pain affecting the head, neck, and face by a trigger point (TrP) in a taut band of particular muscle with its characteristic referral pattern. These taut bands may be active or latent. An active TrP is considered to elicit spontaneous pain symptoms, and its local and referred pain is responsible for the complaints of patients. A latent TrP has clinical features similar to an active TrP, namely, motor dysfunction and/or autonomic responses, and will persist as a taut band without spontaneous pain [1, 2].

Muscle sensitivity is one of the common symptoms of headache disorders. Pain irradiation from trigger points located in the trapezius, posterior neck muscles (splenius cervicis, splenius capitis, semispinalis cervicis, semispinalis capitis, levator scapulae, and suboccipital muscles), temporalis, and sternocleidomastoid muscles can be manifested by headache [3]. Headache and myofascial pain might coexist and share common neural circuits. Treatment of TrP may reduce nociception and headache pain severity and frequency. Although the potential effectiveness of trigger point injections (TrPIs) in different types of headache disorders has not been fully clarified, TrPI is one of the most effective methods among the various treatment modalities in the treatment of myofascial pain. For the management of migraine and chronic tension-type headache, TrPIs to the tender areas with either local anesthetics or saline solution were reported to alleviate the pain and contribute to patients' improvement [4, 5].

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Understanding the relationship between myofascial pain and headache disorders is crucial for a successful treatment of either condition, and it should also be kept in mind that one can perpetuate the other.

10.1 Etiology and Pathogenesis

Although the pathophysiological mechanisms underlying TrP formation are poorly understood, muscle overuse, injured muscle fibers, mechanical overload, or psychological stress may be associated with the formation of TrPs. It has been proposed that TrPs are formed as a result of abnormal depolarization of motor endplates leading to excessive release of acetylcholine in the neuromuscular junction [6]. The presence of muscle fiber tension leads to endogenous shortening, loss of oxygen supply, and increased metabolic activity, and such oxygen requirements on local tissues are associated with autonomic and sensory reflex arcs. Higher levels of algogenic and proinflammatory substances such as substance P, calcitonin gene-related peptide, bradykinin, and lower pH levels activating the ion channels have been detected in active TrPs which are sustained by peripheral sensitization [7]. TrPs might cause peripheral sensitization of muscle nociceptors and might be responsible for the perception of the intensity of pain by sensitizing the trigeminal caudal nucleus, which receives afferent signals from pericranial muscles [8]. Peripheral sensitization may lead to long-term electrophysiological changes in spinal dorsal horn neurons and supraspinal sites (such as the thalamus and cerebral cortex), resulting in central sensitization. Nociceptive inputs from the referred pain to the central nervous system are also related to central sensitization. It has recently been demonstrated that the initial mechanism in the development of tension-type headache (TTH) is sensitization of the central pathways due to prolonged nociceptive inputs that arise from the pericranial muscles [9]. Various pain-inducing substances such as bradykinin, calcitonin gene-related peptide, substance P, tumor necrosis factor alpha, interleukin 1 beta, serotonin, and norepinephrine have been shown in high concentrations in the TrPs located in pericranial myofascial tissues. It should be noted that these mediators seem to be responsible for the pathogenesis of TTH.

10.2 Clinical Characteristics

Studies exploring the prevalence, incidence, and localization of myofascial pain and TrPs in patients with headache disorders are still lacking. Localization of the TrPs varies in patients with headache disorders; however, the back of the neck muscles, temporalis, and sternocleidomastoid muscles are locations where TrPs are generally found. Bilateral, increased stiffness on palpation of the neck and shoulder muscles has been demonstrated in patients with chronic TTH, and is thought to be referred pain originating from TrPs [10].

Ferraci et al. noted head and neck TrPs among women with episodic or chronic migraine [11]. Their results showed that both episodic and chronic migraineurs had a similar number of TrPs, and migraine-related disability scores did not differ among both groups [11]. Fernández-de-las-Peñas et al. reported that patients with unilateral migraine had a unilateral distribution of active TrPs which were located ipsilateral (symptomatic side) to the migraine attacks [12].

10.3 Physical Exam and Diagnosis

Neurological examination and manual TrP examination of the back and head muscles should be performed in patients with chronic headache. Patients with active and/or latent TrPs may report discomfort from pressure. In addition, pain evoked from TrPs has similar descriptions to TrP-referred pain sensations such as a pain that is throbbing, sharp, shooting, or aching in character. Referred pain from TrPs located in the back and head muscles can be elicited by palpating the tender sites with enough pressure until the nail bed turns white. The examiner should press or squeeze the posterior cervical, head, and shoulder muscle sites, trying to evaluate all aspects of the patient's pain. Due to the lack of imaging methods that allow objective inspection of TrPs, diagnosis is only based on the palpation of the muscles.

10.4 Treatment

There has previously been no consistent approach proposed for the treatment of patients with myofascial pain and headache. Treatment options of TrPs vary in terms of medications and technique use; furthermore, there is lack of common consent in the literature, mainly with regard to headache disorders. Local anesthetics (e.g. bupivacaine, procaine, lidocaine), saline (NaCl 0.9%), corticosteroids, and botulinum toxin may be used in various concentrations for TrPI.

In a recent study of Blumenfeld et al., the use of TrPIs in headache treatment among American Headache Society members was evaluated. According to their findings, 75.3% of the headache practitioners in the USA combine TrPIs as a part of their headache management. Chronic TTH (81.5%) followed by chronic migraine (67.7%) were the most common headache disorders in which TrPIs were performed by US headache specialists [13].

Local lidocaine injections into TrPs located in the head muscles have been shown to be a possible valid treatment option for episodic TTH [5]. In a randomized, double-blind, placebo-controlled study of Karadas et al., the effects of TrPIs using lidocaine and saline on the severity and frequency of headache in patients with chronic TTH were compared. After repetitive 3 injection cycles 3 days apart, the number of headache days, headache intensity, number of analgesics used, and

comorbid psychiatric symptoms such as depression and anxiety were found to be significantly reduced among patients injected lidocaine [14].

In a study of Calendre et al., the effectiveness of TrPI was evaluated among patients with episodic and chronic cluster headache. Patients were injected with mepivacaine during an attack to assess TrPIs in both acute and preventive treatment. Eighty-seven percent of patients with chronic cluster headache showed significant improvement with TrPIs when combined with prophylactic drug therapy [15]. Despite the small number of individuals represented in this study, the results are also promising for cluster headache patients.

The effects of blocking greater occipital nerves with TrPI on pain severity and allodynia among episodic and chronic migraineurs were examined by Ashkenazi and Young. The authors reported that both headache severity and allodynia scores were reduced in the trigeminal and cervical dermatomes in all episodic and chronic migraine patients [16]. Although TrPI for pregnant individuals with low back pain has been reported as a valuable option, using TrPIs for headache disorders in pregnancy has not been explored yet.

Studies for trigger point injections in the treatment of headache disorders are reviewed in Table 10.1.

Table 10.1 Studies for trigger point injections in the treatment of headache disorders

Type of headache	Study design	Number of patients	Intervention	Results	Reference
Episodic migraine Chronic migraine (including medication overuse)	Prospective study	52	Ropivacaine	Headache improved after 12 weeks	García-Leiva et al.
Episodic tension-type headache	Randomized, double-blind, placebo-controlled study	108	Lidocaine vs. normal saline	Headache days and VAS scores decreased	Karadaş et al.
Chronic tension-type headache	Randomized, double-blind, placebo-controlled study	48	Lidocaine vs. normal saline	Headache days and VAS scores decreased	Karadaş et al.
Episodic and chronic cluster headache	Case series	12	Mepivacaine	Reduction of attack frequency	Calandre et al.
Episodic and chronic migraine	Prospective, non-controlled	19	A single GON block using lidocaine and triamcinolone and TrPIs using lidocaine	A significant decrease in head pain in 90% of subjects	Ashkenazi et al.

GON great occipital nerve

10.5 Procedure

Before starting a TrPI, the patient should sit on a chair or be in a recumbent position to avoid syncope (lightheadedness or fainting). In order to prepare the injection site to minimize the risk of infection, the skin should be cleansed with ethyl alcohol and iodophors. In our clinical practice, we use and recommend 22–25-gauge (1.5–2.5 inch) needles, depending on the location of the TrP and body habitus. Deeper muscles may require a 21- or 22-gauge (2 or 2.5 inch) needles. When the TrP is identified, it should be stabilized with the clinician's finger or thumb to prevent the TrP from rolling or sliding away from an advancing needle. After inserting the needle into the TrP, the needle should be slowly advanced at a 30-degree angle. Gentle aspiration before the injection is essential to make sure that the needle tip is not located in a blood vessel. Subsequently, the needle can be withdrawn slightly and then redirected to the periphery of the TrP, reinjecting multiple times superiorly, inferiorly, laterally, and medially, therefore repeating the needling and injection process in each direction for a total amount of local anesthetics such as 2–4 mL of 2% lidocaine or 0.5% of bupivacaine. Injections might be performed monthly or in shorter terms. Individualization with regard to the interval between reinjection is beneficial for controlling chronic cases. The dry needling technique for TrP treatment involves a 27-gauge hypodermic needle or acupuncture needle and placing the needle into and around the TrP without any solution. Although the mechanisms behind those procedures are not clear, the needle itself may cause mechanical disruption of muscle tension and aid in the attempt to relieve pain.

Figures 10.1 and 10.2 illustrate the common trigger point injection sites.

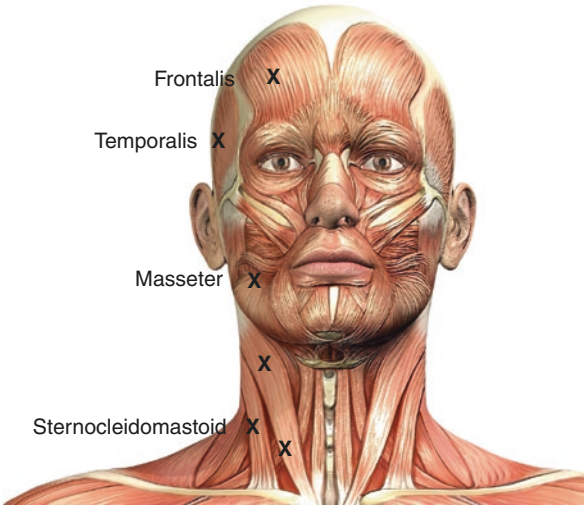

Fig. 10.1 Common trigger point injection sites

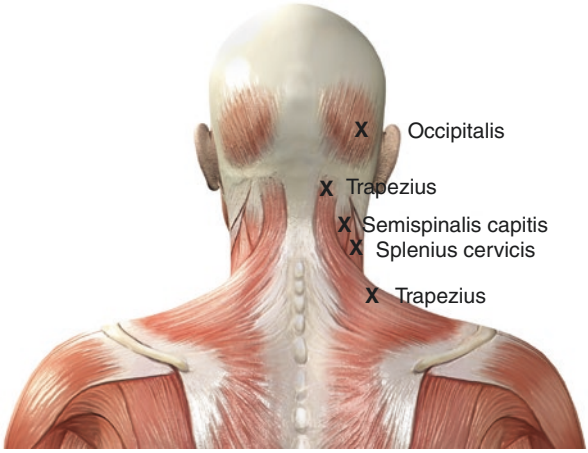

Fig. 10.2 Common trigger point injection sites

10.6 Contraindications and Precautions

Contraindications for TrPI can be listed as a local or systemic infection, an open wound around the injection site, and a medical history of allergic reactions. We highly recommend that patients should be assessed for antiplatelet or anticoagulant agents' use and checked for the international normalized ratio (INR) (if taking warfarin) before the procedure to avoid unanticipated hemorrhage. Unexpected bleeding may also be lessened by aspirating the syringe before injecting the solution to avoid vascular structures.

Lidocaine has a FDA Category B classification, and it would thus be preferred over bupivacaine, which is FDA Category C, as an anesthetic for pregnant patients with TrPs. Iatrogenic pneumothorax has also been reported after TrPIs in the cervicothoracic musculature, in particular needling to the upper trapezius. In patients with unclear body habitus, electromyographic or ultrasound-guided injections may be preferred.

Local anesthetics can cause severe hemodynamic compromise such as hypotension or bradycardia up to a cardiac and respiratory arrest. In order to reduce toxicity, limiting the doses to 300 mg of lidocaine and 175 mg of bupivacaine in a single injection cycle is recommended. As a precaution against direct damage to nerve fibers, performing straight needle insertions and avoiding lateral movements are recommended. Nerve injury may produce the following symptoms: new onset burning and shooting pain, numbness, and paresthesia.

Conclusion

We recommend that when evaluating a patient with headache disorder, TrPs that contribute to the pain symptoms should also be assessed. The key to TrPI treatment of headache disorders is the determining of the areas on the head and neck muscles

from which the patient's pain originates. As TrPs may show a different distribution in each patient, it is essential to locate the TrPs and then use needle insertion at the TrP area. When preparing for treatment strategies, patient selection, the anatomic knowledge, and technical experience should be considered. Unfortunately, no standardized treatment protocols and long-term follow-up studies exist. Evidence-based guidelines for the use of TrPIs in various headache disorders are needed. Further placebo-controlled studies with different doses and concentrations of injections are required for optimal treatment of TrPs in patients with headache. In clinical practice, dry needling and local anesthetic injections could be preferred as a technique of first choice considering the low cost, and botulinum toxin should be reserved for treatment-resistant patients.

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Chapter 11
Potential Role of Acupuncture

Didem Akçalı and Cemal Çevik

Introduction

Acupuncture is penetration of the skin for prevention and treatment of disease and has been used for 4000 years. It integrates the internal and external environment of humans to promote harmony. Acupuncture is an ancient treatment with the first book on the subject written in 200 BC as the "Yellow Emperor's Classic of Internal Medicine" [1]. Recent scientific studies support the notion that acupuncture is an effective intervention for headache, migraine, and back and joint pain [1–3].

Acupuncture-related text states that Chi is the life force of existence. Original Chi is hereditary, Grain Chi is derived from food, and Natural Air Chi comes from air by breathing. There are 12 meridians (channels) and 8 extra channels for this energy to travel in the body. An energetic web is formed among the connections between the meridians through acupuncture points.

Chi embraces the two concepts of Yang and Yin, which are opposite to each other; the balance of Yang and Yin is crucial for healthy living. Acupuncture is at first a protective modality to achieve healthy and balanced living. Deficiency of chi, stagnation of chi, or rebellion causes imbalances of Yang and Yin. Yang symbolizes energy and motion, represented by the sun, masculinity, and power. Yin stands for femininity, shade, damp, and potential [2].

In traditional Chinese medicine (TCM), Yin and Yang are symbolized by five elements: fire, earth, water, metal, and wood. Organs are paired as one Yang and one Yin organ; the stomach, intestines, bladder, and gall bladder are Yang organs, while the heart, lung, liver, kidney, and spleen are Yin organs. Stagnation, excess, or rebellion

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distorts Chi flow between the meridians [1, 2]. In general, a Yang origin is more likely in acute pathologies, and chronic diseases are caused by Yin origin. There are vast amounts of connective tissue and nerve endings among the meridians. Acupuncture has been demonstrated to exert regional and quantifiable effects on brain structures associated with pain and also stimulate gene expression of neurotransmitters [3].

Chi imbalance emerging from stagnations and deficiencies causes lethargy, fatigue, depression, and extremity pain and is treated by the dispersion of Chi by tonification or stimulation. Distortion of Chi because of rebellious Chi results in vomiting or mania caused by Chi flow in the wrong direction [1].

Acupuncture treatment can be performed in various ways such as manual acupuncture, electroacupuncture, laser acupuncture, and auricular therapy. Sterile disposable needles and appropriate equipment must be utilized for acupuncture. Electroacupuncture using 2–10 Hz causes increased endorphine release, and 100 Hz high-frequency stimulation increases dynorphin release. Acupuncture administration increases brain blood flow and regulates the activity of the limbic system and "pain matrix" [4]. The auricular (ear) acupuncture is a microsystem acupuncture consisting of neural mechanisms and innervation. Auricular branch of the vagus nerve, the auriculotemporal branch of the trigeminal nerve, and the great auricular nerve from the second and third cervical roots innervate the auricle, and the mechanism can be explained by the trigeminovascular pathway. There are more than 200 auricular acupoints, and 43 of them have been proven to be therapeutic by the World Health Organization [5]. These points are detected by either electronic stimulators, a vascular autonomic sign, or the pressure test. Permanent auricular needles may be preferred for a prolonged effect. These needles come out spontaneously in time. It is important to warn the patients not to enter an magnetic resonance imaging (MRI) suite with permanent acupuncture needles [6].

In neurophysiological terms, acupuncture activates structures related to the control of pain perception such as prefrontal cortex, cingulate cortex, brainstem, pituitary gland, arcuate nucleus of the hypothalamus, and the periaqueductal gray matter. Serotonergic projections from the raphe nucleus and descending projections to the spinal cord also contribute to analgesia and an anti-inflammatory effect [1].

Many acupuncturists prefer different sets of acupuncture points for the same disease, and these can still be effective. The result is heterogeneous clinical studies that make conducting randomized prospective studies more difficult [7]. Acupuncture is effective for the treatment of chronic pain. Needling at correct acupuncture point locations is important, but sham acupuncture is applied in the control group, and the effect cannot be explained by only a placebo effect [8, 9]. The adenosine receptor reversibly interferes with efficacy of acupuncture-induced analgesia in the presence of caffeine. Local anesthetics also block the acupuncture effect.

11.1 Acupuncture Treatment for Headaches

Headache patients make up 10% of patients applying for acupuncture. Acupuncture is an effective method in migraine and tension-type headache [1]. The mechanism of acupuncture is considered separately for local effects, somatoautonomic reflex,

and systemic effects through neurotransmitters. Acupuncture may interfere with substance P and met-enkephalin for pain modulation in the nociceptive pathway. The mechanism of headache treatment with acupuncture may be via the trigeminal nucleus and the spinal dorsal horn [10].

Acupuncture was administered to volunteer migraine patients, and blood nitric oxide (NO) levels were studied. After the fifth acupuncture session, the NO level decreased by 30% compared to pretreatment in the migraine group. Acupuncture treatment is thought to be effective via serum NO levels [11].

The acupuncture needle causes local trauma where blood flow increases and vasodilation occurs, which is called the axon reflex. Hyperemia around the needle is due to the axon reflex. Stimulation of acupoints on extremities results in the somato-autonomic reflex and a more potent effect [9].

The primovascular system (PVS) binds the membrane, cell, and nucleus together. This connection is different from nerve innervation but related to fascia. PVS is activated when the acupuncture needle is inserted. The needle grasp phenomenon ("deqi sensation") is related to small- and large-diameter fibers. Following trauma, microinflammation and fascia activation cause release of neurochemical mediators, and the analgesic mechanism emerges [10, 12].

When the nerve is blocked or lesioned or the amount of neurotransmitters is scarce, pain relief cannot be ensured by acupuncture. This is important to prove involvement of nerves with acupoints. Some nerves and acupoints coincide anatomically. The median nerve overlies the P6 acupoint, and the deep peroneal nerve is in proximity to ST 44 [13]. Acupuncture points usually coincide with the peripheral nerve course, as well as trigger points and sometimes botulinum toxin injection sites. Acupuncture, trigger point injections, peripheral nerve blocks, and botulinum toxin injections use many common points to treat pain through different origins activating the same mechanism. Most of the muscle trigger points have been shown to correspond with acupoints [12]. Acupuncture points that are important in treating headache are listed in Table 11.1. Coinciding trigger point and botulinum toxin injections are given in Table 11.1 and Fig. 11.1. Onabotulinum toxin A blocks the release of sensory stimuli by inhibiting acetylcholine at the neuromuscular junction. Injection points at the occipitofrontalis, corrugator supercilii, temporalis, and trapezius muscles coincide with acupoints for headache such as Yintang (EX-HN3), Taiyang (EX-HN5), Baihui (GV 20), and GB 8, GB 20, and BL 10 [14] (Fig. 11.1, Table 11.1).

Acupuncture points may be selected according to the pathology (wind, damp, hot, cold, or dry) and the symptoms concomitant with headache such as nausea, vomiting, visual disturbances, cough, and sleep pathologies. Yuan points are usually preferred. Daily sessions for 5 days are needed in severe pain. This is followed by 10 sessions performed once every 2 days. If the headache is mild, ten treatments twice a day are needed. Treatment is selected according to the site of the headache, according to the related meridian.

Temporal throbbing headache implies excessive Yang and deficiency of Yin energy. Tonification of Yin acupoints and drainage of excessive Yang from head acupoints are therefore beneficial. Acupuncture vs. sham acupuncture has resulted in 44.3% vs. 21.4% decrease in headache in one study [15]. There are three types of headaches according to acupuncture knowledge:

Table 11.1 Acupuncture points for headache and common points with trigger point and botulinum toxin injection

Acupuncture meridian	Acupoints	Region	Effect	Common point
Large intestine (LI)	LI 4 (Hegu)	Hand	Analgesic - headache	–
Stomach (ST)	ST 36 (Zusanli)	Leg	Analgesic - frontal headache	–
	ST 3	Face	Trigeminal neuralgia, facial paralysis	–
	ST 8	Head	Lateralized headache	–
	ST 44	Foot	Analgesic point, frontal headache, toothache	–
Gall bladder (GB)	GB 1	Head	Frontal and occipital headache, ocular pain	–
	GB 8	Head	Headache, migraine, vertigo, vomiting	BTI
	GB 14	Head	Headache, eye pain, forehead pain	TPI
	GB 20	Head	Headache, eye pain	TPI BTI
	GB 21	Shoulder	Headache, rigidity of neck	BTI TPI
	GB 34, GB 41, 43	Leg (GB 34), Foot	Headache, shoulder pain	–
	GB 44	Foot	Lateralized headache	–
Bladder (BL)	BL 2	Head	Migraine, frontal headache, supraorbital pain, swelling and pain of the eye	BTI TPI
	BL 4	Head	Headache, nasal congestion	–
	BL 7	Head	Headache, neck pain	–
	BL 10	Head	Headache, migraine Dizziness, neck stiffness	BTI TPI
	BL 62	Foot	Headache	–
	BL 64, 66	Foot	Neck stiffness	
Extrameridian (EX)	Yintang (EX-HN3)	Head	Headache	–
	Taiyang (EX-HN5)	Head	Headache	TPI
Governing vessel (GV)	Baihui (GV 20)	Head	Headache	–
Triple warmer (TW)	TW 5	Arm	Temporal headache	–
	TW 9, TW 10	Arm	Migraine	
	TW 12	Arm	Headache, neck rigidity	
	TW 15	Shoulder	Shoulder pain, acute neck rigidity	
	TW 23	Face	Migraine	TPI

Table 11.1 (continued)

Acupuncture meridian	Acupoints	Region	Effect	Common point
Small intestine (SI)	SI 3, 4	Hand	Pain and rigidity of the head and neck	–
Liver (LR)	LR 3	Foot	Headache	–
Lung (LU)	LU 7	Hand	Migraine, neck stiffness	–

TPI trigger point injection, *BTI* botulinum toxin injection

Fig. 11.1 Sites of injection coinciding with botulinum toxin injection at the occipitofrontalis, corrugator supercilii, temporalis, and trapezius muscles [14]

1. *Yang Ming-type headache*: This type of headache is on the face, often with abdominal pain. There may be some gastrointestinal disturbances. Tension- type headache and sinusitis with rhinorrhea are some examples. These headaches are related to the stomach (ST)-large intestine (LI) meridian pair. Treatment involves the following acupoints: ST 44, LI 4, ST 3, and ST 8.
2. *Shao Yang-type headache*: This headache is typically on the lateral parts of the head, either unilateral or bilateral. Arm, neck, or shoulder pain is also sometimes present. Nausea and vomiting may occur. Examples are migraine and cluster headaches. They are related to gall bladder (GB) and Triple warmer (TW, Sanjiao (SJ)) meridians. Treatment points are GB 1, GB 41 or GB 43, TW 3, or TW 5.
3. *Tai Yang-type headache*: The headache starts from the back of the head and radiates to the eyebrows. Neck pain and urinary disorders may also be present. The bladder (BL) and small intestine (SI) meridians are affected. Treatment points are BL 2, BL 10, BL 64, SI 4, or SI 3 [11, 15].

11.1.1 Migraine

Symptoms associated with migraine represent the disharmony of Chi. Episodic headache is usually in consequence of superficial disruptions of Yang meridians. Acute migraine attack represents a superficial disruption of Chi. Chronic headache becomes disseminated and Yin meridians are also involved. Acupuncture stimulates the nervous system and causes neuromodulation and production of endorphins, serotonin, and gamma-aminobutyric acid (GABA). The effects of acupuncture are demonstrable in the brain by functional magnetic resonance imaging (fMRI) studies. Grabbing of the needle by acupuncture point needling is considered a reaction to neuromuscular trauma. This feeling is considered the Chi flow. The feeling of twirling the needle at the puncture site along the meridian is called DeChi sensation, essential for effect. Needles are left in place for 20–30 minutes [1].

Acupuncture is effective in treating migraine attacks and reducing the frequency of headaches. Acupuncture can be used for prophylactic migraine treatment of inadequately controlled migraine attacks, with fewer side effects [6, 16] (Table 11.1).

When migraine attacks are frequent and intractable, prophylactic treatment is advocated. These treatments cause significant side effects in some patients, and the patients may not agree to use them. Acupuncture is a very effective and long-lasting option for these patients. A Cochrane Database Systematic Review of the effectiveness of acupuncture for migraine prophylaxis was published in 2016 [9, 16].

11.1.2 Cluster Headache

Cluster headache is different from other primary headaches regarding its response to acupuncture. The acupoints used for migraine are not effective in cluster headache. Cluster headache is in fact a trigeminal autonomic cephalalgia with unilateral severe pain that is especially periorbital or temporal within the trigeminal distribution. In one study, an episodic cluster headache similar to ophthalmic branch involvement of trigeminal neuralgia was evaluated. Pain was in the right periorbital and temporal region, and referred to the upper right dental quadrant. Acupuncture was performed to stimulate trigeminal nerve branches on the contralateral side which induces release of serotonin, norepinephrine, and endogenous opioids to the cerebrospinal fluid (CSF) and bloodstream. Acupoint ST 2 was used for the infraorbital branch and BL 2 and Yuyao (EX-HN2) for the supraorbital and supratrochlear nerves. Taiyang (EX-HN5) on the temporalis muscle over the temple and cheek was used for the temporal branch of the zygomatic nerve with success. LI 4 and/or LR 3 (Liver meridian) were added as distant points. The cluster headache ceased after first acupuncture session. After 6 weeks of treatment, no attacks developed for 8 months [17].

11.1.3 Tension-Type Headache

Acupuncture should be considered for treating episodic and chronic tension-type headache. Tender points were treated using ST 8, GB 8, GB 14, GB 20, GB 21, BL 10, Yintang (EX-HN3), and Taiyang (EX-HN5) [17–19]. Ten sessions over a 6-week period treatment are effective whether the headache is due to psychological or physiological effects using various needle placements and needle depths [18]. Acupuncture added to routine care for the treatment of acute headaches reduces the frequency of headaches in the short term [9]. Acupuncture is effective in episodic or chronic tension-type headaches [19].

Acupuncture may suppress the nociceptive trigeminal nucleus caudalis and spinal dorsal horn neurons via modulation of the release of neuropeptides and neurotransmitters [2, 3]. The main acupuncture studies for headache are presented in Table 11.2 [16, 19–21].

According to some studies, patients are being treated with acupuncture even when needle placement may not be accurate. There is a better treatment effect compared to pharmacological treatment only when acupuncture is performed together with pharmacological treatment [7].

The acupuncture points used were TE 5, GB 34, GB 40, TE 20, and GB 20 bilaterally. This treatment was significantly more effective than sham acupuncture in reducing the pain of acute migraine for 2 and 4 hours at each time point [7].

In a few studies, the needle-contact test was used with an algometer to find the most painful area. The acupuncture point was contacted with the needle for 10 s, and the point was needled if there was pain reduction. Semipermeable needles were

Table 11.2 Examples of studies demonstrating effective acupuncture treatment in headache

Headache type	Comment	Literature
Tension-type headache	Level of recommendation C Valuable option	Bendtsen L et al. Eur J Neurol. 2010
	Slightly better effect from acupuncture than from sham	Linde K, et al. Cochrane Database Syst Rev 2009
Migraine	Effective in relieving pain and preventing migraine relapse or aggravation	Li Y et al. Headache. 2009
Prophylactic for migraine	Acupuncture can prevent high pain intensity and frequency as well as disability	Lardon A, et al. Cephalalgia. 2017
	Effective and safe treatment for short-term relief of frequent migraine	Wang Y, et al. Evid Based Complement Alternat Med. 2015
	May be at least as effective as treatment with prophylactic drugs	Linde K, et al. Cochrane Database Syst Rev. 2016
	Reduces symptoms and medication use, both short term and long term, as an adjuvant	Frantisek M, et al. Neuropsychiatr Dis Treat. 2018

then applied. This approach provided acute pain reduction. The most tender points on the ipsilateral anterointernal part of the antitragus, the anterior part of the lobe, and the upper auricular concha were found. The analgesic effect lasted at least 24 hours [6].

11.2 Side Effects

Side effects of acupuncture are bruising, rare vasovagal reactions, sleepiness, increased symptoms requiring treatment, and nausea. Acupuncture is performed with the patient lying to avoid vasovagal attacks. Bleeding is rare even in patients on anticoagulants [1, 20].

Conclusions

Headache and migraine, which are a burden for people and the health system, can be treated effectively and for the long term with acupuncture. Acupuncture provides us with the opportunity to evaluate and treat the patient in a comprehensive way, especially for patients with contraindications or side effects during treatment or a refractory headache. Well-designed new studies are needed for more information about the analgesic mechanism of acupuncture. We hope future medicine will benefit from acupuncture along with others for individual well-being.

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Chapter 12
The Role of Radiofrequency Thermocoagulation

Levent Ertuğrul Inan and Nurten Inan

Introduction

Radiofrequency thermocoagulation (RF) may be a treatment option in headache, especially for intractable cases not responding to medical choices. Cluster headache is a challenging disorder causing extreme suffering for the patient. RF will be a good alternative for such patients. Trigeminal neuralgia, postherpetic neuralgia, occipital neuralgia, cervicogenic headache, and hemicrania continua patients may also benefit from this procedure.

In this chapter, we will focus on RF mechanisms, equipment, and usage in headache cases.

12.1 The Mechanism and Action of Radiofrequency Thermocoagulation (RF) Systems

The RF generator produces a radiofrequency voltage through its output terminals, which are connected to active and reference electrodes (1). While the active electrode generates a heat lesion, the reference electrode provides a return pathway for the RF current. The RF lesion generator has the following functions: continuous impedance measurement; nerve stimulation; monitoring of voltage, temperature, current, and wattage during the procedure; and delivering a pulsed and continuous radiofrequency (Fig. 12.1).

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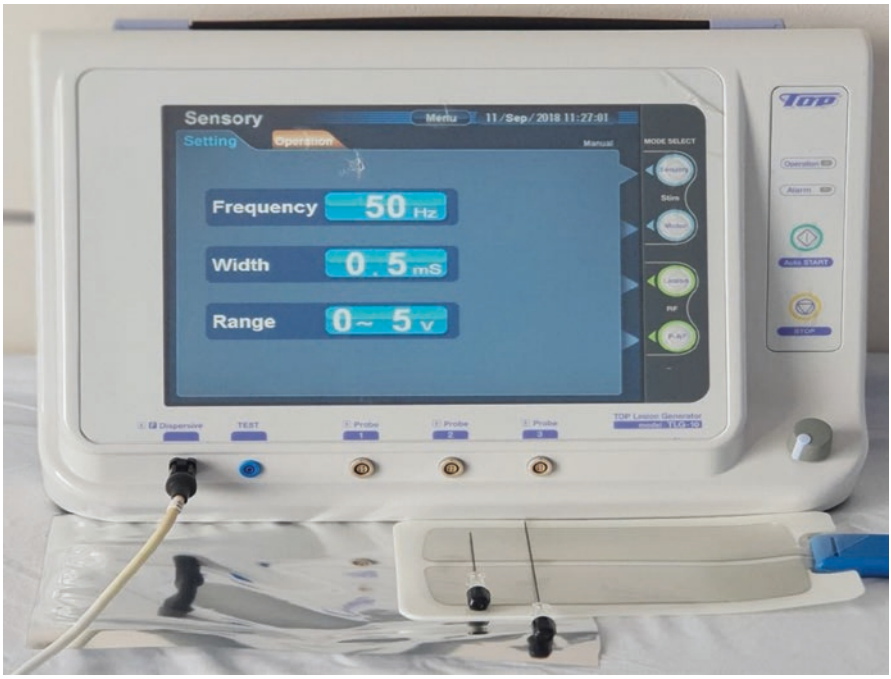

Fig. 12.1 Radiofrequency generator and RF cannulas for pain management

12.1.1 Nerve Stimulator

Nerve stimulation is very important before making an RF lesion. After placement of the needle under fluoroscopy, ultrasound, or CT guidance (depends on the procedure), we have to check the location of the needle with nerve stimulation.

Stimulation at 50 Hz, with up to 1 V is used to measure the distance to the sensory fibers, while stimulation at 2 Hz, with up to 2 V, is used for measuring the distance to the motor fibers. The patient's response to sensory stimulation is paresthesia at the territory of the nerve, while muscle contraction is the response to motor stimulation. If muscle contractions appear after 2 Hz at 0.25–0.3 V, it means that the needle is placed on the nerve; muscle contraction after 2 V stimulation means that the needle is at distance of 1 cm from the nerve. If the needle is not at the expected place, it should be redirected under guidance. If the nerve is damaged (neuropathic), stimulation with 1 V may not give the true distance of the needle [1–3].

12.1.2 Conventional Radiofrequency: Continuous Radiofrequency

Thermal damage is created using electrode tips with 2–5–10 mm active (uninsulated) tip length and 22G (~0.64 mm) diameter in most procedures. Cosman et al. have shown that the diameter of the lesion depends on the size and tip temperature

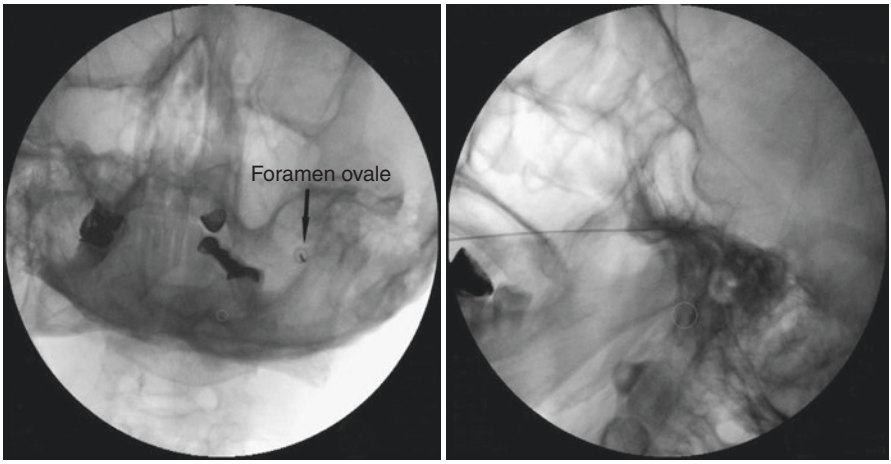

Fig. 12.2 Percutaneous gasserian ganglion radiofrequency ablation under fluoroscopy guidance

of the needle and the diameter of the probe [1–3]. The duration of lesioning is 60–90 s and depends on the clinical procedure. Different types of needles with various sizes and diameters can be used, based on the procedure (Fig. 12.2).

12.1.3 Pulsed Radiofrequency

Pulsed radiofrequency (PRF) is a procedure in which intermittent application of high voltage with a phase of electrical current is followed by a silent phase that allows heat dissipation. During one cycle, the active phase is 20 ms and silent period is 480 ms. This modification from conventional (continuous) radiofrequency (CRF) maintains tissue temperatures below 42 °C and prevents possible tissue destruction [1, 3–5].

The temperature at the active tip of the needle is 40–42 °C. The duration of PRF is 3–9 min and is applied after diagnostic peripheral nerve block in headache disorders. Developments in this field have displayed promising results.

Although the mechanism of analgesic effect of PRF is not fully understood, a change in c-Fos gene expression in the dorsal horn and an increase in activated transcription factor release and reversal of peripheral nerve or dorsal root ganglion ultrastructural changes may be the underlying mechanisms. These effects continue for days after the application of PRF and are not related to the temperature [6]. Van Zundert et al. have shown in their experimental study that the number of c-Fos immunoreactive cells in the dorsal horn was significantly increased in the 60 s continuous RF (67 °C) and 8 min pulsed RF groups with no significant difference between the groups [4].

Ramzy et al. showed increased duration of PRF application to result in better analgesic efficacy without any increase in tissue injury in an animal neuropathic pain model for the sciatic nerve. They applied PRF for 2, 4, 6, or 8 min and found improved pain scores in the rats treated with PRF over time. Pain scores in the inter-

vention groups were better on day 11 compared to day 3. They also found significant improvement in rats treated for 8 min compared to the other groups. Increased duration of PRF application was associated with a significant decrease in IL-6 and TNF-α content in all groups when compared to the control group. They did not find histopathological changes in any group after PRF [6].

12.1.4 Gasserian Ganglion and Trigeminal Nerve Branches (Maxillary and Mandibular) Block and RF

Gasserian ganglion radiofrequency is recommended in medical-treatment-resistant and especially advanced-age trigeminal neuralgia cases. While CRF ablation of the gasserian ganglion provides better pain relief than PRF in trigeminal neuralgia patients, Elawamy et al. obtained the best results with the combination of CRF and PRF [7] (Fig. 12.2).

While the results of gasserian ganglion RFT were demonstrated by various studies, the number of studies on the PRF treatment of the maxillary and mandibular nerve is limited [7–9].

PRF under ultrasound guidance for maxillary and mandibular branches may be the other option for appropriate patients with mild symptoms of trigeminal neuralgia or for patients who are unable to tolerate the medical treatment's side effects [8].

12.1.5 Sphenopalatine Ganglion (SPG) Block and RF

Sphenopalatine ganglion is an important target for the treatment of headaches and facial pain syndromes because of its anatomic localization and its role in the trigemino-cervical reflex. Despite the existence of prospective double-blind, placebo-controlled studies with SPG block (with local anesthetic) in chronic migraine, cluster headache, and trigeminal neuralgia in the literature, there is no prospective randomized study showing the effectiveness of SPG block by RF [9]. However, there are certain cases in the literature that have benefited from RF and promised positive results for prospective well-controlled studies. PRF ablation of SPG may be another treatment choice for trigeminal autonomic cephalalgias (TOC), especially in cluster headache patients who are resistant to medical treatment. Some of the results of these studies are shown in Table 12.1. RF ablation of SPG was performed under fluoroscopy or CT guidance in these studies, and the temperature used was 80 °C for thermal CRF and 42 °C for PRF in most cases. It is difficult to compare the results of CRF and PRF because of the different study designs. There is no standard protocol and the results are different due to the different headache types [9]. Please refer to Figs. 12.3 and 12.4 for SPG PRF applications under fluoroscopy guidance.

Table 12.1 Studies for SPG radiofrequency treatment in headache disorders [9]

Type of headache	Study design	Evidence/grade of recommendation	Intervention	Results	Reference
Chronic cluster headache	Prospective cohort study 15 case	2b/B	Radiofrequency thermocoagulation, 80 °C, 60s × 2 with fluoroscopy guidance	Mean attack intensity, mean attack frequency, pain disability index significantly reduced at 1-year follow-up	Narouze et al. [10]
Cluster headache	Case report 16 cases	4/C	Pulsed radiofrequency 42 °C, with CT guidance	One chronic and 11 episodic (ECH) cluster headache (CCH) patients had partial pain relief within 1.3 days and complete pain relief within 6.3 days after the procedure ECH patients showed rapid pain relief after PRF No pain relapse during 12–30-month follow-up in 91% of ECH patients	Fang et al. [11]
Atypical facial pain, cluster headache Sluder's neuralgia	Retrospective study 15 patients	4/C	Radiofrequency thermocoagulation 80 °C with fluoroscopy guidance	Positive results in Sluder's neuropathy, cluster and atypical facial pain	Oomen et al. [12]

12.1.5.1 Technique

An infrazygomatic approach was used for the SPG pulsed RF under fluoroscopic guidance. Paresthesia was obtained at the root of the nose with 50 Hz, 0.5 V sensorial stimulation. Pulsed RF was performed for 6 min at 42 °C temperature following the administration of 2 ml of 1% lidocaine (Figs. 12.3 and 12.4) (Case 1).

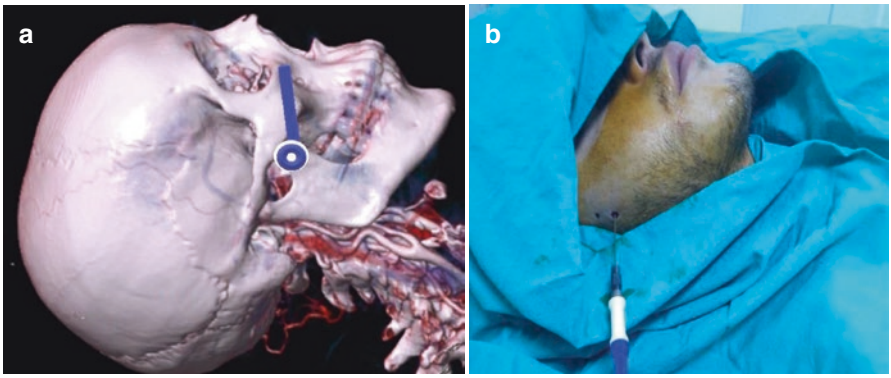

Fig. 12.3 Sphenopalatine ganglion PRF under fluoroscopy guidance in a cluster headache patient. (**a**) Target and direction of the RF cannula. (**b**) Patient position

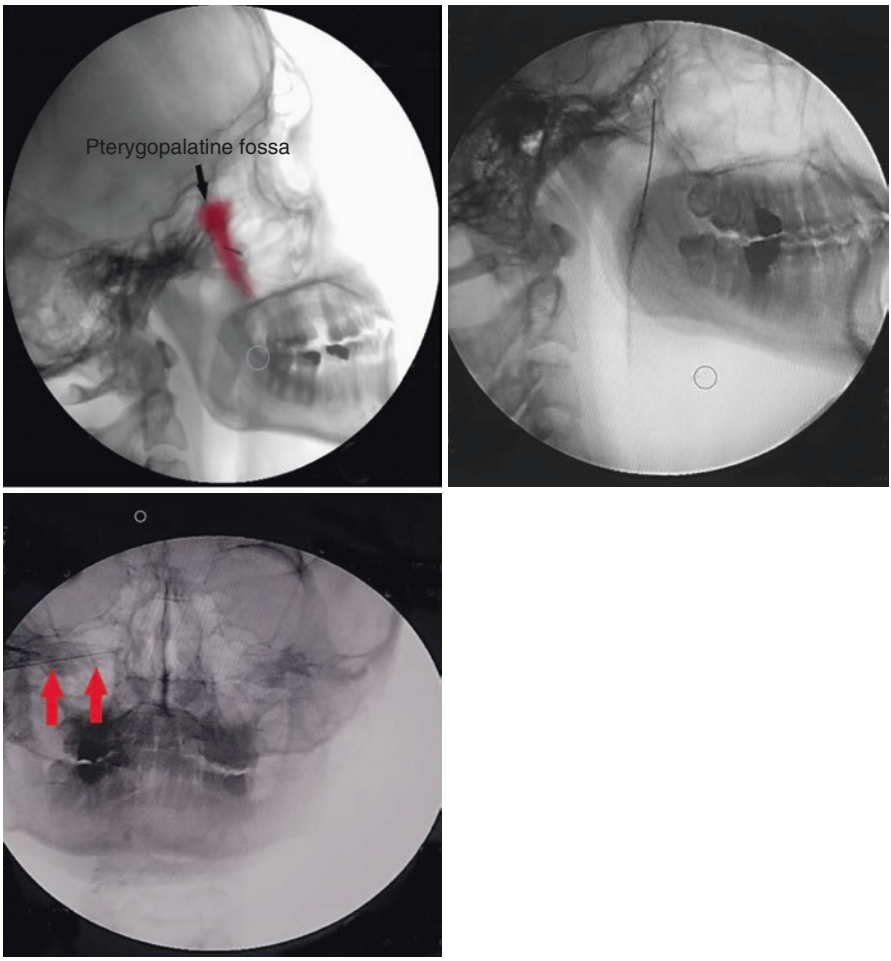

Fig. 12.4 Sphenopalatine ganglion PRF under fluoroscopy guidance in the cluster headache patient. Images of the pterygopalatine fossa and placement of the RF cannula for the SPG block

The frequency and severity of headaches gradually decreased after the procedure and the headache disappeared after 1 month. The duration of the period without headache attacks was about 6 months. After this period, the patient began to experience rare attacks with VAS 3–4 severity, but after 4 months the attacks became more frequent and the VAS was 6–7. Medical treatment was restarted with verapamil and we repeated the interventional procedure with an PRF duration of 10 min. We performed the SPG PRF procedure without any complications (Case 1).

12.1.5.2 SPG PRF Complications

Epistaxis, injury or lesioning of the maxillary nerve, orbita or maxillary sinus penetration, parotid gland puncture, hematoma of the cheek, infection, and hypoesthesia due to PRF lesioning are the possible complications of this procedure. To avoid the complications and ensure true localization of the needle, this procedure should be done under fluoroscopy guidance and correct placement of the needle should be tested with sensorial and motor stimulations before RF lesioning.

Case 1: Sphenopalatine Ganglion Pulsed Radiofrequency Treatment (PRF) Application in Chronic Cluster Headache Resistant to Medical Treatment

A 26-year-old male patient was referred to our clinic for chronic headache resistant to medical treatment. Migraine headaches in his childhood had been followed by pain attacks localized around the right eye, with a duration of 10 s to 5 min, repeating 5–20 times/day, and accompanied by autonomic findings, which appeared at the age of 18. At that time, the diagnosis was paroxysmal hemicrania and remission was obtained with indomethacin.

The headache attacks reappeared 1 year later; the headache duration was increased and diagnosed as cluster headache. It was treated with prednisolone and verapamil. Attacks occurred only in the spring for 2 years, and then became more regular for 6 years. These attacks were localized around the right eye, piercing, very severe (Visual Analog Scale VAS = 9), accompanied by restlessness and autonomic symptoms, recurring 7–8 times/day, and lasting approximately 1 h. Response to oxygen inhalation during the attacks was inadequate.

Prednisolone, amitriptyline, topiramate, triptans, sodium valproate, verapamil, pregabalin, lithium, and indomethacin treatments had no benefit. The neurological findings, brain MRI, brain MR-angiography, and pituitary MRI were normal.

Before the procedure, we explained the intervention to the patient and obtained written informed consent from him.

We performed a transnasal SPG block with 10% lidocaine (0.5 ml) three times with 1-week intervals. During this period, his headache frequency and severity was reduced. Most of his attacks were VAS 4–5 at a frequency of 2–3 times/day. After these diagnostic and prognostic blocks, we decided to perform PRF to the SPG in order to ensure long-term improvement.

12.1.6 Occipital Nerve and PRF

Cervicogenic headache is another type of headache. Interventional procedures such as GON block have been used for its treatment. According to the International Headache Classification, response to the GON block is important for the diagnosis of cervicogenic headache [13]. The greater occipital nerve originates from the dorsal ramus of the medial branch of the C2 and C3 nerves. Pathologies of the C2–C3 facet, atlantoaxial joints, and compression of the C2 nerve may result in cervicogenic headache. Greater occipital nerve (GON), lesser occipital nerve (LON), third occipital nerve (TON), and cervical facet medial branch RF have been used for the treatment of cervicogenic headache and their effectiveness has been shown (see Fig. 12.5). There are no randomized-controlled studies showing comparative effectiveness of CRF and PRF but some case reports have demonstrated promising results [14, 15].

GON block followed by radiofrequency treatment has also been used in various headache cases with positive results [15, 16]. The positive results of GON block in chronic migraine headache, spontaneous intracranial hypotension headache, and cluster headache have been discussed in recent studies (Table 12.2). The long-acting effect of pulse radiofrequency treatment of the GON may be superior to GON block with local anesthetic and steroids. Repetitive PRF of the GON may be necessary in some cases [15].

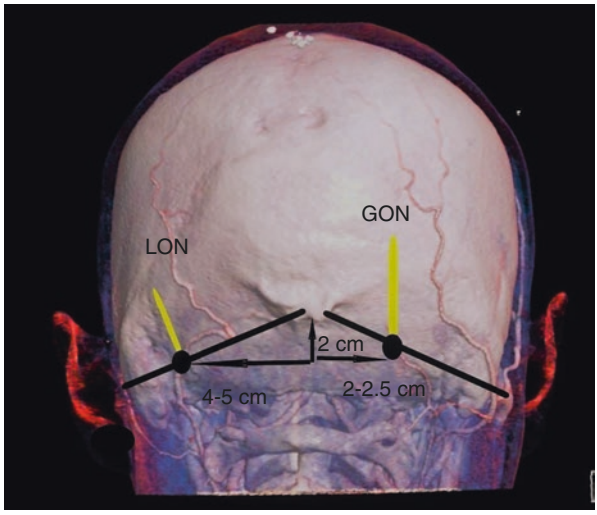

Fig. 12.5 Anatomic landmarks for the needle insertion point for the greater occipital nerve (GON) and lesser occipital nerve (LON)

Table 12.2 Studies for GON radiofrequency treatment in headache disorders

Type of headache	Study design	Evidence/ grade of recomm endation	Intervention	Results	Reference
Spontaneous intracranial hypotension headache/ accidental dural puncture headache	Case report	4/C	(a) Repeated GON block with 1% lidocaine + dexamethasone (b) GON PRF with 6 min duration, 42°, 45 V, 5 Hz, with ultrasound guidance. The procedure was repeated after 11 months	(a) 4 months without headache after the first GON block 6 months pain-free after the second GON block (b) Pain-free for 4 months Mild headache, 1 per week, at 5–8 months 50% reduction of headache days and intensity at 9–10 months Second GON PRF performed at 11 months Complete pain relief after the second PRF	Niraj et al. [15]
Occipital neuralgia and migraine with occipital nerve tenderness	Randomized double-blind comparative effectiveness in 81 patients		2.75 ml 0.5% bupivacaine +2% lidocaine +40 mg/1 ml depot methylprednisolone vs. GON and/or LON PRF with 3 × 2 min duration, 42 °C temperature	Average occipital pain Worst occipital pain Average overall headache pain values were lower in the PRF group than the steroid group	Cohen et al. [16]

Case 2: Long-Term Pain Control with Pulse Radiofrequency Treatment in Cervicogenic Headache

An 86-year-old male patient presented to the algology outpatient clinic with severe right-sided headache. His headache had existed for 3–4 years. It had been mild and had improved with pain-killers at the beginning. During this period, the frequency and severity of pain had gradually increased. It had not disappeared with use of simple analgesics in the last month. Daily VAS revealed

an intensity of 7–8. It spread from the back of the neck to the head and it was one-sided without side shift. The pain increased with neck movements and was not accompanied by autonomic symptoms. The history revealed a cervical fracture that had been treated with conservative treatment 10 years ago. MRI of the cervical vertebrae showed flattening of the cervical lordosis, C1 atlas basis and odontoid migration to the superior aspect, and C1–3, C4–5 lysthesis and arthrosis. The patient did not have any neurological deficits. Cervicogenic headache was diagnosed. Blockade with 2 ml 0.5% bupivacaine was performed because of the right GON sensitivity (Fig. 12.5). After the blockade, the pain disappeared completely and the patient was followed in terms of pain score (VAS), duration and frequency. In 1-week follow-up, he had short periods of pain of VAS 2–3 every day. The GON blockade was repeated. During the second week, the pain intensity was VAS 4–5 but experienced only two times. Local anesthetic blockade was performed again for diagnostic purposes and a positive response was obtained. This was followed by the GON pulse radiofrequency procedure at 42 °C for 10 min. We are still following-up the patient. He has had feelings of fullness and VAS 2–3 pain in his head from time to time for 1 year after the treatment but he no longer has severe pain.

Case 3: Intractable Lesser Occipital Neuralgia Treated with Pulsed Radiofrequency

A 35-year-old male patient presented to the algology outpatient clinic with severe right-sided headache. He had experienced unilateral, paroxysmal, shooting and stabbing pain in the posterior part of the scalp, in the lesser occipital nerve (LON) distribution area for 2 years.

He had tenderness over the LON and the pain was amplified with pressure over the LON. He had used various medical treatments in the last 2 years such as carbamazepine, gabapentin and amitriptyline. The patient reported inadequate pain relief with intolerable side effects with all medical agents.

The patient was admitted to the clinic with 30–40 attacks/day and daily VAS was 7–8/10 with the pain spreading from the back of the upper neck to the head in the sensory distribution area of the LON. He was not on any medication at that time. Physical examination, blood sample analysis, cervical and cranial MRI was normal.

After a diagnostic block of the LON with 2 ml 0.25% bupivacaine and 40 mg triamcinolone, the frequency and severity of pain was reduced. Two weeks later, pulsed radiofrequency (PRF) was applied to the LON at 42 °C, with a duration of 10 min (Fig. 12.5).

After 1 month, the patient had only 1–2 attacks per week with a pain severity of VAS 7. In the second month, he had VAS 2–3 severity pain and 1–2 attacks per week. The LON block with 2 ml 0.25% bupivacaine and triamcinolone was repeated. He did not have severe pain in the LON distribution area after the procedure at other follow-up time points.

Conclusions

RF thermocoagulation is an important and effective method for primary and some secondary headache disorders, as supported by evidence-based data when applied in experienced hands with supportive equipment.

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Chapter 13
The Potential Role of Ozone Therapy

Didem Akçalı and Avni Babacan

Introduction

Medical ozone is a complementary treatment modality for various indications in medicine [1, 2]. Oxygen is converted by a generator to an oxygen–ozone mixture and titrated to various concentrations for medical consumption. Ozone treatment is preferred in many diseases such as diabetes mellitus, neurological diseases, osteoarthritis, other pain syndromes, peripheral artery diseases, and infectious diseases. The equipment used is ozone-resistant, such as glass-based and silicone-coated products. Ozone reacts with latex, PVC, and non-ozone-resistant material. The type and concentration of and the schedule for ozone treatment may vary according to the pathology. There are many routes for the administration of ozone treatment and these are mainly classified as local or systemic (parenteral and rectal) administration. In addition, combination of both the local and systemic routes may be useful for complex medical conditions. Ozone treatment does not cause infections when proper technique and sterile equipment are utilized [2].

13.1 Mechanisms of Ozone Treatment in Medicine

Ozone treatment is used to activate the immune system by increasing the body oxygen content to treat infectious diseases with an antibacterial, antiprotozoal, antiviral, and antifungal effect [1, 3]. Ozone reacts with blood plasma and chemical messengers for activating reactive oxygen species and hydrogen peroxide (H_2O_2). Transient oxidative stress stimulates the immune system and increases the oxygen content of

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the human body. The Madrid Declaration on Ozone Therapy, which is the first extensive reference including recommendations from researchers and physicians performing ozone treatment was released in June 2015 [1, 4].

Mitochondrial energy production decreases in chronic diseases. Ozone treatment stimulates the energy-producing pathways of the cells. Oxygen affinity of the blood cells is increased and this excess oxygen reaches areas where it is needed. Ozone helps the body boost its own healing capacity by its effect on white blood cells. Ozone regulates 2,3-diphosphoglycerate (2,3-DPG) in erythrocytes, and induces the release of nitric oxide (NO) and carbon monoxide (CO), and increases oxygen delivery in ischemic tissues. Ozonated blood leads to a feeling of well-being by the release of endorphins and modifies the biological response [5].

Ozone dissolves in plasma and acts as a pro-drug in a therapeutic window between 10 and 80 μg/ml (0.21–1.68 μmol/ml) in the blood. Important messengers that are produced are H_2O_2 and a mixture of lipid oxygen products (LOPs). The mechanism of effect of rectal ozone is similar; it dissolves immediately in water in the epithelium and reacts with biomolecules to produce H_2O_2 and LOPs. LOPs are absorbed by the lymphatics and venous capillaries and reach the liver and then the whole circulation [6]. During ozonolysis, ozone peroxides are formed and can be considered crucial for the pharmacological effects. Aldehydes are secondary products [5].

Patient responses to mild controlled oxidative stress are variable. The oxidative stress state of patients can be measured by antioxidant activity indicators [4]. Malone dialdehyde (MDA) is a measure for oxidative stress during extracorporeal blood treatment with ozone. Ozone treatment of the blood in the form of major autohemotherapy remarkably increases two cytokines: interferon gamma and tumor necrosis factor alpha [5]. Ozone treatment is beneficial in oxidative-stress-related diseases such as cancer, neurodegenerative diseases, inflammation, and cardiovascular diseases through an antioxidant response. Vitamin C and Vitamin E supplements must be avoided during ozone therapy to ensure a good treatment outcome [6].

Moderate oxidative stress activates nuclear-factor-erythroid 2-related factor 2 (Nrf2), which is essential for antioxidant response elements (ARE) producing many antioxidant enzymes such as superoxide dismutase, glutathione-s-transferase, and catalase. Oxidative stress can be reversed in this way [6]. The analgesic effect is mediated by the induction of IFN-β, activation of superoxide dismutase, and induction of TGF-β. The success rate for medical ozone in pain-related conditions is 50–60% [2].

13.2 Ozone Application Methods

Ozone is effective in low doses but may be toxic in higher doses (principle of hormesis). Major ozone autohemotherapy (MAHT) and rectal ozone insufflation 10–40 μg/ml ozone/oxygen mixture are recommended for systemic application [2].

For systemic diseases, major autohemotherapy (MAHT) is used and is performed by drawing 50–100 ml of venous blood into a sterile single-use pressurized bottle

containing an anticoagulant and infusing it back to the patient after adding an equal volume of an ozone–oxygen gas mixture [7]. Rectal insufflation is used as a systemic method and most of the time preferred for use in intestinal disorders. In the Russian ecole, ozonated saline is used for intravenous infusion [1]. Inhalation of ozone gas is toxic for the respiratory tract. Intraarticular injection, intradiscal injection, etc., are local treatment modalities used in arthritis, sciatica, and vertebral disorders.

During ozone treatment to an individual, oxygen delivery to tissues is improved; the metabolism will be enhanced and the immune system will be activated to release growth factors. This cascade produces a state of wellness by the activation of neuroendocrine mechanisms [6].

Additional effects of ozone therapy are strengthening of the hairs and nails, brightening of the skin, and a healthy appearance. The patients express a happy emotional state with more physical energy and report the ability to fall asleep faster and enjoy a restful sleep [7].

Regular ozone therapy is needed to treat pathological conditions and must be continued by adopting maintenance therapy (8–10 sessions) [6]. Two to three cycles of ozone treatment per year increase the quality of life and decrease disability [2].

13.3 Medical Ozone Experiences in the Algology Department

Medical ozone treatment modalities have been in use at the Gazi University Algology Department as major and minor autohemotherapy, intraarticular injection, transforaminal/intradiscal injection, and myofascial trigger point injection since 2005.

Ozone treatment is preferred as an additional option in patients with headache and fibromyalgia who are unresponsive to medical treatment and lifestyle modifications. Eight to ten sessions of major ozone hemotherapy are performed and can be repeated every 6 months when needed. For patients with resistant neuropathic pain, and especially in those that suffer drug side effects, add-on systemic ozone treatment is used with surprising results. In our study on knee osteoarthritis patients, we used five sessions of intraarticular ozone injections and this treatment provided reduction in pain intensity and increased the functional capacity [8].

13.4 Ozone Treatment in Headache

Ozone treatment is a valuable complementary treatment for incapacitating headaches resistant to treatment [1]. Safe treatment with ozone involves three principles:

1. Give no harm!
2. Increase the dose step by step.
3. Administer within the range of the relevant concentration.

Migraine and primary headaches are treated with major autohemotherapy (MAHT) and rectal insufflation [7]. Lipid peroxidation plays a significant role in migraine pathogenesis [9]. During major ozone autohemotherapy, endothelial nitric oxide synthase (eNOS) is activated and is important to increase NO causing vasodilation and enhanced tissue oxygenation, enhancing the release of oxygen to tissues by shifting the Hb dissociation curve [5]. This mechanism may be crucial for ozone treatment for headache [4, 5, 7]. Enhanced release of NO and CO causes possibly prostacyclin (PGI_2) COX-2 dependent vasodilation [1].

Ozone can be used successfully for immune modulation at doses of 15–20 μg/ml 300 ml twice a week as major autohemotherapy or 15–25 μg/ml max. 300 ml rectal for rectal ozone insufflation [10].

13.5 Scientific Evidence

The literature on ozone treatment for headache is limited. In Table 13.1, prominent studies in headache patients treated with ozone are summarized (Table 13.1) [7, 11, 12]. Among these, only Kotov's study is a controlled study. Randomized placebo-controlled studies are needed to confirm the therapeutic effect of ozone for headaches.

Scientific evidence for ozone treatment is available for knee osteoarthritis and herniated lumbar discolysis. Knee osteoarthrosis can be effectively treated by para-articular ozone treatment, resulting in pain reduction and increased function.

Table 13.1 Studies for treatment of headache with ozone (reorganized according to Refs. [7, 11, 12])

Patients	Dose, Sessions	Results	Author, Year
Randomized trial 40 patients—ozone 28 patients—control 64% migraine without aura 36% migraine with aura	1200 μg/l, 8–9 sessions, intravenous ozonated saline	25% improvement in headache attack and severity 58% no attack for 5 months	Kotov, 2000
Five patients, refractory migraine	Twice a week, then weekly	Pain relief for at least 6 months	Clavo, 2013
10Y, frontal, daily temporal headache	25 μg/ml 120 ml, rectal, twice a week, 10 sessions	2 attacks/month	Apuzzo, 2016
51Y, apical headache, attacks lasting 3 days	Twice a week, 200 ml MAHT, 8 sessions	Complete pain relief	

Evidence is not clear for intraarticular ozone treatment for knee osteoarthrosis [13]. Ozone treatment is used as paravertebral lower-back injections or intradiscal treatments for lower-back pain. After ozone treatment, the analgesic effect of ozone increases and is sustained for a period of time. Ozone was not found to be superior to hyaluronic acid for osteoarthritis [14]. Intradiscal ozone treatment has II-3 level of evidence (strength of recommendation 1C) and paravertebral or paraforaminal ozone injection has been declared to have II-1 level of evidence (strength of recommendation 1B) [15].

13.6 Ozone Therapy Side Effects

- Accidental inhalation may cause burning of eyes, coughing, nausea or vomiting, or mild headache.
- Rectal ozone may cause mild discomfort, a feeling of passing gas, gurgling, or mild cramps.
- Herxheimer (healing) reaction may be seen as the sign of detoxification and healing. Flu-like symptoms or temporarily feeling worse is an indication to continue the therapy. This is actually the natural healing process.
- Hot sensation in the lower abdomen.
- Increased appetite and sleepiness [2].

13.7 Ozone Therapy Contraindications

Medical ozone treatment is contraindicated in severe coagulation abnormalities, uncontrolled hyperthyroidism, Glucose-6-Phosphate Dehydrogenase deficiency, chronic relapsing pancreatitis, and acute or subacute myocardial infarction. It is also not performed during the first trimester of pregnancy, in ozone allergy and acute alcohol intoxication, and following recent myocardial infarction [9, 14].

Conclusion

Severity of oxidative stress is the distinguishing factor between effective therapy with ozone and toxic reactions. The efficiency of ozone therapy in the treatment of headache needs to be evaluated in further randomized controlled clinical studies with more patients. Headache, and especially migraine, treatment with ozone therapy is a long-lasting, safe, effective, and inexpensive add-on treatment option when treating pain, at least for intractable headache patients. Ozone treatment can be a valuable option before other treatments, especially in intractable headache patients.

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Chapter 14
Peripheral Neuromodulation on the Refractory Headache Disorders

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Introduction

The medical treatment of patients with chronic primary headache syndromes is particularly challenging, and, in many cases, even higher doses of preventive medication are ineffective, and adverse side effects frequently complicate the course of medical treatment. In these cases, patients can profit from the emerging diversity of invasive and noninvasive neuromodulatory techniques. Practical application of noninvasive neuromodulation reportedly dates to Roman times when Galen used marbled electric rays to treat headache, pain, and epilepsy [1]. Various forms of neuromodulation have been used in the past 50 years for different indications, like occipital nerve stimulation (ONS) in presumed occipital neuralgia in the late 1990s and deep brain stimulation (DBS) of the posterior hypothalamic area in cluster headache in 2001 [2]. This development involves some advantages for the affected patients; neuromodulation is in principle reversible, it allows dynamic adjustment of stimulation parameters, and, unlike the mostly transient benefit from pharmacological nerve blocks, it can exert prolonged effects. In this chapter, the most used peripheral neurostimulation techniques in primary headaches are reviewed, with special regard to their advantages and downsides.

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14.1 Occipital Nerve Stimulation (ONS)

The ONS mechanisms involved in ONS efficacy are multiple. Spinal and supraspinal actions are probably involved. Modulation at the level of the spinal cord via convergence of trigeminal nerve and upper cervical afferents (C2/C3) in the trigemino-cervical complex is hypothesized as a nexus to explain efficacy of chronic stimulation of the occipital nerve [3].

Central mechanisms are also involved. Suboccipital stimulation modulates the activity in the left pulvinar and anterior cingulate cortex and produces an activation of the dorsal rostral pons. Experimental evidence also suggests a contribution of descending pain modulating pathways in mediating the analgesic effects of peripheral nerve stimulation. Peripheral nerve stimulation is a potential minimally invasive way to control pain [4].

Open-label data in 91 medically intractable chronic cluster headache (CCH) patients treated with ONS have shown favorable outcomes with a reduction of more than 50% of attacks in around 70% of patients with cluster headache [5]. Magis et al. implanted ONS in 15 patients with refractory CCH, followed for up to 5 years. One patient was explanted due to infection, 11 (80%) had 90% improvement, with 60% becoming pain-free for prolonged periods, while 2 patients did not respond or described mild improvement. Side shift with infrequent contralateral attacks occurred in 36%, and/or isolated ipsilateral autonomic attacks were described without pain in 36% [6].

Burns et al. retrospectively reviewed outcomes from 14 patients over 17.5 months on average. The first patient was implanted unilaterally and improved, but then the attacks shifted side; hence, all subsequent patients were implanted bilaterally. Ten of 14 patients reported improvement, 3 had improvement of 90%, 3 had moderate improvement 40%, and 4 had mild improvement (20–30%) [7]. Another study by Fontaine et al. also showed similar encouraging results in 13 patients implanted bilaterally, as 10/13 patients had an improvement of about 50% [8]. Brewer et al. reported success in 4/5 patients. One patient had a 50% improvement, one a 70% improvement, and one an 80% improvement, one was "doing very well," and ONS did not work for one [9]. Mueller et al. implanted ONS in 10 patients with CCH and found a frequency and/or intensity improvement in 90% of them [10], and Strand et al. used a unilateral microstimulator (Bion) in three develop drug-resistant CCH (drCCH) patients also showing a long-term benefit for up to 5 years [11]. Our team implanted bilateral ONS in 16 drCCH patients; follow-up range was 1–8 years. Eight patients were asymptomatic, two patients changed to episodic attacks, four patients had improvement of >50%, one patient had no improvement, and one patient shifted to contralateral CH. Complications were two electrode migrations, three battery replacements, and three explants due to infection. ONS is safe, but the rate of complications is high in the long-term follow-up [12].

ONS has also been described as effective in hemicrania continua (HC) and SUNCT. Lambru et al. described the outcome of nine medically intractable SUNCT

(n = 6) and SUNA (n = 3) patients treated with bilateral ONS. All but one patient showed substantial improvements. Four patients became pain free, two almost pain free, and two had a remarkable reduction in attack frequency and severity [13]. Two case series in patients suffering from chronic migraine found a reduction of attack frequency or headache severity of more than 50% along with relevant improvements of migraine-associated disability in more than 85% of the participants. Despite these promising initial findings, larger studies have yielded ambiguous results. And three larger randomized clinical trials have failed to show meaningful and conclusive improvements in their experimental period in patients with chronic migraine [14, 15].

In practice, the greater occipital nerve (GON) is stimulated using a subcutaneous electrode crossing the nerve trajectory, to obtain paresthesias in the GON territory. ONS can be set up bilaterally or unilaterally, but because of the lower invasiveness of the procedure, and the risk of switching sides, bilateral stimulation of the occipital nerve is recommended.

Large number of patients successfully treated in unblinded studies with good efficacy in trigeminal autonomic cephalgias and moderate efficacy in open-label studies/case series on patients with chronic migraine. As bilateral implantations are now standard in most centers, it is the method of choice for non-side-locked trigeminal autonomic cephalgias. The side effects reported for ONS are usually mild but frequent, especially in the long-term. Electrode migration rates needing surgical revision are highly variable between groups, from 0% to 30%. Another technical problem is the use of high current intensities, leading to frequent battery depletion, which can potentially be avoided by the implantation of rechargeable batteries. Infection is also described in 3–5%. The patient's self-reported intolerance to paresthesias and tension feeling in the cable joining the electrode to the battery can be significant for some. One important consequence not collected as an adverse event, but important in the patient daily life, is limitation of physical activity to avoid electrode migration [14, 15].

14.2 High Cervical Spinal Cord Stimulation (hcSCS)

High cervical stimulation of the dorsal column was studied prospectively in a small sample of refractory chronic cluster headache patients (n = 7) with a mean follow-up of 23 months. Continuous stimulation (except for one patient with intermittent use) led to an impressive and immediate reduction of mean attack frequency from 6.0 to 1.4 with a responder rate of 86%. However, dislocation of electrodes, rapid depletion of batteries, and lead breakage occurred in five out of seven patients with frequent revisions. As in other unilateral approaches, two patients reported a side shift of attacks. Although the underlying concept is intriguing and hcSCS is probably more effective than ONS, the high rate of complications strongly argues against its clinical use [16].

14.3 Sphenopalatine Ganglion Stimulation

The sphenopalatine ganglion (SPG) has been a target for various lesional or local anesthetic techniques to treat cluster patients for over a century. The SPG is an extracranial structure lying in the pterygopalatine fossa, containing parasympathetic and sympathetic components. Because of its direct and indirect connections to somatic and visceral nerve structures of the face and to the trigeminovascular system, the superior salivary nucleus (SSN), and the hypothalamus, the SPG participates in cluster headache pathophysiological outflow and was chosen as a therapeutic target with some successful results. High-frequency SPG stimulation may primarily activate parasympathetic neurons or pre-/postganglionic parasympathetic nerve fibers and may physiologically block parasympathetic outflow, resulting in an acute effect on head pain and autonomic symptoms. In 2010, Ansarinia et al. placed temporary SPGs to treat six drCCH patients. They triggered CH attacks with alcohol, nitroglycerin, and other provoking techniques. They reported 18 attacks of CH in 5 patients. SPGs induced a complete resolution of pain in 11 acute events and partial resolution (>50% relief) in 4 events. Side effects were a transient mild facial pain, epistaxis, and a severe cluster attack in one patient [17].

A multicenter, randomized, controlled study (pathway CH-1) was performed in Europe, using an implantable microstimulator surgically positioned on the SPG in 32 patients for the acute treatment of chronic cluster headache. Pain relief was achieved in 67.1% of full stimulation-treated attacks, compared to 7.4% of sham-treated and 7.3% of sub-perception-treated attacks ($P < 0.0001$). Although the study was designed for acute treatment, a preventive response was observed in some patients. Nineteen of 28 (68%) patients experienced a clinically significant improvement: 7 (25%) achieved pain relief in 50% of treated attacks and 10 (36%) a 50% reduction in attack frequency, and 2 (7%) had both acute and preventive effect. Five serious adverse events occurred (three lead revisions and two explants). Most patients (81%) experienced transient, mild/moderate loss of sensation within maxillary nerve regions, consistent with dental or oral procedures [18]. A responder rate of 61% was maintained in a population of 33 medically refractory chronic cluster headache patients followed for 24 months while receiving on-demand, acute SPG stimulation. Forty-five percent of patients were acute responders, 33% were frequency (preventive) responders, and six of these patients experienced both types of response [19].

In the long-term follow-up studies, the efficacy of the stimulation remains after 2 years SPG stimulation appears as a promising innovative, efficient, and safe therapeutic solution for patients suffering from severe CH. SPG stimulation has showed its efficacy to abort CH attacks versus placebo stimulation, suggesting that it is particularly adapted for CH patients who are not sufficiently improved by currently available abortive treatments such as sumatriptan and oxygen. Additionally, the pilot study suggested that repeated SPG stimulation might have a preventive action on CH attack frequency. A new study in patients with chronic cluster, performed in the United States with bigger number of patients, has confirmed the results of the European study (American Headache Society, San Francisco, 2018).

14.4 Vagus Nerve Stimulation

There are numerous connections between the nucleus tractus solitarius and spinal trigeminal nucleus. Early studies suggest that inhibition of pain by vagus nerve stimulation (VNS) occurs by direct inhibition of vagal afferents to the caudal trigeminal nucleus, as an acute effect [20]. More recent evidence suggests that VNS may also inhibit pain by reducing glutamate levels in the trigeminal nucleus caudalis, which is in line with the longer-lasting preventive effects of VNS [21]. Vagus nerve stimulation (VNS), a well-established neuromodulation treatment for epilepsy and medication-resistant depression, has been successfully used open label in CH, chronic migraine (CM), and high-frequency episodic migraine (HFEM).

Historically, approved VNS devices were surgically implanted, while more recently, noninvasive VNS methods have been designed to avoid the risks of invasive approaches. *gammaCore*® was developed as a noninvasive vagus nerve stimulation (nVNS) portable device for transcutaneous stimulation of the cervical branch of the vagus nerve. ACT1 was a randomized, double-blind, sham-controlled study conducted in the United States. It demonstrated that nVNS as acute treatment produced a therapeutic response within 15 minutes and pain relief that was sustained through 60 minutes in patients with episodic CH [22]. ACT2 study also compared nVNS and a sham device with respect to efficacy and safety in the acute treatment of episodic CH (eCH) and chronic (cCH). In this study, nVNS was superior to sham therapy for acute treatment of attacks in patients with eCH but not those with cCH or in the total population. nVNS was safe and well tolerated in all patients. These results confirm and extend findings from the previous ACT1 study and demonstrate that nVNS is an effective acute attack treatment option for patients with eCH, with a favorable risk/benefit profile [23]. On the other hand, Barbanti et al. studied the efficacy of nVNS (*gammaCore*®) in patients with HFEM and CM. In this open-label, single-arm, multicenter study, patients with HFEM or CM self-treated up to three consecutive mild or moderate migraine attacks that occurred during a 2-week period by delivering two 120-s doses of nVNS at 3-min intervals to the right cervical branch of the vagus nerve. Of the 50 migraineurs enrolled (CM/HFEM: 36/14), 48 treated 131 attacks. The proportion of patients reporting pain relief, defined as $a \geq 50\%$ reduction in visual analog scale (VAS) score, was 56.3% at 1 h and 64.6% at 2 h. Of these patients, 35.4% and 39.6% achieved pain-free status (VAS = 0) at 1 and 2 h, respectively. When all attacks ($N = 131$) were considered, the pain relief rate was 38.2% at 1 h and 51.1% at 2 h, whereas the pain-free rate was 17.6% at 1 h and 22.9% at 2 h [24].

The current data confirm that nVNS is well tolerated and safe and is associated with treatment satisfaction and therapeutic adherence. From a risk-benefit perspective, nVNS therapy achieved pain relief without serious side effects, which may decrease patients' reliance on migraine medications and, in turn, lower the risk of medication overuse. *gammacore*® is approved by FDA for acute migraine in 2018. Besides, transcutaneous stimulation of the auricular branch of the vagal nerve (t-VNS) has been used in the treatment of chronic migraine. A monocentric randomized, controlled, double-blind study was conducted showing that the procedure

was safe and effective. The mean reduction of headache days after 12 weeks of treatment exceeded that reported for other nerve stimulating procedures [25].

14.5 Supraorbital Transcutaneous Stimulation (STS)

Transcutaneous stimulation of the supraorbital nerves using transcutaneous electric nerve stimulation technology by the *Cefaly*® device (STX-Med, Liège, Belgium) is another noninvasive peripheral neuromodulation method that has shown some positive results in migraine treatment. With reusable electrodes, a steady current at 16 mA is delivered to the end branches of the trigeminal nerve. A treatment session lasts 20 minutes and should be applied once daily for prophylactic treatment. An initial double-blind, randomized, sham-controlled trial (PREMICE study) investigated the efficacy of the *Cefaly*® device in 67 patients with migraine for the reduction of migraine days, migraine attacks, headache days, and intake of acute medication. In the treatment group, the 50% responder rate was 38% compared with 12% in the sham device group. Adverse events were not reported in the study. In a larger internet-based open-label study, the *Cefaly*® device was investigated in 2313 patients with headache who rented the device for a 40-day trial period. After a testing period of 58.2 days on average, 46% of the 2313 renters were not satisfied and returned the device, but the compliance check showed that they used it only for 48.6% of the recommended time. The remaining 54% of participants were satisfied with the treatment. Ninety-nine (4.3%) participants of the 2313 reported one or more adverse events, but none of them were serious [26].

In 2016, additional statistical analyses were performed on the outcome measures presented by Schoenen et al. to account for covariates. A rank analysis of covariance was performed, using the nonparametric Spearman's rank correlation coefficient. The results showed that age and disease duration do not influence study outcomes. However, the number of migraine days during the 1-month baseline period had an influence on the decrease in migraine days during the third month of treatment. In the original publication, the difference between verum and sham groups in the reduction of migraine days (respectively, 22.7% and 24.9%) just missed the significance threshold ($p = 0.054$). However, when baseline migraine days are considered as a covariate, this difference becomes significant ($p = 0.044$) [27].

This new analysis indicates that the beneficial effect of Cefaly for migraine prevention might be greater in patients with more frequent migraines, which is of interest for clinical practice. Cefaly was approved by FDA for acute migraine treatment in 2017.

14.6 Nonpainful Remote Electrical Stimulation (NRES)

Electrical stimulation has been extensively used, keeping the general rule of applying the stimulation adjacent to or within the same dermatome of the painful body location. It is considered an effective yet weak tool for pain reduction. The rationale

is an activation of pain inhibitory centers, via the conditioned pain modulation (CPM) effect; remote noxious stimuli can exert a generalized analgesic effect. This is by the descending analgesia tracts originating at brainstem centers and terminating at spinal, including cervical trigeminal, nuclei. Since use of pain to inhibit another pain is not clinically appealing, we use nonpainful conditioning; we and others have shown that robust nonpainful conditioning stimuli are sufficient in many cases to induce pain inhibition. Presumably, the threshold for activation of the inhibitory pain control system is lower than that of pain perception. In a prospective, double-blinded, randomized, crossover, sham-controlled trial efficacy of remote nonpainful electrical upper arm skin stimulation in reducing migraine attack pain has been evaluated [28]. In 71 patients (299 treatments) with evaluable data, 50% pain reduction was obtained for 64% of participants based on best of 200-μs, 150-μs, and 100-μs pulse width stimuli per individual vs 26% for sham stimuli. Greater pain reduction was found for active stimulation vs placebo; for those starting at severe or moderate pain, reduction to mild or no pain occurred in 58% (25/43) of participants (66/134 treatments) for the 200-μs stimulation protocol and 24% (4/17; 8/29 treatments) for placebo ($p = 0.02$) and to no pain occurred in 30% (13/43) of participants (37/134 treatments) and 6% (1/17; 5/29 treatments), respectively ($p = 0.004$). Earlier application of the treatment, within 20 minutes of attack onset, yielded better results: 46.7% pain reduction as opposed to 24.9% reduction when started later ($p = 0.02$).

Nonpainful remote skin stimulation can significantly reduce migraine pain, especially when applied early in an attack. This treatment may be proposed as an attractive nonpharmacologic, easy to use, adverse event free, and inexpensive tool to reduce migraine pain.

14.7 Caloric Vestibular Stimulation (CVS)

CVS is a widespread clinical tool used both to diagnose balance disorders and to confirm the absence of brainstem function. Historically, water or air irrigators have been used to warm or cool the external auditory canal. Both warming and cooling temperature changes create convection currents in the endolymphatic fluid of the horizontal semicircular canal. These currents cause cupular deflection, which alters the tonic firing rate of the vestibular nerves and, in turn, elicits broad autonomic responses, including the vestibular-ocular reflex.

The potential for CVS to provide effective prophylaxis for episodic migraine is supported by several findings. First, while the precise pathology underlying migraine remains largely unknown and the neural circuits involved are widespread, results from several neuroimaging studies consistently suggest that migraine is a neurological disorder involving brainstem dysfunction. This hypothesis is relevant because the brainstem is among the many neural regions activated by CVS, a set of strong pathways corroborated by the well-established diagnostic sensitivity of CVS to brainstem dysfunction. Anatomical tracing studies have demonstrated dense and often reciprocal connections between the vestibular nuclei, located within the pons

and medulla, and other brainstem regions implicated in migraine—including the periaqueductal gray, the parabrachial nucleus, the locus coeruleus, the reticular formation, the dorsal spinal and mesencephalic trigeminal nuclei, and the dorsal raphe nuclei. Furthermore, recent transcranial Doppler sonography data demonstrate that CVS treatment with the device elicits changes in cerebrovascular dynamics that point to brainstem neuromodulation. A multicenter, parallel-arm, block-randomized, double-blinded, placebo-controlled clinical trial was conducted to determine the superiority of CVS therapy over placebo treatment [29].

After 3 months of treatment, active-arm subjects exhibited significantly fewer migraine days (-3.9 ± 0.6 from a baseline burden of 7.7 ± 0.5 migraine days). These improvements were significantly greater than those observed in control subjects (-1.1 ± 0.6 from a baseline burden = 6.9 ± 0.7 migraine days) and represented a therapeutic gain of -2.8 migraine days, CI = -0.9 to -4.7, $P = 0.012$. Active arm subjects also reported greater reductions in acute medication usage and monthly pain scores compared to controls. No adverse effects on mood, cognition, or balance were reported. Subjects completed the trial with an average rate of 90% treatment adherence. No serious or unexpected adverse events were recorded. The rate of expected adverse events was similar across the active and the placebo groups, and evaluation confirmed that subject blinding remained intact. CVS appears to provide a clinically efficacious and highly tolerable adjuvant therapy for the prevention of episodic migraine.

Conclusions

The variety of neuromodulatory approaches has enlarged our therapeutic options significantly, especially in drug-refractory patients with chronic cluster headache and chronic migraine. Implants require surgical expertise, are relatively costly, and are still restricted to a minority of patients. However, noninvasive transcutaneous stimulation techniques, like STS, VNS or e NRES, shown efficacy, tolerability, and less adverse effects. The main challenge will be the development of an effective stimulation paradigm and the determination of the most reasonable region to stimulate, both depending on the baseline pathophysiological hypothesis. It is important to develop new strategies that are less invasive and easier to use for the patient.

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Chapter 15
Sample Cases (Treatment Response to GON Blocks in Chronic Migraine)

Levent Ertuğrul Inan and Ömer Karadaş

Introduction

The effectiveness of greater occipital nerve (GON) blocks with local anesthetics in migraine has been evaluated by several researchers [1–27]. Positive results of this procedure have been shown in many studies from 1999 to 2018. Several reviews and meta-analyses have been published on this procedure [2, 3, 7, 25, 27]. A recent meta-analysis, including seven randomized controlled studies, has shown the effectiveness of this procedure in reducing pain intensity and analgesic medication consumption in migraine patients [7]. Nevertheless, there is no standardization in the literature about the application technique, dose of the local anesthetic, and the number of the injections needed for treatment [3]. After reviewing the published references on this subject, we are able to propose some approaches at this point. Further studies on this topic will broaden and clarify our present knowledge.

The results of the studies show that

1. Adding corticosteroids to local anesthetics has no beneficial effect in migraine [9].
2. Repeating GON blocks weekly is beneficial, especially in the first month [4].
3. Unilateral block effectiveness is similar to that of bilateral blocks [14].

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4. Lidocaine should be preferred in pregnant women [16].
5. There is no particular symptom or finding to predict effectiveness of GON blocks [15, 17–20].
6. Ultrasonography may be useful to locate the GON more precisely. However, injection of local anesthetics at the 1/3 medial point of the line between the mastoid process and the protuberentia occipitalis externa may be effective [11, 21].
7. The presence of anesthesia after the block at the territory of the GON proves the effectiveness of block [3].
8. Palpation of the occipital artery and injecting medial to it may decrease side effects [23].
9. Side effects are rare but informed consent should be signed beforehand and first aid and resuscitation measures should be ready as it is an interventional procedure [23].
10. Searching for a hemorrhagic diathesis before the procedure and avoiding injection in patients who have had posterior fossa surgery are recommended [22, 23].
11. GON blocks may be an option for patients who have failed with their home medications or who do not want to use drugs [25, 26].
12. GON blocks and onabotulinum toxin A injections may also be used to treat patients according to algorithm [26].
13. GON blocks can be used in medication overuse headache during acute therapy [12].
14. GON blocks are safe and can be appropriate for children and pregnant patients, and also in patients that must avoid using many drugs (patients with kidney or liver disease) [16, 24].

15.1 Method

The GON block technique in our study group was similar in all of our follow-ups. The GON block was administered at the 1/3 medial point of the line between the mastoid process and protuberentia occipitalis externa in all patients. The patient sat on a chair next to the examination table and put his/her head on his/her arms, which were placed on the examination table to prevent possible trauma during the injection. The site of the injection was cleaned and disinfected using a local antiseptic solution; 1.5 ml of 0.5% bupivacaine diluted in 1 ml of saline was administered into the disinfected area subcutaneously using a 26G 0.45 × 13 mm needle. Injections were administered just superior to the occipital bone. During the procedure, the injector was pulled back 1 mm upon reaching the periosteum and the substance was administered accordingly.

Local pressure was applied for 2–3 min to spread the solution and prevent bleeding. All patients that received GON blockade were observed in the department for about an hour following the injection to confirm the absence of any adverse effects.

The procedure and the frequency of the GON block can vary from center to center, but we generally perform GON blocks weekly in the first month. We then per-

Table 15.1 Results of the GON blocks in migraine cases

	Age/gender	Diagnosis	FR BB	FR 1M	FR 2M	DUR BB	DUR 1M	DUR 2M	VAS BB	VAS 1M	VAS 2M
1	40/F	CM	15	6	10	5.4	7.35	9.4	5.8	4.8	5
2	38/F	CM	30	14	17	12	8.6	13.3	9.6	9	9.8
3	36/F	CM	15	6	4	11	18.3	13	6.6	7.3	7
4	44/F	CM	15	10	8	12	8.2	7.9	6.9	4.1	5.1
5	48/F	CM + MOH	22	11	8	16	8.2	6.8	8.5	4.8	4.7
6	29/F	CM + MOH[a]	18	10	7	12	7.5	6	8.2	5.1	4.9
7	42/F	CM[b]	20	13	8	12	8.2	7.8	9.1	7.8	7.2

FR headache frequency (days/month with headache), *DUR* headache duration (hours), *VAS* visual analog scale score, *BB* before block, *1M* 1 month after block, *2M* 2 months after block, *CM* chronic migraine, *MOH* medication overuse headache

[a]Triptan overuse headache

[b]Migraine with visual aura

form two more blocks per month and follow the patient. Additional blocks can be performed according to the patient's clinical outcome.

Results of the GON blocks in migraine cases are shown in Table 15.1.

All these chronic migraine patients' results showed that using GON blocks with this technique with bupivacaine at this dosage seems to be effective in decreasing the headache frequency. Some patients report a decrease in the mean headache duration and mean severity with VAS. When we overview other therapeutic choices such as medical treatment and other interventional procedures such as onabotulinum toxin and emerging agents such as monoclonal antibodies, GON blocks in chronic migraine may be an effective alternative treatment option.

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Epilogue

The current peripheral nerve interventions in the headache management can be employed for attack, bridge, and/or prophylactic treatment. For practical purposes, the diagnosis, indications, adverse effects, which peripheral nerve to choose, the right intervention, timing, time interval, and the dosage are critical components to achieve high rates of efficacy.

Important points are as follows:

- The convergence of the trigeminal nerve particularly ophthalmic division with cervical 1 and 2 nerves at the second-order neuronal level is the key feature for targeting the C2 nerve (GON) or C2/C3 nerve LON in the management. Parasympathetic system either through sphenopalatine ganglion, or via vagus nerve or suprabulbar control from the cerebral cortex probably plays a role in the headache.
- The action mechanisms of drugs: Local anesthetics bind to voltage-gated sodium channels in its inactivated state, prolong the duration of inactivation, and prevent the firing of neurons and propagation of the action potentials. Corticosteroids show their effects by their anti-inflammatory, weak membrane stabilizer properties and by inhibiting unmyelinated C-fiber transmission. Botulinum toxin (BoNT) prevents acetylcholine release at the neuromuscular/neuroeffector junctions by cleaving SNARE proteins. BoNT also inhibits the release of neuropeptides associated with pain such as substance P and calcitonin gene-related peptide.
- The indications and contraindications of blocking peripheral nerves originated from either the trigeminal nerve or upper cervical nerves are needed to be known.
- Trigger point injections and dry needling are highly effective supportive methods for TTH and cervicogenic headache disorders mainly.
- Interventions have advantages in children, pregnancy, or elderly population without any systemic side effect.

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- Botox is a well-known method for not only chronic migraine but also some indications of episodic migraine and other headache disorders like trigeminal neuralgia.
- Ozone and acupuncture are important options for intractable TTH and chronic headache disorders including migraine with an effective methodology.
- Peripheral neuromodulation is a developing area and hope future developments with evidence-based data.

We expect that clinicians and pain physicians will find the information in this book beneficial and use them in their daily practice.

Appendix

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Headache Diary

Dear ….

This diary follows your headache attacks and organizes your optimum management. Please write each of your attacks on different rows and define your headache characteristics as much as possible. If you like to note other than mentioned characteristics please do not hesitate using the other side of the paper. Many thanks for your cooperation.

Dr……….

Date	Duration of attacks (minute)	Localization (unilateral/ bilateral)	Severity (VAS)	Associated features of headache attacks (please check each of the following features)					Note (please define analgesic pill, menstruation, known triggers, etc.)
				Nausea	Vomiting	Photo phobia	Phono phobia	Motion sickness	

Please note additional features of your headache attacks into the other side of the paper if you need.

Headache Questionnaire for Outpatient Departments

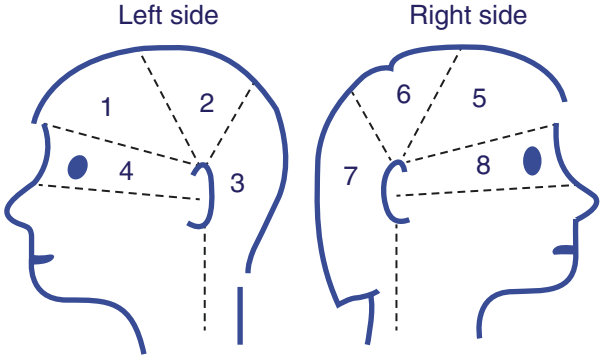
Name Surname	……
Date	_____._____._____ Day Month Year
Age	….. years/months
Gender	1) Male 2) Female
BMI	
When did you experience the first headache attack?	…… years old
Do you have recurrent headache disorders?	1) Yes 2) No
The frequency of headache disorders when they started	… per month or year
The frequency of headache disorders at the last month	… per month
Mean duration of headache attacks	… hours/minutes/seconds

Please mark the severity of headache attacks on the line. "0"means no headache, and "10" means that maximum headache severity most of the headache attacks

0 1 2 3 4 5 6 7 8 9 10

Quality of headache attacks	1. Throbbing 2. Stabbing 3. Non-throbbing (dull) 4. Others (please define) ……

Localization of headache attacks (please define and indicate if they were bilateral)



Associated features of headache attacks		
	Before attacks	During the attacks
□ Nausea		
□ Vomiting		
□ Sensitivity to light		
□ Sensitivity to noise		
□ Sensitivity to odor		
□ Sensitivity to touching the scalp or face/neck		
□ Dizziness		
□ Vertigo		
□ Motion sickness		
□ Neurological dysfunction □ Visual disturbance □ Motor disturbance □ Sensory disturbance □ Speech disturbance □ Balance disturbance □ Consciousness disturbance		
□ Autonomic features □ Ptosis □ Facial swelling □ Rhinorrhea □ Pupillary changes		

Triggers of headache attacks	□ Busy days □ Closed living environment □ Watching TV □ Playing PC, iPad, etc. □ Heavy exercise □ Fasting □ Sleep disturbance □ Sunny days □ Cold weather □ Windy weather □ Stress □ Menstrual cycle (if its applicable)
Relieving situations of headache attacks	□ Lying down □ Sleeping □ Eating something □ Taking analgesic pills □ Taking supplements or herbal drugs □ (Provoked) vomiting □ Massage, breath exercise, yoga, etc. □ Others (please define)

Medical history of the patient	□ Head Trauma □ Epileptic seizure □ Atopic disorders □ Rhinitis □ Conjunctivitis □ Asthma □ Motion sickness □ Rheumatological disorders (please define) □ Hematological disorders (please define) □ Sleep disorders (please define) □ Psychiatric disorders □ Anxiety disorders (OCD, social phobia, school phobia, etc.) □ Depressive disorders □ ADHD □ Substance abuse □ Cardiac abnormality (PFO, vascular event, etc.) □ Others (please define)
How many pills did you have in the past month for your headache attacks?	…… per month (please define)
Do you take any drugs for preventing headache attacks?	……. (please define)
Have you ever had an interventional medical treatment for your headaches?	□ Peripheral nerve block (please define) □ RF thermocoagulation □ Peripheral nerve stimulation (please define) □ Others (please define)
Have you ever had an intervention for preventing a headache attack?	□ Peripheral nerve block (please define) X …. times □ RF thermocoagulation X …. times □ Peripheral nerve stimulation (please define) X …. times □ Onabotulinum toxin A injections X …. times □ Acupuncture X …. times □ Dry needle X …. times □ Trigger point injection X …. times □ Ozone management X …. times □ Others (please define)

Glossary

Acupuncture Acupuncture involves the insertion of very thin needles through your skin at strategic points on the body.

Attack management Specific medications or interventions for relieving headache features during the attack period.

Auriculotemporal nerve (ATN) A nerve that originates from the back part of the mandibular nerve and travels alongside the superficial temporal vein and artery, which supplies nerves to several regions on the sides of the head.

Auriculotemporal neuralgia Unilateral or bilateral paroxysmal, shooting or stabbing pain in the posterior part of the scalp, in the distribution(s) of the auriculotemporal nerves, sometimes accompanied by diminished sensation or dysaesthesia in the affected area and commonly associated with tenderness over the involved nerve(s).

Bridge therapy A therapy intended to serve as a bridge from the attack and preventive managements of headache disorders.

Cervicogenic headache Headache caused by a disorder of the cervical spine and its component bony, disc, and/or soft tissue elements, usually but not invariably accompanied by neck pain.

Chronic daily headache A headache disorder for more than 4 h on more than 15 days/month. Some people experience these headaches for a period of 6 months or longer.

Chronic migraine Headache occurring on 15 or more days/month for more than 3 months, which, on at least 8 days/month, has the features of migraine headache.

Chronic tension-type headache A disorder evolving from frequent episodic tension-type headache, with daily or very frequent episodes of headache, typically bilateral, pressing or tightening in quality and of mild to moderate intensity, lasting hours to days, or unremitting.

Cluster headache Specific headache disorder defined as attacks of severe, strictly unilateral pain that is orbital, supraorbital, temporal or in any combination of these sites, lasting 15–180 min and occurring from once every other day to eight times a day.

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Great occipital nerve (GON) A nerve that is the main sensory nerve to the occipital area and has been associated with various pain syndromes such as occipital neuralgia, cervicogenic headaches, and migraines.

Headache Specific pain disorders located on the head and neck area.

Hemicrania continua Persistent, strictly unilateral headache, associated with ipsilateral conjunctival injection; lacrimation; nasal congestion; rhinorrhea; forehead and facial sweating; miosis, ptosis, and/or eyelid edema; and/or with restlessness or agitation.

Interventional techniques Feasible treatment options performed using specific instrumentations in experienced hands for headache management.

Lesser occipital nerve (LON) A nerve that is a cutaneous branch of the cervical plexus that innervates the skin of the neck and scalp posterior and superior to the auricle.

Local anesthesia The name of a group of techniques used to induce absence of sensation in a specific part of the body.

Medication overuse headache (MOH) Headache occurring on 15 or more days/month in a patient with a preexisting primary headache and developing as a consequence of regular overuse of acute or symptomatic headache medication (on 10 or more or 15 or more days/month, depending on the medication) for more than 3 months.

Migraine Specific type of headache disorders with repeated defined phenotype together with associates and comorbidities.

Neuromodulation A specific procedure with the alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body.

New daily persistent headache Persistent headache, daily from its onset, which is clearly remembered. The pain lacks characteristic features, and may be migraine-like or tension-type-like, or have elements of both.

Nociception The sensory nervous system's response to certain harmful or potentially harmful stimuli.

Occipital neuralgia Unilateral or bilateral paroxysmal, shooting, or stabbing pain in the posterior part of the scalp, in the distribution(s) of the greater, lesser, and/or third occipital nerves, sometimes accompanied by diminished sensation or dysaesthesia in the affected area and commonly associated with tenderness over the involved nerve(s).

Onabotulinum toxin-A management Onabotulinum toxin A (BoNT-A) is an approved treatment for the prevention of chronic migraine (CM), one of the most disabling and burdensome of human conditions.

Ozone management A safe, inexpensive, and effective clinical tool with a wide range of therapeutic applications including migraine and some headache disorders.

Peripheral nerve block A procedure in which an anesthetic agent is injected directly near a nerve to block pain.

Postdural puncture headache Headache occurring within 5 days of a lumbar puncture, caused by cerebrospinal fluid (CSF) leakage through the dural puncture.

Posttraumatic headache Headache caused by traumatic injury to the head.

PREEMPT protocol A specific protocol approved by FDA and other national agencies for migraine and cluster headache management with application onabotulinumtoxin-A on 31 point, per point 5 unite, totally 155 unite.

Preventive (prophylactic) management Specific medications or interventions for preventing next headache attacks and associates.

Refractory headache attack Specific headache disorders could not relieve after more than three relevant headache management options according to guidelines.

RF thermocoagulation Radiofrequency current is used to heat up a small volume of nerve tissue, thereby interrupting pain signals from that particular area.

Sphenopalatine ganglion (SPG) A ganglion is a group of nerve cells linked to the trigeminal nerve located behind the nose that carry information about sensations, and play a role in autonomic functions such as tearing and nasal congestion.

Supraorbital nerve (SON) A nerve that is a continuation of the frontal nerve, which is one of the three main branches of the ophthalmic division (V1) of the trigeminal nerve (the fifth cranial nerve).

Supraorbital neuralgia Unilateral or bilateral paroxysmal, shooting or stabbing pain in the posterior part of the scalp, in the distribution(s) of the supraorbital nerves, sometimes accompanied by diminished sensation or dysaesthesia in the affected area and commonly associated with tenderness over the involved nerve(s).

Supratrochlear nerve (STN) A nerve that is a branch of the frontal nerve and supplies sensory innervations to the bridge of the nose, medial part of the upper eyelid, and medial forehead.

Tension-type headache (TTH) Most frequent type of primary headache disorders with or without pericranial tenderness and specific pathophysiological phenotypic presentation.

Transcutaneous direct current stimulation (tDCS) A form of neurostimulation that uses constant, low direct current delivered via electrodes on the head; it can be contrasted with cranial electrotherapy stimulation that generally uses alternating current the same way in order to improve some headache disorders.

Transcutaneous electrical nerve stimulation (TENS) A specific technique involves the use of low-voltage electric currents to treat pain.

Transcutaneous magnetic stimulation (TMS) A noninvasive procedure that uses magnetic fields to stimulate nerve cells in the brain for modulating neuronal functions in order to improve some headache disorders including migraine.

Trigeminal autonomic cephalgias (TACs) Specific group of headache disorders defined as sharing the clinical features of unilateral headache and, usually, prominent cranial parasympathetic autonomic features that are lateralized and ipsilateral to the headache.

Trigeminal neuralgia A disorder characterized by recurrent unilateral brief electric shock-like pains, abrupt in onset and termination, limited to the distribution of one or more divisions of the trigeminal nerve and triggered by innocuous stimuli.

Trigger point injection An effective treatment modality for inactivating trigger points and providing prompt relief of symptoms from myofascial pain syndrome and some headache disorders.