MEDICA REVIEW | Vol. 10, No. 2, 2022 | ISSN 2660-6801
International Medical Humanities Review / Revista Internacional de Humanidades Médicas
https://doi.org/10.37467/gkarevmedica.v10.3227

THERAPY WITH LOCAL ANESTHETIC IN A PATIENT WITH PRIMARY HEADACHE AND LIPID KERATOPATHY

Case Report and Pathophysiological Discussion

ANDREA CATALINA NASSAR TOBÓN[1], PAOLA ANDREA PÉREZ BENJUMEA[2], DAVID VINYES[3]

[1,2] San Rafael University Hospital Clinic of Bogotá, Colombia
[3] Institute of Neural Therapy and Regulatory Medicine, Sabadell, Barcelona, Spain

KEYWORDS

Primary bilateral lipid keratopathy
Headache
Therapy with local anesthetics
Neural therapy

ABSTRACT

A headache is characterized as a craniofacial pain that may derive from any involvement of the structure of the head, neck or cranial cavity. It may be associated with any pathology, negatively affecting the quality of life of the individuals afflicted by it. We present the case of a woman with bilateral lipid keratopathy associated with a headache of a moderate to severe intensity, refractory to treatment with non-steroidal anti-inflammatory drugs, treated with lidocaine 1% injections in supraorbital and infraorbital nerves. A clear improvement was observed in visual symptoms and headache with a decrease in symptom frequency, duration and intensity. The improvement lasted over 6 months, which positively impacted the patient's quality of life. The treatment was well tolerated and no adverse effects were observed. In this case, local injections of lidocaine showed a favorable outcome. Well-designed studies should be conducted to elucidate the role of LA for this condition.

Received: 21/ 02 / 2022
Accepted: 10/ 03 / 2022

Introduction

A headache is characterized as a craniofacial pain that may derive from any involvement of the structure of the head, neck or cranial cavity. These are entities that share a characteristic pathophysiology, with well-defined clinical manifestations, influenced by individual symptomology (Rasmussen & Olesen, 1992).

In adult populations, 90% of cases have had at least one episode of headache at some time, whereas, in 50-60% of cases, the frequency is variable and repetitive (Ruiz et al., 2010), becoming an important cause of loss of money due to the disability it generates at the occupational level (Vos et al., 2012); an example of this is the European Community that, according to statistics, reports expenses of around 286 million euros (Olesen et al., 2012). The classification proposed by the International Headache Society (IHS) in January 2018 (Goadsby & Evers, 2020) (Table 1), allowed a proper classification, which is paramount for proper diagnosis and treatment (Olesen et al., 2013).

Table 1. Classification of Headaches (IHS)

Primary	
1. Migraine	1.1. Migraine without aura, 1.2. Migraine with aura, 1.2.1. Migraine with typical aura, 1.2.1.1 Typical aura with headache, 1.2.1.2 Typical aura without headache, 1.2.2. Migraine with brain stem aura, 1.2.3 Hemiplegic migraine, 1.2.3.1 Familial hemiplegic migraine, 1.2.3.1.2. Familial hemiplegic migraine type 1, 1.2.3.1.2 Familial hemiplegic migraine type 2, 1.2.3.1.3 Familial hemiplegic migraine type 3, 1.2.3.1.4 Familial hemiplegic migraine, other loci, 1.2.3.2 Sporadic hemiplegic migraine, 1.2.4. Retinal migraine 1.3. Chronic migraine, 1.4. Migraine complications, 1.4.1 Status migrainosus, 1.4.2 Persistent aura without infarction, 1.4.3 Migrainous infarction, 1.4.4 Migraine aura triggering seizure, 1.5 Probable migraine, 1.5.1 Probable migraine without aura, 1.5.2 Probable migraine with aura, 1.6 Episodic syndromes that may be associated with migraine, 1.6.1 Recurrent gastrointestinal disorders, 1.6.1.1 Cyclic vomiting, 1.6.1.2 Abdominal migraine, 1.6.2 Benign paroxysmal vertigo, 1.6.3 Benign paroxysmal torticollis
2. Tension headache	2.1. Infrequent episodic tension headache, 2.1.1. Infrequent episodic tension headache with pericranial muscle involvement, 2.1.2. Infrequent episodic tension headache without pericranial muscle involvement, 2.2.2. Frequent episodic tension headache, 2.2.1. Frequent episodic tension headache with pericranial muscle involvement, 2.2.2. Frequent episodic tension headache without involvement of pericranial muscles, 2.3. Chronic tension headache, 2.3.1. Chronic tension headache with involvement of pericranial muscles, 2.3.2. Chronic tension headache without involvement of pericranial muscles, 2.4. Probable tension headache, 2.4.1. Probable episodic infrequent tension headache, 2.4.2. Probable episodic frequent tension headache, 2.4.3. Probable chronic tension headache
3. Trigeminal autonomic headaches	3.1. Cluster headache, 3.1.1. episodic cluster headache, 3.1.2. Chronic cluster headache, 3.2. Paroxysmal hemicrania, 3.2.1. Episodic paroxysmal hemicrania, 3.2.2. Chronic paroxysmal hemicrania, 3.3. Short-lasting unilateral neuralgiform headache, 3.3.1 Short-lasting unilateral neuralgiform headache associated with Conjunctival Injection and Tearing (SUNCT), 3.3.1.1 Episodic SUNCT, 3.3.1.2 Chronic SUNCT, 3.3.2 Short-lasting unilateral neuralgiform headache is associated with Cranial Autonomic Symptoms (SUNA), 3.3.2.1 Episodic SUNA, 3.3.2.2 Chronic SUNA, 3.4. Continuous hemicrania, 3.5. Probable trigeminal autonomic headache, 3.5.1 Probable cluster headache, 3.5.2 Probable paroxysmal hemicrania, 3.5.3 Probable short-lasting unilateral neuralgiform headache, 3.5.4 Probable hemicrania continua
4. Other primary headaches	4.1. Primary stabbing headache, 4.2. Primary cough headache, 4.3. Primary exercise-related primary headache, 4.4. Primary headache associated with sexual activity, 4.5. Hypnic headache, 4.6. Primary thunderclap headache, 4.7. Continuous hemicrania 4.8. Persistent daily headache
Secondary	
5. Headache attributed to trauma or injury of the neck and/or head, 6. Headache attributed to cranial or cervical	

	vascular disorder, 7. Headache attributed to non-vascular intracranial disorder, 8. Headache attributed to substance use or suppression, 9. Headache attributed to infections, 10. Headache attributed to homeostatic disorders, 11. Headache or facial pain attributed to cranial disorders, of neck, eyes, ears, nose, sinuses, teeth, mouth and other facial or cranial structures, 12, Headache associated with psychiatric disorders.
Painful cranial neuropathies, facial pain and other headaches	13. Painful cranial neuropathies and other facial pain, 14. Other headache disorders.

These entities may be associated with any pathology, negatively affecting the quality of life of the individuals afflicted by it, as in this case of a patient who has bilateral idiopathic lipid keratopathy, a rare disease where there is an opacification of the cornea secondary to lipid deposits. It is classified as primary or idiopathic, and secondary. The most frequent clinical manifestations are photophobia, epiphora, blurred vision and decreased visual acuity (Castro-Rebollo et al., 2009; Miranda,et al., 2016). Diagnosis is clinical, paraclinical, and with biopsy. Treatment is with steroids, laser, photodynamic therapy (PDT), fine needle diathermy (FND), and penetrating keratoplasty (PKP) (Pang et al., 2019).

Since their origin, local anesthetics (LA) have been used for their therapeutic effects, in addition to their anesthetic effect. Therapy with local anesthetics (TLA) (in Central Europe also known as neural therapy) is an effective method to treat chronic pain (Weinschenk, 2012; Rey et al. 2021). In neural therapy (NT), the injection treatment makes use of the regulatory functions and plastic properties of the nervous system, especially its autonomic part (Engel, 2022), and it has been found to be a therapeutic alternative for people with a diagnosis of primary headache (Nassar et al., 2021). This technique's primary purpose is to serve as something other than local anesthesia. In addition to nerve-blocking and membrane-stabilizing effects, a wide range of attributes have been related to LAs (Cassuto et al., 2006, Hollmann et al., 2004). LAs also appear to have a profound anti-inflammatory effect through polymorphonuclear neutrophil mediators and free radical release (Hollmann et al., 2004). TLA has a safety profile, prolonged action beyond pharmacological duration, and additional favorable effects on microcirculation (Egli et al., 2015, Nazlikul et al., 2018).

Below, we discuss the case of a patient with primary headache and lipid keratopathy, who received treatment with TLA and showed an adequate response and tolerance to the treatment followed; with a decrease in symptom frequency, duration, and intensity.

Case report

A 53-year-old female patient who shows, since she was 18 years old, a sensation of a whitish spot predominantly in the right eye and subsequently, in the left eye, which progressively deteriorated the visual fields in 70% and 20%, respectively, associated with ocular irritation, photophobia, and scintillating scotomas. She attended multiple medical examinations without a clear diagnosis and without abnormal laboratory findings. An angiography determined a diagnosis of bilateral lipid keratopathy (Figure 1 and 2).

During the evolution of the lipid keratopathy, the patient reported 3 to 4 crises of bilateral fronto-orbital pulsating headache per week, with an average duration of 5 hours and of intensity 8/10 (VAS). Pain worsened working in front of the computer and sometimes disabling her in her daily life.

She progressively developed symptoms of nausea, occasionally emesis, tinnitus and constant photophobia; therefore, she self-medicated with acetaminophen, ibuprofen, diclofenac, acetaminophen plus codeine, and tramadol without any improvement whatsoever.

Consequently, she attended a neurology outpatient clinic, receiving a normal neurological examination and needing further neuroimaging studies due to no abnormal findings. TLA was indicated.

The intervention consisted of injections of preservative free 1% lidocaine without epinephrine in the scalp and in supraorbital and infraorbital nerves. Therapy in the scalp involved 0.2 cc subcutaneous injections several inches apart around the largest diameter of the head. For the injection into the supraorbital and infraorbital nerves, 0.5cc of lidocaine 1% were infiltrated in the vicinity of the supraorbital (Figure 3) and infraorbital (Figure 4) foramina, respectively. Immediately after the

first intervention, the patient reported a clear improvement of the associated blurred vision. One week later, there was a 90% improvement in visual symptoms and in headache pain, which was also less frequent and shorter. Three months later, the symptoms reappeared, with pain intensity VAS 4/10, and a second session were conducted. Again, there was a clear improvement of symptoms for three months. Thus, interventions were performed every 3 months, with a total of 5 sessions. It was possible to observe that the symptoms returned with decreasing intensity each time. The patient was completely pain-free at follow-up visits 6 and 7 and continued to report a marked improvement in visual symptoms, so no further interventions were performed.

Figure 1. Angiographic study of the right eye.

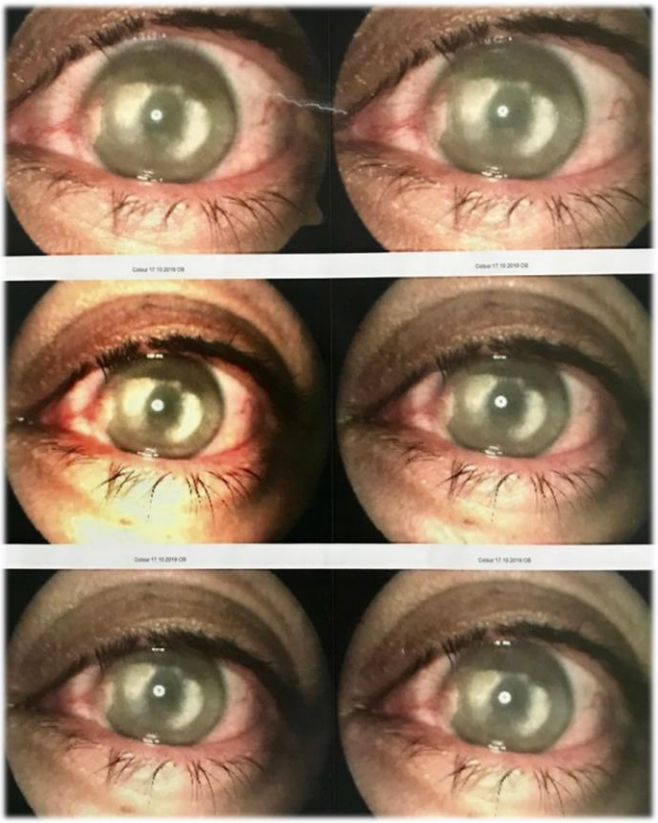
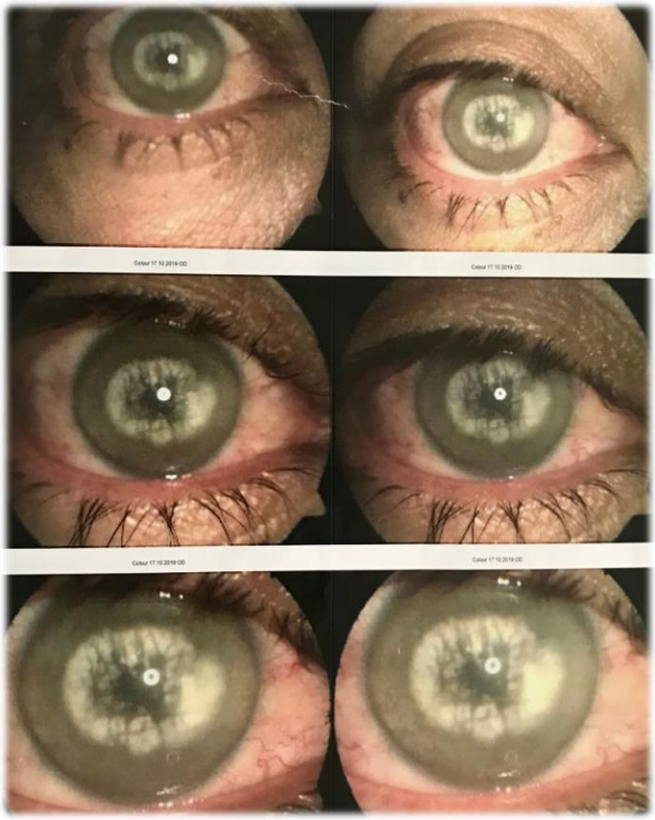


Figure 2. Angiographic study of the left eye.



Source for both figures: San Rafael University Hospital Clinic of Bogotá

Discussion

One of the most prevalent reasons for visiting the emergency room (Volcy, 2008), as well as in outpatient consultations (Loreto, 2014), is the clinical picture of headache, a pathology that is described as the presence of craniofacial pain originating in the head, neck, or cranial cavity (Rasmussen & Olesen, 1992) usually related to a recurrent and disabling symptomatology worldwide (Burch et al., 2018); it largely affects youth, without a large number of comorbidities and predominant in females in the reproductive stage (Buse et al., 2013).

Thus, for a good clinical practice with therapeutic and prognostic guidelines, the IHS classified into 3 divisions: primary, secondary, and cranial neuropathies (Goadsby & Evers, 2020) (Table 1).

It is key to take a very good medical history: age at onset of symptoms, location, pain characteristics, evolution time, frequency, duration, intensity, associated symptoms (Clinch, 2001), emphasizing warning signs or "red flags" (Do et al., 2019). The review by systems and the physical and neurological examination should be aimed at searching pathological findings such as: papilledema, optic atrophy, retinal hemorrhage, cranial nerve injury, epiphora, rhinorrhoea, Horner's syndrome, pain in the temporomandibular joint, or hardening of the temporal artery on palpation, ear involvement, motor, sensory, coordination, or gait deficits, as well as meningeal signs (Locker et al.,

2006). It should be noted that finding abnormalities in the neurological examination is one of the best predictors of lesions in the central nervous system (Edlow et al., 2008) and, therefore, will require complementary studies (Olesen et al., 2013).

Thus, laboratories must evaluate infectious or inflammatory processes or red line involvement; hemogram, glycemia, blood chemistry, liver enzymes to study metabolic causes and acute phase reactants, including erythrocyte sedimentation rate (ESR) to study temporal arteritis in cases where the value exceeds 40 mm/h (Clinch, 2001; Do et al., 2019; Locker et al., 2006). At the same time, neuroimaging tests performed will either be with computed tomography (CT) or magnetic resonance imaging (MRI), choice which will result from the diagnostic suspicion and their availability (Clinch, 2001; Locker et al., 2006). In addition, if the clinical picture is related to a diagnosis of meningitis and signs of endocranial hypertension or involvement of the central nervous system of the patient with cancer or HIV are documented, a lumbar puncture is performed (Baraff et al., 2010; Rothman et al., 1999).

Therefore, treatment is characterized by being multifactorial (Hickman, 1983), initially improving lifestyle, controlling comorbidities and, most importantly, tailoring the treatment to each patient. In the acute phase, analgesics can be formulated, avoiding their abuse to prevent side effects or prolonged symptoms. For changes in the frequency, duration, and intensity of episodes, prophylactic treatment is used, including anticonvulsants, beta-blockers, calcium-antagonists, tricyclic antidepressants and selective serotonin reuptake inhibitors, which are prescribed for a period of 3 to 6 months (Hickman, 1983; Scottish Intercollegiate Guidelines Network, 2020), and considering improvement the decrease in symptom frequency, duration, and intensity by 50% (Scottish Intercollegiate Guidelines Network, 2018).

As supplemental interventions we propose applying botulinum toxin type A (Onabotulinum Toxin A-Botox) (Dodick et al., 2010), acupuncture, physical therapy, neurofeedback, peripheral pericranial blocks, and NT (Nassar et al., 2021).

In this case, the patient has bilateral idiopathic lipid keratopathy, an entity characterized by corneal opacification secondary to the deposition of yellowish-white substances or lipoid deposits (Castro-Rebollo et al., 2009). It is a rare disease, with no clear distinction in prevalence according to gender or age, which causes relatively symmetrical bilateral deposits and a progressive but slow development (Castro-Rebollo et al., 2009). It is classified as primary or idiopathic due to the intrinsic alteration of the local keratinocyte with necrosis or by the presence of an inflammation in the corneo-scleral limbus causing the vascularization of the cornea and thus favoring lipid deposition (Castro-Rebollo et al., 2009). On the other hand, when classified as secondary, it is characterized by corneal involvement, vascular exudation, alterations in lipid metabolism, infectious diseases such as *Herpes simplex virus* (HSV), *Herpes zoster virus* (HZV), trachoma or trauma (Levy et al., 2005; Miranda et al., 2016).

The most frequent clinical manifestations are photophobia, epiphora, ocular irritation, foreign body sensation, decreased visual acuity or a usually whitish spot (Castro-Rebollo et al., 2009; Silva-Arautjo et al., 1993).

The diagnosis is made by taking limbal conjunctival tissue and corneal button, taking them under electron microscopy examinations and staining; in addition to tissue dissections, Baker, Sudan Black B and oil red stains are performed, which help the diagnosis if they are positive for intra and extracellular fats. The first and second staining systems represent findings of phospholipids and the third one of triglycerides (Silva-Arautjo et al., 1993).

Treatment is with steroids, fluorescein-enhanced argon laser therapy, photodynamic therapy (PDT), fine needle diathermy (FND), and penetrating keratoplasty (PKP) (Pang et al., 2019).

In this case report, in addition to the patient's ophthalmologic treatment, we performed TLA (NT), observing a progressive improvement in the frequency, duration, and intensity of the headache until the patient was pain free and with a 90% improvement in her visual symptoms. The treatment was well-tolerated and no adverse effects were observed. Since it is a minimally invasive technique, the treatment can be performed on an outpatient basis.

We considered that TLA, by injecting the pericranial nerves, especially the supraorbital (Figure 3) and infraorbital (Figure 4) nerves, terminal branches of the ophthalmic (V1) and maxillary (V2) nerves, respectively, which in their path have filaments up to the eyelids and conjunctiva (Blumenfeld

et al., 2013; Silva-Arautjo et al., 1993), applying a minimal amount of LA, usually lidocaine 1%, could have an effective therapeutic effect.

Figure 3. Supraorbital nerve

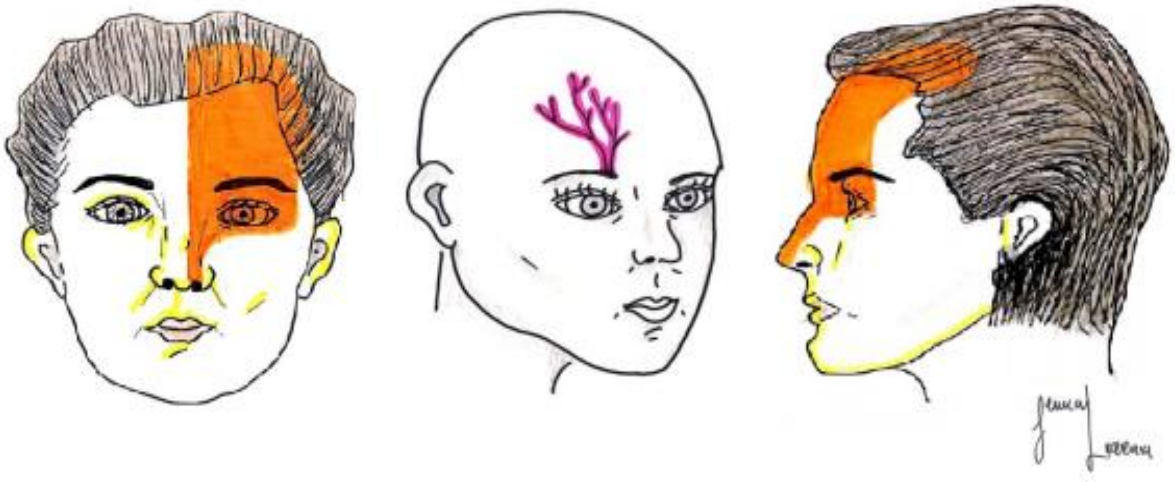
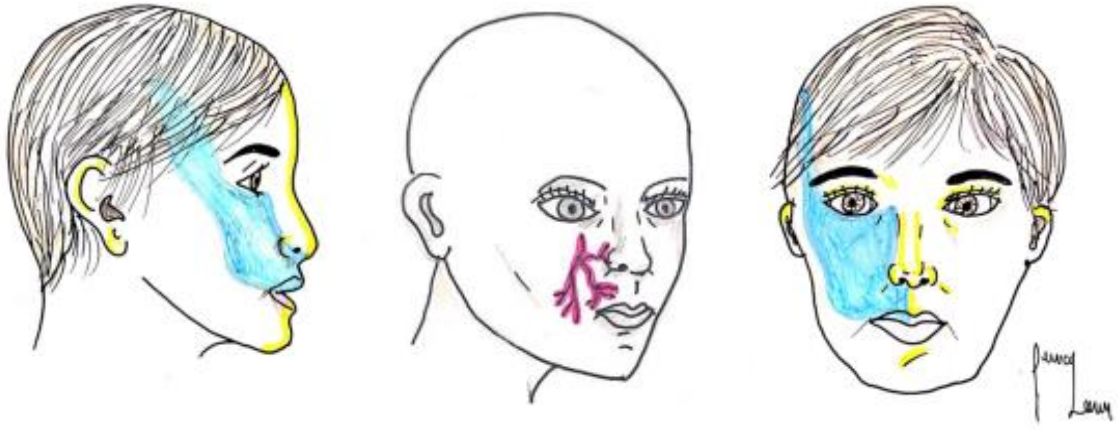


Figure 4. Infraorbital nerve



Source for both figures: Images by Jessica Lorena Vásquez García

It is known that LAs are drugs that have a fast therapeutic effect facilitating the interruption of nerve impulse conduction by blocking the sodium current during depolarization (Santos et al., 2017). An example of this occurs with lidocaine, which exerts its effect primarily on damaged nerves, preventing depolarization of neuronal membranes, decreasing the proliferation of active sodium channels, blocking their activation in traumatized tissues or tissues with scar tissue (Eipe et al., 2016). But the main purpose of NT (TLA) is to serve as something other than local anesthesia.

In this case, the objective is the generation of a directed stimulus (set by the needle prick) and the short-term selective extinction of other stimuli (by the LA), in the sense of a *reset* influence on both the organization of the nervous system and tissue perfusion (Egli, et al., 2015; Cassuto et al., 2006). Current understanding indicates an interaction between sensory and sympathetic nerve fibers, as well as the immune system and inflammation (Chavan et al., 2017). Sympathetic nervous system plays an important part in the pathological positive feedback loops related with chronic pain and inflammation. Consequently, with TLA (NT) there is a chance to regulate the hyperinflammation by influencing the Sympathetic nervous system, temporarily disrupting the pathological positive feedback loops (Fischer et al., 2022). Therefore, the LA therapeutic effect usually outlasts the lasting effect of the anesthesia by far (Rey et al, 2021, Engel et al. 2022).

In recent decades, a wide range of attributes have been related to LAs beyond their anesthetic effect, lasting longer than their anesthetic effect and with lower doses than those required to block Na+ channels. These properties have been related to their effects on K+ and Ca2+ channels (Scholz, 2002), inhibitory effects on G protein coupled receptors (Cassuto et al., 2006) and inhibitory effects on *N*-methyl-D-aspartate (NMDA) receptors (Hahnenkamp et al., 2006).

LAs also appear to have a profound anti-inflammatory effect (Hollmann, et al., 2004) and can interrupt the release of proinflammatory substances at the neuron end plate (Watkins et al.,2001). LAs may interrupt the vicious circle of nociceptors described by acting on different pathogenic mechanisms involved in pain perception, such as sympathetic excitation, vascular alteration, neurogenic inflammation, and muscle contraction. (Egli, et al., 2015; Cassuto et al., 2006). Thus, LAs used in NT (TLA) are believed to reduce pathological nociceptive activity and eliminate the pathological memory of the sympathetic nervous system, providing long-term pain relief (Egli, et al., 2015).

As in our case, the reduction of perceived pain after each session is a common observation of NT; this is considered a beneficial diagnostic sign and if necessary, additional sessions may be performed (Egli, et al., 2015). Several authors have reported the impact on health-related quality of life, measured by the SF-36 before and after NT (TLA), in patients with primary headache (Nassar et al., 2021). For these reasons, TLA (NT) may be useful in treating headache attributed to eyes disorders.

Conclusion

We have described a woman with bilateral lipid keratopathy associated with a headache, which ameliorated after treatment with local anesthetic therapy. TLA (neural therapy) may be a first-line or adjunctive therapy to pharmacologic treatment for primary and/or secondary headaches associated with visual symptoms of ophthalmologic diseases such as lipid keratopathy. Although the literature is still scarce, the good results described show that through this procedure, it is possible to achieve a temporary relief of symptoms in an effective and safe manner with minimal risks and complications. Well-designed studies should be further conducted to elucidate the role of LAs for this condition.

Abbreviations

PDT: Photodynamic Therapy
FND: Fine Needle Diathermy
LA: Local Anesthetic
NT: Neural Therapy
TLA: Treatment with Local Anesthetics
PKP: Penetrating Keratoplasty
TAC: Computed Axial tomography
RM: Magnetic Resonance Imaging
HSV: Herpes Simplex Virus
HZV: Herpes Zoster Virus

Acknowledgements

The authors would like to thank the teaching and research group, the scientific and general management of the San Rafael University Hospital Clinic of Bogotá, as well as the department of internal medicine, and the artist and graphic designer Jessica Lorena Vásquez García for the creation of figures 3 and 4, who granted copyright for the case in question.

Funding sources

Authors received no external funding to conduct this study.

Conflict of interests

The authors declare that they have no conflicts of interest.

Consent for publication

After obtaining the patient's written informed consent for the publication of this case report and the accompanying images, it was submitted to the Research Ethics Committee of the San Rafael University Hospital Clinic of Bogotá, with its subsequent approval. A copy is available for review.

References

Baraff, L.J., Byyny, R.L., Probst, M.A., Salamon, N., Linetsky, M., & Mower, W.R. (2010). Prevalence of herniation and intracranial shift on cranial tomography in patients with subarachnoid hemorrhage and a normal neurologic examination. *Academic Emergency Medicine, 17*(4), 423–428. https://doi.org/10.1111/j.1553-2712.2010.00704.x

Blumenfeld, A., Ashkenazi, A., Napchan, U., Bender, S.D., Klein, B.C., Berliner, R., Ailani, J., Schim, J., Friedman, D. I., Charleston IV, L., Young, W.B., Robertson, C.E., Dodick, D.W., Silberstein, S.D., & Robbins, M.S. (2013). Expert consensus recommendations for the performance of peripheral nerve blocks for headaches - A narrative review. *Headache, 53*(3), 437–446. https://doi.org/10.1111/head.12053

Burch, R., Rizzoli, P., & Loder, E. (2018). The Prevalence and Impact of Migraine and Severe Headache in the United States: Figures and Trends From Government Health Studies. *Headache, 58*(4), 496–505. https://doi.org/10.1111/head.13281

Buse, D.C., Loder, E.W., Gorman, J.A., Stewart, W.F., Reed, M.L., Fanning, K.M., Serrano, D., & Lipton, R.B. (2013). Sex differences in the prevalence, symptoms, and associated features of migraine, probable migraine and other severe headache: Results of the American Migraine prevalence and prevention (AMPP) study. *Headache, 53*(8), 1278–1299. https://doi.org/10.1111/head.12150

Cassuto, J., Sinclair, R., & Bonderovic, M. (2006). Anti-inflammatory properties of local anesthetics and their present and potential clinical implications. *Acta Anaesthesiol Scand., 50*(3), 265–282. https://doi.org/10.1111/j.1399-6576.2006.00936.x

Castro-Rebollo, M., Montes-Moloón, M., & Pérez-Rico, C. (2009). Queratopatía lipoidea primaria bilateral. *Archivos de La Sociedad Espanola de Oftalmologia, 84*(5), 263–266. https://doi.org/10.4321/s0365-66912009000500008

Chavan, S.S., Pavlov, V.A., & Tracey, K.J. (2017). Mechanisms and Therapeutic Relevance of Neuro-immune Communication. *Immunity, 46*(6), 927-942. https://bit.ly/3yiN66n

Clinch, C.R. (2001). Evaluation of acute headaches in adults. *American Family Physician, 63*(4), 685–692. https://doi.org/10.1016/s1443-8461(01)80045-9

Do, T.P., Remmers, A., Schytz, H.W., Schankin, C., Nelson, S.E., Obermann, M., Møller Hansen, K., SInclair, A.J., Gantenbein, A.R., & Schoonman, G.G. (2019). Red and orange flags for secondary headaches in clinical practice: SNNOOP10 list. *Neurology, 92*(3), 134–144. https://doi.org/10.1212/WNL.0000000000006697

Dodick, D.W., Turkel, C.C., Degryse, R.E., Aurora, S.K., Silberstein, S.D., Lipton, R.B., Diener, H.C., & Brin, M.F. (2010). OnabotulinumtoxinA for treatment of chronic migraine: Pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. *Headache, 50*(6), 921–936. https://doi.org/10.1111/j.1526-4610.2010.01678.x

Edlow, J.A., Panagos, P.D., Godwin, S.A., Thomas, T.L., & Decker, W.W. (2008). Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients Presenting to the Emergency Department With Acute Headache. *Annals of Emergency Medicine, 52*(4), 407–436. https://doi.org/10.1016/j.annemergmed.2008.07.001

Egli, S., Pfister, M., Ludin, S., Puente de la Vega, K., Busato, A., & Fischer, L. (2015). Long-Term Results of Therapeutic Local Anesthesia (Neural Therapy) in 280 Referred Refractory Chronic Pain Patients. *BMC complementary and alternative medicine*, *15*, 200. https://bit.ly/3AsjMwP

Eipe, N., Gupta, S., & Penning, J. (2016). Intravenous lidocaine for acute pain: an evidence-based clinical update. *BJA Education, 16*(9), 292–298. https://doi.org/10.1093/bjaed/mkw008

Engel, R., Barop, H., Giebel, J., Ludin, S.M., & Fischer, L. (2022) The Influence of Modern Neurophysiology on the Previous Definitions of "Segment" and "Interference Field" in Neural Therapy. *Complement Medicine Research, 29*(3), 257-267. https://doi: 10.1159/000522391

Fischer, L., Barop, H., Ludin, S.M., & Schaible, H.G. (2022). Regulation of acute reflectory hyperinflammation in viral and other diseases by means of stellate ganglion block. A conceptual view with a focus on Covid-19. *Autonomic Neuroscience*, *237*, 102903, 1-13. https://doi: 10.1016/j.autneu.2021.102903

Goadsby, P.J., & Evers, S. (2020). International Classification of Headache Disorders - ICHD-4 alpha.

Cephalalgia, *40*(9), 887–888. https://doi.org/10.1177/0333102420919098

Hahnenkamp, K., Durieux, M., Hahnenkamp, A., Schauerte, S., Hoenemann, C., Vegh, V., Theilmeier, G., & Hollmann, M. (2006). Local Anaesthetics Inhibit Signalling of Human NMDA Receptors Recombinantly Expressed in Xenopus Laevis Oocytes: Role of Protein Kinase C. *British Journal of Anaesthesia, 96*(1), 77-87. https://doi:10.1093/bja/aei271

Hickman, F.R. (1983). Guideline for primary care management of headache in adults. I*nternational Journal of Mathematical Education in Science and Technology, 14*(4), 445–448. https://doi.org/10.1080/0020739830140409

Hollmann, M., Herroeder, S., Kurz, K., Hoenemann, C., Struemper, D., Hahnenkamp, K., & Durieux, M. (2004). Time-dependent Inhibition of G Protein-coupled Receptor Signaling by Local Anesthetics. *Anesthesiology*, *100*(4), 852-860. https://bit.ly/3ykBMqw

Levy, J., Benharroch, D., & Lifshitz, T. (2005). Bilateral severe progressive idiopathic lipid keratopathy. *International Ophthalmology, 26*(4–5), 181–184. https://doi.org/10.1007/s10792-007-9032-2

Locker, T.E., Thompson, C., Rylance, J., & Mason, S.M. (2006). The utility of clinical features in patients presenting with nontraumatic headache: An investigation of adult patients attending an emergency department. *Headache, 46*(6), 954–961. https://bit.ly/3P7P0h9

Loreto, M. (2014). Headaches, Assessment and Initial Management. *Rev.Med.Clin.Condes, 25*(4), 651–657.

Miranda, S., Tandón, U., Medina, F., Hernández, D., & Viera, D. (2016). Degeneración nodular de Salzmann: a propósito de un caso. *Archivos de La Sociedad Canaria de Oftalmología*, *27*, 11–15. https://mdc.ulpgc.es/utils/getfile/collection/scoft/id/531/filename/561.pdf

Nazlıkul, H., Ural, F.G., Öztürk, G.T., & Öztürk, A. (2018). Evaluation of neural therapy effect in patients with piriformis syndrome. *Journal of back and musculoskeletal rehabilitation*, *31*(6), 1105–1110. https://doi.org/10.3233/BMR-170980

Nassar, A.C., Geney, M.C., Martínez, F.H., Muñoz-Sellart , M., & Vinyes, D. (2021). Improving the Quality of Life of Patients with Headache Treated with Neural Therapy. MEDICA REVIEW. I*nternational Medical Humanities Review / Revista Internacional De Humanidades Médicas, 9*(1), 13–28. https://doi.org/10.37467/gkarevmedica.v9.3015

Olesen, J., Gustavsson, A., Svensson, M., Wittchen, H. U., & Jönsson, B. (2012). The economic cost of brain disorders in Europe. *European Journal of Neurology, 19*(1), 155–162. https://doi.org/10.1111/j.1468-1331.2011.03590.x

Olesen, J., Bes, A., Kunkel, R., Lance, J. W., Nappi, G., Pfaffenrath, V., Clifford Rose, F., Schoenberg, B. S., Dieter, S., Tfelt-Hansen, P., Welch, K. M. A., Wilkinson, M., Germaine Bousser, M., Diener, H. C., Dodick, D., First, M., Goadsby, P. J., Göbel, H., Lainez, M. J. A., ... Wöber-Bingöl, C. (2013). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia, 33*(9), 629–808. https://doi.org/10.1177/0333102413485658

Pang, Y., Zhang, Q., & Bao, Y. (2019). A CARE-compliant article: ipsilateral progressive idiopathic lipid keratopathy: A case report. *Medicine, 98*(35), e16589. https://bit.ly/3AxX6vv

Rasmussen, B.K., & Olesen, J. (1992). Symptomatic and nonsymptomatic headaches in a general population. *Neurology, 42*(6), 1225 LP – 1225. https://doi.org/10.1212/WNL.42.6.1225

Rey, M., Muñoz, M., Catalán, M., & Vinyes, D. (2021). Treatment of Localized Vulvar Pain with Neural Therapy: A Case Series and Literature Review. *Complement Med Res, 28*(6), 571-577. https://doi.org/10.1159/000514945

Rothman, R.E., Keyl, P.M., McArthur, J.C., Beauchamp, N.J., Danyluk, T. & Kelen, G D. (1999). A decision guideline for emergency department utilization of noncontrast head computed tomography in HIV-infected patients. *Academic Emergency Medicine, 6*(10), 1010–1019. https://doi.org/10.1111/j.1553-2712.1999.tb01184.x

Ruiz, M., León, C., Castillo, J., Martínez, M., Sánchez, S., & Quintela, E. (2010). Distribución por diagnósticos de las cefaleas que acuden a los servicios de urgencias de atención primaria. *Semergen, 36*(1), 10–15. https://doi.org/10.1016/j.semerg.2009.10.002

Santos, S., Cuadrado, M.L., Guerrero, A.L., Huerta, M., Porta, J., Pozo, P., & Pareja, J.A. (2017). Guía consenso sobre técnicas de infiltración anestésica de nervios pericraneales. (Consensus recommendations for anaesthetic peripheral nerve block). *Neurología, 32*(5), 316–330. https://doi.org/10.1016/j.nrl.2016.04.017

Scholz, A. (2002). Mechanisms of (Local) Anaesthetics on Voltage-gated Sodium and Other Ion Channels. British Journal of *Anaesthesia, 89*(1), 52-61. https://doi:10.1093/bja/aef163

Scottish Intercollegiate Guidelines Network. (2018). Pharmacological management of migraine : a national clinical guideline. Healthcare Improvedment Scotland, 45. https://bit.ly/3uqotn6

Silva-Arautjo, A., Tavares, M.A., Lemos, M.M., Soares, M.I., Castro, J., & Salgado, J. (1993). Primary lipid keratopathy: a morphological and biochemical assessment. *British Journal of Ophthalmology, 77,* 248–250.

Volcy, M. (2008). Cefalea en el servicio de urgencias: nuevos conceptos en el diagnóstico, la epidemiología y el tratamiento. *Acta Neurol Colomb*, *24*(4) 118–133. https://bit.ly/2K3Dzs7

Vos, T., Flaxman, A. D., Naghavi, M., Lozano, R., Michaud, C., Ezzati, M., Shibuya, K., Salomon, J. A., Abdalla, S., Aboyans, V., Ackerman, I., Aggarwal, R., Ahn, S. Y., Ali, M. K., AlMazroa. M. A., Alvarado, M., Anderson, H. R., Anderson, L. M., Andrews, K. G., Atkinson, C., ... Murray, C. J. L. (2012). Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: A systematic analysis for the Global Burden of Disease Study 2010. *The Lancet, 380*(9859), 2163–2196. https://doi.org/10.1016/S0140-6736(12)61729-2

Watkins, L., Milligan, E., & Maier, S. (2001). Glial activation: A driving force for pathological pain. *Trends in neurosciences, 24,* 450-5.

Weinschenk, S. (2012) Neural therapy - a review of the therapeutic use of local anaesthetics. *Acupunct Rel Ther, 1*(1), 5–9. https://doi.org/10.1016/j.arthe.2012.12.004