

Once-Weekly Nocturnal Ocular Choroidal Vascular Decongestion by Topical Long-acting Timolol Ophthalmic Solution Applied to Headache-Ipsilateral eye to Prevent Weekend-Migraine Attacks: Smartphone-app Assisted Case Report of 2 Patients for 3-years and a Brief Mechanistic Review

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Abstract

This clinical study evaluates over medium-to-long term the hypothesis that intermittent spontaneous ocular choroidal vasculature-related congestive and nociceptive corneoscleral envelope distention have a pathogenetic role in genesis of episodic lateralizing migraine headache attacks. No neuro-anatomic or -physiologic difference prevails between the three divisions of the trigeminal nerve, but migraine dominantly affect the ophthalmic division. Use of topical ophthalmic solution for managing acute headache attacks of migraine has given contradictory results in controlled trials. I report the distribution of weekend-migraine headache attacks on a single-participant (N=1) level for 2 patients over a 3-year period (2017-2020) without misuse of any recreational drug other than caffeine on week-days. After a run-in basal period of 6-months recorded on their Smartphones app, with their informed consent, a trial was carried out with topical long-acting β -blocker timolol maleate 0.5% w/v ophthalmic solution once weekly on Saturday night just before sleeping with no other advice to promote nocturnal sleeping or early awakening the next morning; only alcohol binge was proscribed. No week-end attacks of lateralizing migraine headache were reported in the 2 patients over a period of 3- years, a long-term consistent response. The biologically-plausible and defensible mechanistic link between migraine, intraocular pressure, ocular choroidal vasculature, nociceptive corneoscleral envelope aberration, and the pharmacologic basis for therapeutic ocular hypotension for prophylaxis of migraine headache attacks is elucidated for the first time in migraine literature.

Keywords: weekend migraine; intraocular pressure; choroidal vascular circulation; optical coherence tomography; ophthalmic division of trigeminal nerve; migraine pathogenesis; corneoscleral nociceptive neural traffic; timolol maleate; ocular hypotension; migraine preventive therapy; cranial autonomic nervous system

ABBREVIATIONS

AMT – amitriptyline

BP – blood pressure

CSD – cortical spreading depression

CT – choroidal thickness

IOP – intraocular pressure

OCT – optical coherence tomography

RNFL – retinal nerve fibre layer

SD – spreading depression

SS -- scintillating scotoma

TCA–tricyclic antidepressants

TM - timolol maleate

V1 – ophthalmic division of trigeminal nerve

Introduction

Despite advanced technology and a vast literature, including neuroimaging, genetic studies, and artificial intelligence, pathophysiology of migraine remains obscure, and, therefore, its management both pharmacologic and non-pharmacologic remains devoid of defensible and robust therapeutic principles [1,2,3]. Primary involvement of the ophthalmic division (V1) of the trigeminal nerve rather than pan-trigeminal nerve aberration is apparent clinically and holds a fundamental neuro-ophthalmologic, neuro-

pharmacologic, and neuro-endocrinologic integrative promise in migraine research [4-9]. Critical limitations of cortical spreading depression (CSD) as a pathogenetic mechanism for development of lateralizing discrete headache attacks of migraine have been elaborated [4-6,9-11]. CSD has no nociceptive or algogenic influence in mice, as reviewed [4-6,11]. Homonymously distributed SS has never been recorded or drawn by migraine patients or pictorial artists suffering migraine [12,13], as reviewed [4-6]. The typical biphasic migrainous visual aura is a positive visual phenomenon of shimmering lights usually restricted to one half of the visual field followed within minutes by negative symptoms in the affected area akin to a blank scotoma or hemianopia [14]. Nasal visual field involvement by migrainous SS has never been reported [12-14]. More importantly, visual aura and photophobia both disappear along with development of blindness; in addition, the migraine aura is rendered too short or colourful or non-visual (auditory) or dysmorphic (change of shape) [15]. The value of retinal input to the development of SS becomes most clearly evident after enucleation of one or both eyes [15-19], as recently reviewed [4].

Migraine is prominently linked to stress (maladaptive “allostatic load” [20] or “burnout stress/emotional exhaustion” [21] or “maladaptive coping strategy” or “dysfunctional stress-response [22-24]), with the greatest susceptibility to headache attacks evidenced in the post-stress or let-down period [25-27]. There is no definitive link between CSD and either stress or the post-stress / let-down phase. CSD, conversely, has a well-established “protective” or “adaptive” neuronal role as well as vascular pre-conditioning role, as recently reviewed [5,9,11]. Cortical hyperexcitability is another favoured pathogenetic concept [28], but the established migraine preventive effect of amitriptyline (AMT) that prevents combined synaptic reuptake of both serotonin and norepinephrine to cause cortical excitation that, in turn, can manifest tremor, seizure, and the serotonin syndrome makes such a theory highly unlikely (see below) [5,11,29,30]. Migraine has also been conceived of as being a consequence of either sensory dysfunction of the brain stem and hypothalamic nuclei [31] or an idiopathic self-limited dural inflammation (discussed below).

No brain neuronal (visual cortex or thalamic/hypothalamic or brainstem or dural inflammation) theory for migraine can explain: (i) lateralizing headache over several decades; (ii) headache-aborting or -ameliorating effect of nausea/vomiting; (iii) unambiguous neuroanatomical involvement of the ophthalmic division of the trigeminal nerve (V1) rather than the pan-trigeminal nerve; (iv) attack-preventive efficacy of drugs that do not cross the blood-brain barrier (BBB) such as atenolol, nadolol, and verapamil; (v) spontaneous onset and offset of protean self-limited (4-72 hours) headache attacks; (vi) delayed onset of headache for several hours or a few days after exposure to the headache trigger, in particular stress, nitroglycerin administration, or alcohol imbibition; or (vii) headache-aborting action of triptans, without evidence of the drug crossing BBB or effecting any brain neuronal action [4-9,11].

Development of weekend attacks of migraine is an idiosyncratic proclivity found in a subgroup of patients variably attributed to change or sudden disappearance of stress during the weekend, increased consumption of alcohol at the beginning of the weekend, or fasting due to missed breakfast, or personality-related neuropsychiatric factors, or caffeine-withdrawal either alone or in a variable combination of these factors [32-36]. The link between caffeine withdrawal and headache was elaborated in the early half of the 20th century [37,38]. Caffeine-containing beverages and proprietary analgesics containing caffeine may be particularly relevant to the migraine population with a reduction or delay in caffeine intake on days-off [32]. Sleep appears

to be of particular importance to the migraine cohort, underscoring a complex biphasic pathophysiologic relationship [39]. Sleep serves both as a migraine trigger as well as appears to have a definitive therapeutic role in managing migraine headache. Select medications with sedative side-effects, such as tricyclic antidepressants (TCA), including AMT, are common evidence-based agents used at tertiary-care headache centres to prevent migraine [40,41].

Optical coherence tomography (OCT) may be useful to assess the thickness of the peripapillary retinal nerve fibre layer (RNFL), the macula, and the ocular choroid thereby increasing understanding of pathophysiology of migraine [42]. Ganglion cell layer, RNFL, and choroidal thickness (CT) are significantly thinner in patients with migraine, with duration of disease affecting the choroid predominantly [43]. CT, however, not unexpectedly, varies in patients with chronic migraine [44]. CT is largely dependent on its vascular supply that is 10-20 times that of the cerebral circulation.

In this case report, a non-sedating topical ocular hypotensive agent with vasoconstrictive potential over the highly-vascular ocular choroidal bed has been used to prevent genesis of week-end migraine attacks. The roles of intraocular pressure (IOP), OCT-related changes in choroidal circulation, nociceptive distensibility of corneoscleral envelope, and therapeutic ocular hypotony are discussed in the context of migraine.

CASE REPORT

I report the temporal distribution of lateralizing migraine headache attacks in 2 patients over a 3-year period. The 2 male patients, both 20 years of age, maintained record of their unilateral fronto-temporal pulsating right-sided migraine headaches for 6-months with their Smartphone app prior to the clinical trial of ocular hypotensive and choroidal decongestive therapy with long-acting timolol maleate (TM) ophthalmic solution 0.5% w/v. Diagnosis of migraine was made in accord with the International Classification of Headache Disorders-3 [45]. In both patients, Sunday mornings emerged as being the exclusive day of developing a lateralizing headache attack with definitive morbidity (>5/10 on the visual analogue scale invariably requiring proprietary analgesic consumption) following oversleeping over Saturday night. Both patients, after written informed consent, agreed to undertake once-weekly ipsilateral topical ocular therapy with TM 0.5% w/v before sleeping only over the weekend. The United States Food and Drug Administration (FDA) ethically permits use of an agent already in the market for a new indication.

The physical examination of both patients was unremarkable. Particular attention was paid to heart rate and blood pressure (BP) to eliminate any systemic cardiovascular effect(s) of ocular administration of beta-blocker. One patient, VV, was found to have mild-to-moderately elevated BP readings (systolic <140 mm Hg) with Marfanoid habitus. He was placed on long-acting propranolol-80 mg once daily and indapamide 1.5 mg daily, and was inducted into the trial only after his systolic BP was consistently recorded below 120 mm Hg for 4-weeks on 8 occasions. Both patients were instructed to use a single drop of topical TM ophthalmic solution 0.5% w/v once per week only in the right eye just before going to sleep on Saturday night, while maintaining light pressure on the inner canthus on the right side and keeping both eyes closed for approximately 2-3 minutes. While recording of systemic BP and heart rate was focused upon during clinic visits in the first 4-weeks, the patients were instructed to record their own heart rates by a pulse oximeter daily upon awakening in the morning for the first four weeks of TM topical therapy. No significant changes in basic cardiovascular parameters of BP or heart rate were noticed after initiation of

TM topical therapy. Systemic hypotension (systolic BP <110) and bradycardia (heart rate <60) were not recorded.

These 2 patients did not report week-end lateralizing headache attacks while on ipsilateral-eye TM ophthalmic solution therapy over 3 years, ie, 100% specific relief. During this period of 3-years, the 2 patients did not report significant headache (ie, intensity >5/10 or requiring proprietary analgesics) on days other than the weekend. No side effects, ocular or systemic, were reported by either of the 2 patients over the 3-year period.

DISCUSSION

Saturday (or weekends or holidays) seems to be the predominant day for migraine attacks for a large subgroup (195 of 1085, ie 17.97%) during relaxation after a stressful period (see above) [46,47].

To understand the intriguing phenomenon of post-stress or relaxation-related weekend-migraine, there is a critical need to consider a primary pathogenetic nociceptive cranial physiologic system that is offered a considerable degree of neuro-vascular protection *during* stress by the antinociceptive, vasomotor, and behaviour control vasopressin-serotonin-noradrenaline tripartite nexus [4,6,9,48]. Such a cranial “adaptive” or “protective” physiologic system would offer *limited* protection to migraineurs who frequently develop stress-related/post-stress headache attacks. Conversely, persons who do not develop migraine attacks during or following stress, probably have *unlimited* neuro-endocrine protection offered by such a neuro-endocrine nexus. To put the clinical value of such “intrinsic protection” into clinico-epidemiological perspective, although only 15-20% (approximately 1 billion people) [2] of the general population develop migraine, the experience of stress is almost global. “Stress is life and life is stress - Hans Selye’s words gather emphasis as homeostasis becomes better understood [4-7,9,49]. Besides stress, variable exhaustion of such “protective” neuro-endocrine system also probably underlies: (i) characteristic delay in onset of headache following nitroglycerine ingestion or infusion, alcohol imbibition, and a variety of other clinical stimuli and situations in *some* but not all migraineurs; and (ii) protean nature of headache attacks in the same migraine patient or between migraineurs, with characteristic variability in frequency, severity, disability, and comorbidity [4-6,9,48]. A systematic study of stress [49] has not been undertaken in migraine [4-7,9].

As a neuroanatomically consistent and biologically-plausible generator of exclusive but spontaneous V1 neural traffic, the eye probably has a critical pathogenetic role in migraine, that is clearly distinct from prevailing neuronal/vascular/neurovascular theoretical concepts [4-6,8,9]. As discussed above, presence of the eye is essential to manifest SS and lateralizing migraine headache. Scintillating scotomata of migraine are distributed non-homonymously sparing the nasal visual field(s) [4,12,13]. Eucleation of one or both eyes remits SS as well as migraine headache, as reviewed recently (see above) [4]. Ontogenetically, the retina is a real part of the CNS. Spreading depression phenomenon in monocular amphibian retinal tissue, first described by Gouras, has remarkable resemblances to Leão’s CSD [50]. Electrophysiological characteristics of retinal spreading depression are identical with those of CSD [51]. Retinal spreading depression limited by geometrical neuroanatomy of the living eye allows a better comprehension of non-homonymous nasal-visual field sparing migrainous SS.

Neuro-ophthalmologically, IOP and its association with choroidal vascular circulation, appears to be the key factor in both occurrence of migraine attacks as well as link of headache to BP [6,7,9]. A large number of migraine triggers appear to be linked to higher IOP whereas key migraine remitting factors including pharmacotherapeutic agents are associated with relative

ocular hypotony [6,7,9]. The choroidal vascular circulation, measured indirectly by OCT, indicates the state of congestion of the eye that in turn, determines antidromic corneoscleral nociceptive V1 neural traffic. Maintenance of relative ocular hypotony over the weekend in these 2 patients very likely prevented development of weekend-migraine attacks over a period of 3-years. Theoretically, such pathogenetic but subliminal changes in ocular choroid and IOP take place in the prodromal phase of migraine, and, are therefore immeasurable. Even home tonometry would not be helpful for headache attacks that develop upon arising from sleep, as discussed herein. Administration of a single drop of topical TM ophthalmic solution to the ipsilateral eye is a salient feature of this study. Scientific value of this clinical open trial could be improved in future studies with placebo control. Randomized trials with TM 0.5% w/v ophthalmic solution for abortive management of acute migraine attacks have given variable results [52,53]. Acute attacks of migraine headache reflect the “efferent limb” of migraine, with development of advanced and symptomatic V1-algogenic neural traffic and a different clinical approach [4].

Pan-trigeminal involvement is unlikely in primary headaches, including migraine [4-9,11]. The V1 of the trigeminal nerve appears to have a primary role in clinical phenotype as well as in pathogenesis of migraine. Cranial ANS is apparently the single most important factor in understanding genesis of typically lateralizing headache of migraine through a trait or genetically inherited *asynchronous* catecholaminergic innervation of ocular choroidal vascular circulation [4]. Asymmetric sympathetic nervous system innervation of the ocular choroidal circulation likely underlies *differential (right-left) or bilateral* subliminal exhaustion of the “protective cranial neuroendocrine system”, that in turn, manifests clinically as lateralizing migraine headache (unilateral, bilateral, side-shifting, or side-locked).

CONCLUSION

This prospective and extended trial with TM ophthalmic solution provides the first biologically-plausible and pharmacologically-sound evidence for long-term prevention of weekend migraine headache attacks using a topical medication. The scientific basis of pathophysiology of migraine is advanced in a logically-defensible and theoretically-structured manner.

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