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Combination of Tanacethum Partenium, 5-Hydrossitriptophan (5-Http) and Magnesium in the Prophylaxis of Episodic Migraine without Aura (AURASTOP®) An Observational Study

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Abstract

Objective: The study aim is to verify whether treatment with a new combination of tanacethum partenium, 5-hydrossitriptophan (5-http) and magnesium (Aurastop®) reduces headache frequency and intensity in patients suffering from episodic migraine without aura when used in migraine prevention. **Methods**: Forty patients, suffering from migraine without aura for at least 6 months with monthly frequency of 3 to 8 crises and presence of headache of 4 to12 days, were enrolled in this open study and treated orally with Aurastop twice daily for 3 months. The primary endpoint was reduction of migraine frequency (headache days per month) over an observation period of 3 months. The secondary endpoint was a composite of monthly frequency and intensity of pain crises, analgesics use (number of medications) and subjective change of pain intensity. **Results:** All the parameters significantly improved at the end of treatment with Aurastop. We observed a significant reduction of the number of headache days (from 8.8 ± 2.0 before treatment to 2.7 ± 1.7 post treatment, $p < 0.001$), as well as of the number of attacks (from 5.0 ± 1.2 per month to 2.1 ± 0.9 per month, $p < 0.001$), of pain intensity (from Visual Analogic Scale [VAS] 6.9 ± 1.0 to 3.3 ± 1.5, $p < 0.001$), and of the number of analgesics assumed by each subject (from 8.5 ± 1.6 per month to 2.4 ± 1.5 per month, $p < 0.001$). No serious adverse events were observed. **Conclusion**: Though obtained in the setting of an open-trial, our findings suggest that the new combination of tanacethum partenium, 5-hydrossitriptophan (5-http) and magnesium (AURASTOP®) is a promising approach for migraine prevention and warrant further investigation to confirm the safety and efficacy of this treatment.

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Keywords: Migraine without aura; NMDA receptors; Tanacetum parthenium

Introduction

A number of epidemiologic studies have consistently indicated that the prevalence of migraine is about 15 - 18 % among women and 6 % among men in Western Countries, with a pick between 22 and 55 years[1]. Migraine is a chronic, disabling disease, with high impact in terms of social and economic costs[2]. Based on these characteristics, the WHO has recently included migraine among the 20 most disabling diseases affecting women between 15 and 45 years of age[3]. In particular, chronic headache has become the leading cause of disability and abuse of medical resources, accounting for up to 80 % of the whole economic budget for public healthcare. In Italy, the direct and indirect costs of migraine have been estimated to be about 6 billion euros per year. The identification of migraine sufferers as well as the most appropriate management of these cases represents, therefore, a field of need. In this regard, it is generally accepted that a prophylactic treatment for migraine should be started for patients suffering disabling migraine for at least 4 days per month, or when pain crises do not respond to symptomatic medications.

The main goal of migraine prophylaxis is to reduce the frequency of attacks and patient disability, as well as to improve quality of life. A prophylactic therapy is considered effective when it reduces of at least 50 % the frequency of migraine attacks.

Agents that have been considered for migraine prophylaxis according to several national and international guidelines include, among the others, beta-blockers, calcium antagonists, serotonin reuptake inhibitors, anti-depressants, anti-epileptics, phytotherapics[4], and magnesium.

Although the mechanisms of action of these molecules in migraine prevention are poorly known, their effects on the vessel wall, on neurons, as well as on specific neurotransmitters involved in migraine biology have been hypothesized based on numerous pre-clinical observations.

The biological origin of migraine, in fact, is likely multifactorial. Clinical studies suggest abnormal cortical, cerebrovascular, and immune functions. However, it is now well-accepted that the pain, persistence and throbbing features of migraine are mediated by increased sensitivity (i.e. sensitization) and the ensuing activation of sensory neurons innervating intracranial meninges and their related large blood vessels. These are the first-order neurons in the migraine pain pathway. Given the increasing importance placed on central and peripheral sensitization in the pathogenesis of migraine, the mechanisms of activation of trigeminal sensory afferents take on a central role. Sensitization results from the local release of neuropeptides that cause vasodilatation (mediated by calcitonin gene-related peptide) and an increase in vascular permeability (mediated by substance P and neurokinin A) accompanied by mast cell activation. Mast cells, members of the innate immune system, participate in numerous physiological and pathophysiological conditions.

The emergence of a local inflammatory response in the meninges is widely viewed as a potential contributor to the activation and sensitization of meningeal nociceptors during migraine. Activation of resident immune cells such as mast cells, which are a prominent feature of the intracranial meninges, is likely to serve as a critical step in promoting enhanced excitability of meningeal nociceptors.

Activation and sensitization of primary afferent meningeal nociceptive neurons, the peripheral arm of the trigeminal-vascular system, appears to constitute one of the earliest events promoting the intracranial pain of migraine. These observations thus posit that meningeal mast cells, by virtue of their proximity both to meningeal blood vessels and nociceptive axons, may release a host of pro-inflammatory/algesic mediators responsible for the vasodilatatory phase of migraine associated with throbbing pain. These data suggest that controlling meningeal nociceptor excitability might be achieved by acting on mast cell activation.

A proposed mechanism of action involves parthenolide specifically binding to and inhibiting IκB kinase complex IKKβ. IKKβ plays an important role in proinflammatory cytokine-mediated signaling. Parthenolide may also interact with TRPA1 nucleophilic sites, suggesting that feverfew antimigraine effect derives from its ability to target TRPA1. TRPA1 partial agonism, together with desensitization and nociceptor defunctionalization, ultimately resulting in inhibition of CGRP release within the trigeminovascular system, may contribute to the antimigraine effect of parthenolide[5-7].

Glutamate is another neuropeptide likely involved in migraine pathogenesis. Actually, as it exerts an excitatory effect on first and second order neurons and it is involved in the activation of the trigeminovascular system, it is implicated in both migraine attack and the activity of the "migraine generator" in the brainstem. This makes it a key player in the activation and propagation of cortical spreading depression.

N-methyl-D-Aspartate (NMDA) is the post-synaptic glutamatergic receptor involved in central sensitization and cortical spreading depression, as demonstrated by its activation during migraine attacks[8]. NMDA receptors are activated by increased synaptic levels of glutamate, while they are inhibited by magnesium[9-11].

Glutamate levels are regulated by kynurenine[12] which metabolizes l-triptophan in kynurenic acid (KYNA) and quinolinic acid (QUINA). The NMDA receptor antagonist KYNA, in particular, inhibits glutamatergic pathway by blocking glutamate release and neurotransmission through its action on glycin Glu N1 binding site. It has been recently observed that in migraineurs the kynuretic pathway is shifted towards the conversion of KYNA in Antralinic Acid (ANA), as supported by the elevated plasma levels of ANA and the reduced concentration of KYNA and QUINA in these patients, with the consequent loss of inhibitory control on glutamate and its excitatory effects.

ANA has also a direct neurotoxic effect through the release of free radicals. Low plasma levels of KYNA may be considered a reliable marker of NMDA receptor activation.
Cerebral levels of KYNA can be increased by the assumption of its precursor 5-HTP[13].

Based on the mechanisms described above, the combination of 3 components, tanacetum parthenium, 5-HTP, and magnesium is expected to synergistically influence the biologic pathways involved in migraine pathogenesis, and, therefore, to have a therapeutic potential in migraine prevention.

Patients and Methods

Patients with episodic migraine as defined by the International Headache Society[14] were consecutively recruited among those referring to the Headache Center of the Istituto Clinico Citta' di Brescia. Criteria for patients selection were: 1) age between 18 and 65 years; 2) diagnosis of migraine without aura, according to the International Headache Society; 3) migraine for at least 6 months with a monthly crisis frequency ranging from 3 to 8, 4) headache duration ranging from 4 to12 days per month, and 5) no other migraine preventive therapies. Patients with psychiatric co-morbidity, suffering from other types of acute or chronic pain, or with concomitant kidney failure, neurological or oncological diseases or pregnancy were considered non-eligible for the study.

The primary endpoint of the study was modification of migraine frequency (headache days per month) over an observation period of 3 months. The secondary endpoint was a composite of monthly frequency and intensity of pain crises, analgesics use (number of medications) and subjective change of pain intensity.

Patients who qualified for the study did not receive any prophylactic treatment for the first month since their enrollment in the study, then they received an association of Tanacetum Parthenium 150 mg (1, 2 mg of Partenolide), 5-HTP 20 mg, Magnesium 185 mg (Dietary supplement Aurastop®, Aesculapius Farmaceutici) twice daily for 3 months.

At baseline evaluation all patients underwent a thorough neurological examination and were carefully instructed on how to keep record of migraine attacks in their headache diary on

a day-to-day basis. In particular, they were instructed to register: 1) attacks frequency, pain intensity (using the VAS scale, ranging from 1 to 10) and duration; 2) response to analgesics based on a self-rate scale ranging between 1 (minimum response) and 5 (maximum response) over the time period (1 month) with no preventive therapy and that (3 months) taking Aurastop. Safety was evaluated by treatment discontinuation rate and the occurrence of serious and otherwise adverse events.

Statistical Analysis

Categorical variables are reported as counts and percentages. Dependent variables were compared by McNemar's $\chi 2$ analysis. Wilcoxon's signed rank test was used to compare migraine characteristics before and after treatment. Statistical analyses were performed using SPSS 21.0 (IBM SPSS Statistics 2013, Armonk, NY, USA).

Results

Overall, 40 patients (15 males/and 25 females; mean age, 35, 6 years, range, 19 - 54) were enrolled in the study. One out of the 40 patients withdrew after 1 month of treatment because of non-improvement and one was lost to follow-up.

The results of the analysis are summarized in Table 1. We observed a significant reduction of the number of headache days (from 8.8 ± 2.0 before treatment to 2.7 ± 1.7 post treatment, $p < 0.001$), as well as of the number of attacks (from 5.0 ± 1.2 per month to 2.1 ± 0.9 per month, $p < 0.001$), of pain intensity (from VAS 6.9 ± 1.0 to 3.3 ± 1.5, $p < 0.001$), and of the number of analgesics assumed by each subject (from 8.5 ± 1.6 per month to 2.4 ± 1.5 per month, $p < 0.001$; Figure 1). None of the patients reported any treatment-related adverse events.

Table 1: Migraine characteristics before and after prophylactic treatment with Aurastop.

Migraine characteristics	Baseline	Post-treatment	p-value
Pain intensity (0 to 10)	6.9 ± 1.0	3.3 ± 1.5	< 0.001
Number if attacks/month	5.0 ± 1.2	2.1 ± 0.9	< 0.001
Number of days/month	8.8 ± 2.0	2.7 ± 1.7	< 0.001
Number of analgesics	8.5 ± 1.6	2.4 ± 1.5	< 0.001
Analgesics (yes/no)	41(100.0)	35(89.7)	0.125

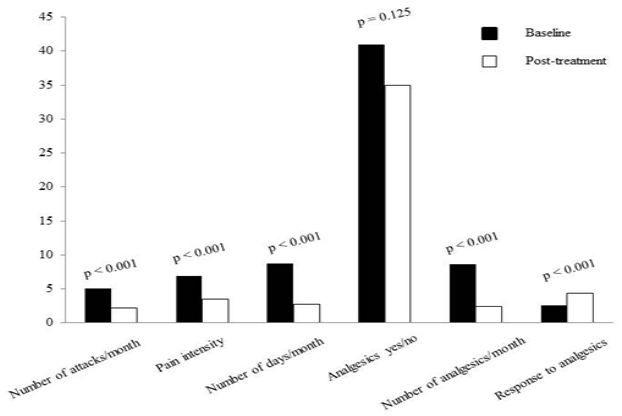

Figure 1: Comparison of individual migraine characteristics according to treatment-phase.

Another notable finding derived from the analysis of the headache diaries, was that the results at the 3-month time point reported above were already detectable after one month of prophylactic therapy with Aurastop.

Discussion

The results of the present study highlight the efficacy and the safe profile of the combination of Tanacetum Parthenium, 5-HTP and magnesium in migraine prophylaxis. Both, the frequency and the duration of migraine attacks as well as the intensity of pain improved significantly in most of the patients treated. These findings, in addition to the more favorable response to analgesics and the need of a reduced number of these medications in patients receiving Aurastop lead to the speculation that the 3 molecules in combination might act synergistically on different pathways involved in migraine biology: neurogenic inflammation, neural transmission, and central sensitization. The well-known phenomenon of Cortical Spreading Depression (CSD), involved in the pathogenesis of both migraine without aura and migraine with aura, has been consistently related to the status of inter-critical cortical brain hyperexcitability of migraineurs. This emphasizes the physiologic role of magnesium in the regulation of such a neuronal excitability. Among the many actions, intracellular magnesium acts as a physiologic calcium-antagonist, thus reducing the toxic effects of calcium, whereas suboptimal concentrations of magnesium favor free radical accumulation within the cell, which, in turn, may trigger a migraine attack. Furthermore, magnesium inhibits NMDA receptors, which are involved in the glutamate-dependent excitatory pathways at the basis of the neurogenic inflammation. Moreover, brain concentration of kynurenic acid (Kyna), a tryptophan derivative which further acts as an endogenous NMDA receptor antagonist, increases with increasing serum levels of its precursor 5HTP. Giving 5HTP as a drug may, therefore, increase Kyna levels and influence Kyna pathways, leading to the inhibition of peripheral NMDA receptors and the consequent activation of the trigeminovascular system, as well as of CSD.

Finally, TRPA1 and NMDA receptors with glutamate and calcitonin-gene-related peptide (CGRP) play a key role in neurogenic inflammation, which leads to the sensitization of trigeminal nucleus caudalis in the lower brainstem and upper cervical cord and, consequently, of all structures involved in the central transmission of nociceptive information.

Molecules proved to be migraine generators act as TRP receptors activators. These, in turn, generate neurogenic inflammation leading to painful attacks through the release of CGRP from perivascular nerve terminals. Such a cascade might be interrupted by partenolide, a TRP receptors inhibitor. Partenolide is, moreover, a powerful inhibitor of nitric oxide synthase and, consequently, of nitric oxide (NO) production. All the findings observed in the present study can, therefore, be interpreted as clinical manifestation of the interference with the phenomenon of central sensitization, as well as with the central transmission of nociceptive information at synaptic level, TRPA1 channels, and NMDA receptors determined by Aurastop.

Conclusion

In spite of the methodological limitations inherent in the present pilot, observational study lacking a control group, our findings emphasize the potential influence of the combination of different molecules on the complex biologic mechanisms causing migraine. In particular, tanacetum parthenium + 5-HTP + Magnesium appear as a promising association of molecules for migraine prophylaxis with an excellent safety profile. Further clinical trials are warranted in order to investigate the potentials of this compound in preventing migraine, either given alone or in combination with other molecules.

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A Combination of *Tanacetum parthenium*, *Griffonia simplicifolia* and Magnesium (Aurastop®) as Symptomatic Acute Treatment for Migraine Aura: A Retrospective Cohort Study

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Abstract

Background: effective treatments for migraine aura and related symptoms are not yet well established. In the last years, several herbal and/or nutraceutical preparations have been proposed as potential treatment. We report the results of a retrospective analysis on the synergistic effect of three nutraceutical components (*Tanacetum parthenium*, *Griffonia simpliciofila* and Magnesium, Aurastop®) as symptomatic treatment of migraine aura and related symptoms. **Method:** Forty-nine subjects with headache with aura were recruited from the headache Center of the Istituto Clinico Citta' di Brescia to enter the studied that consist to treat the first 3 aura attacks as usual and the next 3 taking a tablet of Aurastop at the beginning of the aura phenomena. They had to describe aura and headache characteristics of previous three attacks (t1) and the modification of these parameters with the assumption of Aurastop® for the following three attacks (t2). **Results:** A significant reduction (>50%) in aura duration (t1 = 33.6 ± 10.1 minutes vs. t2 = 9.4 ± 6.2 minutes, $p < 0.01$ FWER corrected) as well as in overall disability (median [interquartile range]) (t1 = 5[4 - 5] vs. t2 = 1[1 - 2], $p < 0.01$ FWER corrected) was evident. Furthermore, modification of aura type as well as a series of parameters more related to headache (number of headache attacks, duration, intensity, utilization of analgesics and response to symptomatic treatment) was influenced by Aurastop® utilization ($p < 0.01$ FWER corrected). No significant adverse effects were recorded after the assumption of Aurastop®. **Conclusions:** the combined and synergistic effect of *Tanacetum parthenium*, *Griffonia simpliciofila* and Magnesium (Aurastop®) highlights the idea that symptomatic treatment potentially modulating cortical spreading depression could deserve attention to miti-

gate aura and related symptoms (migraine as well as long-lasting discomfort). Further blinded, placebo-controlled studies on larger groups are warranted.

Subject Areas

Neurology

Keywords

Migraine Aura, Cortical Spreading Depression, NMDA Receptor

1. Introduction

Epidemiological studies have reported a high lifelong prevalence of headache in women (15% - 18%) and men (6%), with a peak in the adult phase (25 - 55 years) and a consequent significant impact on working activity and quality of life [1]. As a disabling disease, headache represents a growing social problem with high direct and indirect economic costs [2]. Headache has been considered among the 20 most invalidating diseases in women between 15 and 45 years of age by World Health Organization [3]. Approximately one fifth of patients with migraine suffer from aura [4], defined as a transient neurological phenomenon with gradual spreading, that can either precede or accompany headache onset [5]. Whereas visual disturbances represented the most common clinical presentation, sensory and language symptoms may be reported, in line with the slow spreading of a cortical perturbation across the brain, moving from posterior to anterior regions [6] (cortical spreading depression, CSD), followed by a long-lasting depression [7] [8]. The utilization of 5-hydroxytryptamine 1B/D agonists (triptans) significantly relieved migraine pain and disability with a concomitant increased quality of life [9]. Unfortunately, effective treatments for aura signs and symptoms (in particular for those patients with substantial disability due to aura duration and severity) are not yet well established. Up to now, intranasal ketamine has shown to be effective in reducing severity (but not duration) of long-lasting aura [10]. Moreover, small studies or isolated case reports supported the role of a series of drugs in aborting migraine aura [11] [12] in modulating migraine with aura in particular, but none of these treatments is currently used in clinical practice. In the last years, several herbal and/or nutraceutical preparations have been proposed in the management of migraine and related symptoms like aura [13]. In particular: 1) feverfew (*Tanacetum parthenium*) as potential treatment in reducing aura duration and complexity [14] through Parthenolide inhibition of nitroglycerin-induced neuronal activation in specific brain nuclei, like dorsal root ganglia (DRG) [15]; 2) *Griffonia simplicifolia* (as a herbal supplement of 5-hydroxytryptophan (5-HTP)); interestingly, 5-HTP could reduce N-methyl-D-Aspartate (NMDA) receptors aberrant activity in trigeminal-vascular system, as well as in CSD developing, principally through

the activity of its precursor (kynurenic acid) acting as an endogenous NMDA receptor antagonist [16]; and finally 3) Magnesium, the lack of this intracellular cation may promote CSD through several mechanisms involving serotonin receptors, nitric oxide synthesis/release as well as NMDA receptors [17]. All these observations prompted the present study, aimed to test the synergistic effect of these three components (*Tanacetum parteninum*, *Griffonia simpliciofila* and Magnesium, Aurastop®) as symptomatic treatment of migraine aura and related symptoms.

2. Methods

1) Subjects. Patients with headache fulfilling ICHD-3 beta criteria for Migraine with Aura [18] were recruited from the Headache Centre, Istituto Clinico "Città di Brescia", Brescia, Italy during the month of june, july and august 2016. Diagnosis of headache was made by two experienced headache specialists (GDV, DC), and each patient underwent a detailed clinical and neurological examination. The following inclusion criteria were considered: 1) subject aged between 18 and 60 years old; 2) a diagnosis of Migraine with Aura (ref) with at least 3 episodes of aura/year with a minimum aura duration of 20 minutes. As exclusion criteria, changing in preventive treatment during observation period has been considered. This study was an audit of outcome and, as such under Italian guidelines, did not require ethics committee approval.

2) Aurastop®. Aurastop® has been proposed as supplement with the combination of *Tanacetum parteninum* (150 mg extracted at 0.8% = 1.2 mg of active Parthenolide), *Griffonia simpliciofila* (100 mg of 5-HTP) and Magnesium (185 mg of magnesiopidolate).

3) Study design. At baseline (t0), the natural history of aura phenomenology was studied. To this purpose, each patient received a migraine headache diary, to keep track of aura and headache characteristics of the following 3 episodes. In particular, aura subtype (only visual, visual and somatosensory, visual, somatosensory and speech/language symptoms (here defined as complex)) aura duration, disability (on a scale ranging from 0 to 5), presence of concomitant/following headache characteristics (duration, intensity (NRS-11 scale) [19], utilization of usual home pain medications (triptans, nonsteroidal anti-inflammatory drugs) and response to symptomatic treatment) were considered. After three episodes of aura (with or without migraine) migraine headache diary of each patients were re-evaluated (t1) considering inclusion/exclusion criteria and aura characteristics. Indeed, each patient received a blister with 3 tablets of Aurastop®, with the instruction to assume a tablet of Aurastop® at the beginning of the following 3 auras, recording aura characteristics on migraine headache diary as usual. Each patient and migraine headache diary data were further evaluated (t2) after these three aura episodes. As primary endpoint, we considered an >50% aura duration and patient overall disability reduction. Furthermore, modification of aura type (visual, visual and sensory, complex) as well as migraine characteristics modification (number of headache attacks, duration, intensity, utili-

zation of analgesics and response to symptomatic treatment) were considered as secondary endpoints.

4) Statistical analysis. SPSS package (v. 17.0, Chicago, IL, USA) was employed to run statistics for group differences in clinical characteristics before and after Aurastop® treatment. Continuous variables (aura duration and headache duration) were expressed as mean ± standard deviation (mean ± SD) whereas categorical variables (overall disability, aura type, headache characteristics (duration, intensity, utilization of analgesics and response to symptomatic treatment)) were reported as median and [interquartile range, IQR]. Group comparisons (pre-vs post-treatment) were assessed by Wilcoxon (matched-pairs) Signed Ranks Test (as non-parametric test for continuous variables measured on two occasions) and Marginal Homogeneity Test (as non-parametric test for categorical variables (>2 categories), measured on two occasions). The statistical threshold corrected for multiple comparisons (family wise error rate (FWER) with Bonferroni correction, $\alpha = 0.05/8$) was set to $p < 0.006$ [20]).

3. Results

Forty-nine subjects with a diagnosis of headache with aura (ICHD-3 beta criteria) entered the study (mean age 31, 30 (min 19, max 54 years old), gender = 21 male −28 female), considering aura and headache characteristics of previous three attacks (t1) and the modification of these parameters with the assumption of Aurastop® for the following three attacks (t2). As reported in **Table 1**, a significant reduction (>50%) in aura duration (t1 = 33.6 ± 10.1 minutes vs. t2 = 9.4 ± 6.2 minutes, $p < 0.01$ FWER corrected) (**Figure 1(a)**) as well as in overall disability

Table 1. Primary and secondary endpoints for Aurastop® treatment.

	Pre-treatment (t1)	Post-treatment (t2)	p
Aura duration, minutes	33.6 ± 10.1	9.4 ± 6.2	<0.01*
Aura type, code	1[1 - 1]	1[1 - 2]	<0.05§
Disability, score	5[4 - 5]	1[1- 2]	<0.01§
Headache attacks, number	3[3 - 3]	2[2 - 3]	<0.01§
Headache duration, minutes	24.9 ± 7.4	5.1 ± 5.0	<0.01*
Headache intensity, NRS-11 score	8[7 - 9]	3[2 - 4]	<0.01§
Home medications utilization, number	3[3 - 3]	1[1 - 3]	<0.01§
Response to symptomatic treatment, score	2[1 - 2]	4[4 - 5]	<0.01§

Continuous variables (aura duration and headache duration) were expressed as mean ± standard deviation (mean ± SD) whereas categorical variables (overall disability, aura type, headache characteristics (duration, intensity, utilization of analgesics and response to symptomatic treatment)) were reported as median and [interquartile range, IQR]. Aura type has been defined as follows: 1 = only visual, 2 = visual and somatosensory, 3 = visual, somatosensory and speech/language symptoms (here defined as complex). NRS-11: 11-point pain intensity numerical rating scale [18]; Group comparisons (pre vs. post treatment) were assessed by Wilcoxon (matched-pairs) Signed Ranks Test* (as non-parametric test for continuous variables measured on two occasions) and Marginal Homogeneity Test§ (as non-parametric test for categorical variables (>2 categories), measured on two occasions). The statistical threshold corrected for multiple comparisons (family wise error rate (FWER) with Bonferroni correction).

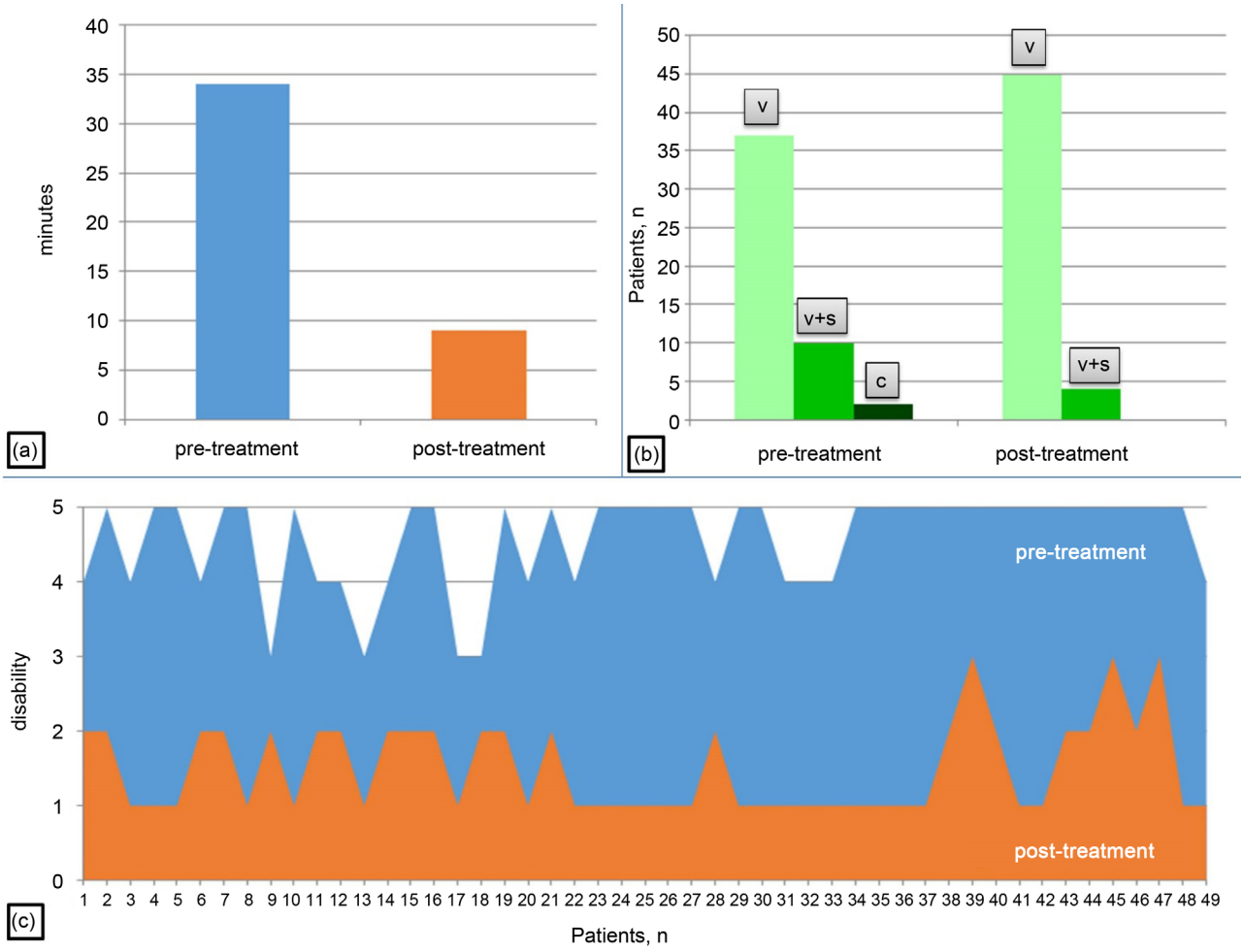

Figure 1. Effect of Aurastop® treatment on aura duration, aura type and overall disability. Panel A: aura duration (in minutes) reduction after Aurastop® treatment; Panel B: aura type modification after Aurastop® treatment. v: visual, v + s: visual and sensory, c: complex, n: number; Panel C: overall disability reduction after Aurastop® treatment, n: number.

(median [interquartile range]) (t1 = 5[4 - 5] vs t2 = 1[1 - 2], $p < 0.01$ FWER corrected) (Figure 1(c)) were evident after Aurastop® assumption, fulfilling the primary endpoints. Especially for overall disability, at baseline >90% of patients presented an high degree of disability (4 or 5), whereas post-treatment overall disability was of 1 or 2 (>90%). Furthermore, modification of aura type as well as a series of parameters more related to headache characteristics were considered as secondary endopoints of Aurastop® treatment. For aura type, a significant reduction in aura complexity was reported ($p < 0.05$ FWER corrected), with no complex aura and reduced sensory aura at follow-up, balanced by an increasing in visual aura prevalence (Figure 1(b)). Considering the headache after aura, 4 patients experienced 3 attacks of migraine with aura at baseline (t1) with only aura phenomenon (migraine aura without headache) in the three further attacks at follow-up (t2). For headache characteristics, a statistically significant reduction ($p < 0.01$ FWER corrected) in the number of headache attacks, duration, intensity, number of analgesics used and response to symptomatic treatment were reported (see Table 1) after treatment with Aurastop®. No significant ad-

verse effects as well as worsening of the clinical picture were recorded after the assumption of Aurastop®.

4. Discussion

Migraine aura has always been considered as an accessory symptom of a significant proportion of migraine attacks. Even if the International Classification of Headache Disorders (ICHD) defined a range duration of aura symptom between "5 - 60 minutes", in clinical practice migraine aura often lasts significantly longer, not only for neurological symptoms (visual, sensory, etc.) but also for the feeling of prostration, uneasiness and lack of concentration (as indexes of high cortical dysfunctions) that frequently accompany migraine aura, with a relevant impact on the global disability experienced by the patients [21] [22] [23]. From this point of view, therapeutic approach for migraine aura would be key in ameliorating "real-life" disability (working, driving, etc.), rather than simply attenuating pure neurological symptoms of aura. In the present study, a combined supplement of *Tanacetum parthenium*, *Griffonia simpliciofila* and Magnesium (Aurastop®) has shown to be effective as symptomatic treatment of migraine aura, with a significant reduction of aura duration as well as the overall disability perceived by the patient. Compared to previous attacks of aura, Aurastop® treatment also seems to act on the magnitude of neurological signs and symptoms characterizing migraine aura, with a significant reduction in the aura complexity (no complex aura and reduced sensory aura at follow-up, balanced by an increasing in visual aura prevalence, compared to baseline). Moreover, the frequency and the intensity (as well as the need of symptomatic treatment for migraine) were also significantly modulated by Aurastop® utilization. Altogether, these findings pointed toward a potential effect of this combined supplement on the probable neurobiological underpinning of aura, namely the cortical spreading depression (CSD). An early "switching off" of CSD could modulate aura symptoms and even subsequent migraine [24] [25]. Interestingly, all the components included in Aurastop® demonstrated a selective action on migraine aura development. For *Tanacetum parthenium* (and its derivate Parthenolide) the inhibition of nitric oxide synthesis, NF-kB activation and proinflammatory cytokines synthesis represented key mechanisms [26]. Moreover, *Tanacetum parthenium* seems to act as partial agonist of transient receptor potential ankyrin 1 channel (TRPA1), causing its desensitization and defunctionalization, with a consequent inhibition of calcitonin gene-related peptide (CGRP) release in trigeminovascular system actually considered as a key mechanism in the genesis of migraine [27] [28]. From this point of view, Pathenolide could exert its antimigraine effect toward a TPRA1-mediated reduction of neurogenic vasodilatation in the trigeminovascular system. As a further step, 5-HTP (from *Griffonia simpliciofila* supplement) entered kynurenine pathway as kinurenic acid that was able to act as an endogenous NMDA receptor antagonist, blocking glutamatergic activity. In migraine patients, kynurenine pathway perturbation was related to an aberrant unidirectional metabolization of kinurenic acid in antralic acid

(promoting itself free radical production), with a consequent loss of the inhibitory action on glutamatergic acid and its excitatory activity [16] [29]. Thus, low plasmatic levels of kinurenic acid could be considered as an effective proxy of NMDA receptor activity [29]. Finally, magnesium deficiency has been related to CSD [30], as well as to free radical formation and NMDA modulation of glutamatergic activity [31] [32]. However, several limitations should be accounted with regard to the present study. In particular, as a retrospective study, no blinded control group has been included, and a placebo effect cannot be completely ruled out, also considering the oral assumption of Aurastop®, and its potential effect on aura duration. In conclusion, the combined and synergistic effect of *Tanacetum parteninum*, *Griffonia simpliciofila* and Magnesium (Aurastop®) highlights the idea that migraine aura would deserve treatment: the earlier the CSD interruption, the greater the gain on aura and related symptoms (migraine as well as long-lasting discomfort). Further blinded, placebo-controlled studies on larger groups are warranted to confirm the efficacy of the combined utilization of *Tanacetum parteninum*, *Griffonia simpliciofila* and Magnesium in migraine aura and related symptoms.

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