



# 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 simplicifolia* 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 simplicifolia* and Magnesium (Aurastop®) highlights the idea that symptomatic treatment potentially modulating cortical spreading depression could deserve attention to miti-

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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

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## 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 simplicifolia* 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 simplicifolia* (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 patient was 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  $\pm$  standard deviation (mean  $\pm$  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]).

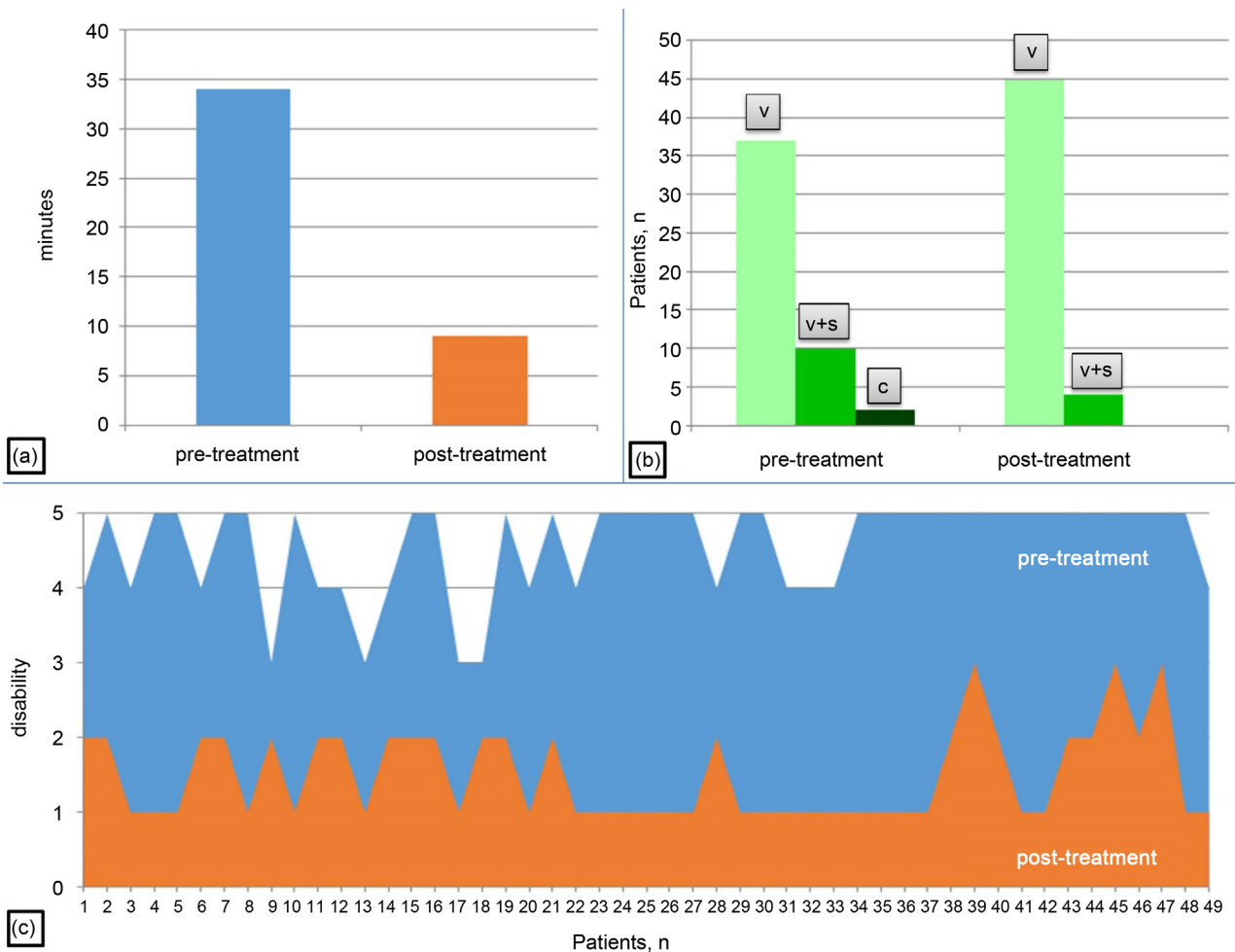
### 3. Results

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  $\pm$  10.1 minutes vs. t2 = 9.4  $\pm$  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 $\pm$ 10.1	9.4 $\pm$ 6.2	<0.01 <sup>*</sup>
Aura type, code	1[1 - 1]	1[1 - 2]	<0.05 <sup>§</sup>
Disability, score	5[4 - 5]	1[1 - 2]	<0.01 <sup>§</sup>
Headache attacks, number	3[3 - 3]	2[2 - 3]	<0.01 <sup>§</sup>
Headache duration, minutes	24.9 $\pm$ 7.4	5.1 $\pm$ 5.0	<0.01 <sup>*</sup>
Headache intensity, NRS-11 score	8[7 - 9]	3[2 - 4]	<0.01 <sup>§</sup>
Home medications utilization, number	3[3 - 3]	1[1 - 3]	<0.01 <sup>§</sup>
Response to symptomatic treatment, score	2[1 - 2]	4[4 - 5]	<0.01 <sup>§</sup>

Continuous variables (aura duration and headache duration) were expressed as mean  $\pm$  standard deviation (mean  $\pm$  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<sup>§</sup> (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]) ( $t_1 = 5[4 - 5]$  vs  $t_2 = 1[1 - 2]$ ,  $p < 0.01$  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 endpoints 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 ( $t_1$ ) with only aura phenomenon (migraine aura without headache) in the three further attacks at follow-up ( $t_2$ ). 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 simplicifolia* 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, Parthenolide could exert its antimigraine effect toward a TRPA1-mediated reduction of neurogenic vasodilatation in the trigeminovascular system. As a further step, 5-HTP (from *Griffonia simplicifolia* 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 metabolism of kinurenic acid in antral 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 simplicifolia* 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 simplicifolia* and Magnesium in migraine aura and related symptoms.

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