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Tanacetum, Parthenium, Griffonia Simplicifolia and Magnesium as Symptomatic and Prophylactic Treatment for Headache in Paediatric Patients

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Abstract

Each component of the novel phytotherapic combination of Tanacethum, Parthenium, Griffonia, simpliciofila, and Magnesium (AURASTOP®) acts on a different target among the main mechanisms involved in the pathophysiology of migraine and of the aura itself: sensitization of trigeminal vascular system, central sensitization and activation of the migraine generator located in the brainstem, through glutammate and kynurenine pathways and the cortical spreading depression.

Scope of the study is to evaluate the efficacy and safety of AURASTOP® nutraceutical combination in children and adolescents with primary headaches in the absence of other comorbidities.

To pursue the aim of this study, it has been used two validated questionnaires: Migraine Disability Assessment (MIDAS) and the six-item Headache Impact Test (HIT-6). Treatment with AURASTOP® has been conducted for 3 months, with two sachets day. Compliance of patients was monitored weekly by means of a weekly exchange of emails or phone calls to parents.

Overall, 42 children overall, 25 female (59.52%) and 17 male (40.48%) were included in the study. The average age of children at the time of enrollment was 10.59 ± 3.18 years. Comparing pre-treatment (46.48 ± 8.35) and post-treatment (9.78 ± 18.16) data, a reduction in mean MIDAS scores was shown. Moreover, if we consider the shifts between the classes of MIDAS score, before and after the treatment, 1/42 patients (2.38%) had worsened, 9/42 patients (21.43%) did not improve 10/42 (23.91%) improved by 1 class, 12/10 patients (28.57%) improved by 2 classes, 10/42 (23.91%) improved by 3 classes. The improvement of disability related to the headache has proved statically significant (Fisher's exact test). Similarly, the reduction of HIT-6 scores post-treatment (46.48 ± 8.35) in comparison with pre-treatment (62.55 ± 5.50) was statistically significant ($P < 0.05$).

The results of the present study support the efficacy and safety of the combination of Tanacetum Parthenium, 5-HTP and magnesium (AURASTOP®) in migraine prophylaxis and as symptomatic treatment in paediatric patients with headache.

Keywords: Headache; Nutraceuticals; Pediatric; Migraine

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Introduction

Headache is a common complaint among children that occurs in up to 75% of adolescents and 25% of young children; it is also the most common neurological disease observed in clinical practice[1,2]. The World Health Organisation (WHO) declared headache in the top twenty disorders among all worldwide diseases causing ictal disability[3]. The International Headache Society classification system is distinguished into primary and secondary headache disorders[4].

In particular, migraine without aura and tension-type headache (TTH), both primary disorders, are the 2 most common types of headaches in children and adolescents. A migraine is a primary headache and has an important socioeconomic impact on children's and parents' quality of life and relationships[5]. The mean prevalence of (non-migraine) headaches is 54.4% (95% confidence interval [CI], 43.1–65.8) and the mean prevalence of migraine is 9.1% (95% CI, 7.1–11.1)[6]. For these reasons, the clinical approach to an infant with headache should be systematic and seek early recognition and management[7].

Migraine can be defined as a paroxysmal disorder with a natural fluctuation between a low and high frequency pattern. Its etiology is complex and includes modifiable and non-modifiable risk factors. It is a chronic, painful syndrome with aspects such as psychiatric comorbidities, decreased quality of life, and environmental factors that can all influence the success of its treatment. A high and increasing attack frequency can lead to chronic migraine, which then becomes resistant to acute as well as prophylactic migraine medications. Chronic migraine is defined as having more than 15 headache days in a month, with at least half of these showing migraine features for a period of at least 3 months[8].

Pharmacological treatment is the first choice for migraine, but there are adverse effects and contraindications which limit the use of drugs in children. There is increasing evidence of the efficacy and tolerability of some complementary approaches such as nutraceuticals in the management of headache disorders[9]. Nutraceuticals are complementary therapies that include dietary supplements in the form of vitamins and minerals. In the last few years, some nutraceutical preparations such as magnesium, CoQ10, vitamin D, melatonin, and others have been proposed as potential treatment for headaches in childhood. Triptans could be used more often as a first or a second choice for treating migraine attacks in adolescents[10]. The pathophysiology of migraine involves many different mechanisms including the modulation of central and peripheral pain structures and release of vasoactive peptides.

This study aims to evaluate the use and self-perceived efficacy and tolerability of three nutraceutical components - Tanacetum parteninum, Griffonia simpliciofila and magnesium – in children and adolescents with primary headaches without other comorbidities. The three components act upon the four main mechanisms involved in the patho-physiology of different types of headache: cortical spreading depression (CSD), sensitization of the trigeminal vascular system, central sensitization and activation of the migraine generator at the brainstem's level.

Tanacetum parteninum as a potential treatment in reducing aura duration and complexity through parthenolide inhibition of nitroglycerin-induced neuronal activation in specific brain nuclei, like dorsal root ganglia[11,12];

Griffonia simpliciofila as a herbal supplement of 5-hydroxytryptophan (5-HTP); interestingly, 5-HTP could reduce N-methyl-D-Aspartate (NMDA) receptor aberrant activity in trigeminal vascular system, as well as in CSD developing, principally through the activity of its precursor (kynurenicacid) acting as an endogenous NMDA receptor antagonist[13];

Magnesium, the lack of which may promote CSD through several mechanisms involving serotonin receptors, nitric oxide synthesis/release as well as NMDA receptors[14]. All these observations prompted the present study, aimed to test the synergistic effect of these three components (Tanacetum, parthenium 75 mg, Griffonia simpliciofila 250 mg and Magnesium 100 mg- AURASTOP®, Table 1) as symptomatic treatment of migraine aura and related symptoms.

The treatment period was 3 months following a 4 week baseline period without prophylactic treatment. Patients were assessed before treatment and at the end of the 3-month-treatment phase for days with migraine, migraine pain, burden of disease, and subjective evaluation of efficacy. Table 1

Table 1: Average content of AURASTOP®

	Average content
Griffonia Simpliciofila	250 mg
Tanacetum	75 mg
Magnesium	100 mg

Materials and Methods

Participants and recruitment

We enrolled 42 participants with the diagnosis of migraine with and without complying with the third edition of the International Classification of Headache Disorders (ICHD-3). Before the preliminary examination, the parents of children filled in from the timetable to evaluate frequency of the headache episodes, severity and duration of each headache episode, and number of days that pain medications are used to treat the headache and possible triggers. During the interview, it has been investigated the family and scholastic framework, in particular the attention of the doctor was directed towards the specific moment when the symptom was developed.

As a result of the preliminary evaluation, which ensures the presence of inclusion criteria and the absence of exclusion criteria, 42 children aged 4 to 18 years of either sex have been enrolled and assessed with the aid of two questionnaires: Migraine Disabilitity Assessment (MIDAS) and the six-item Headache Impact Test (HIT-6).

The recruitment has been performed by paediatricians in Headache Clinic, Giovan Battista Grassi Hospital, Rome, Italy, from June 2016 to June 2018.

This study was conducted in accordance with the regulatory standards of Good Clinical Practice and the Declaration of Helsinki.

Questionnaire design

To pursue the aim of this study, two validated questionnaires have been employed: MIDAS and HIT-6.

MIDAS is a short questionnaire conceived to measure

headache-related disability. It is a short, easy to use questionnaire with 7 items. The first 5 questions assess completely lost days and days with a reduced productivity of at least 50%, which add up to give the MIDAS total score. The frequency and intensity of the headache over the past 3 months are assessed by the last 2 questions. The MIDAS grading system categorises(Table 2) the total score into Class I to IV, from minimal or infrequent disability with a score of 0-5 (Class I) to severe disability with score 21 more (Class IV)[15].

Figure1: Classes of MIDAS score

HIT-6 was designed to provide a global measure of adverse headache impact and was developed to use in the screening and monitoring of patients with headaches in both clinical practice and clinical research. The HIT-6 items measure the adverse impact of headache on social functioning, role functioning, vitality, cognitive functioning, and psychological distress. The HIT-6 also measures this verity of headache pain. This validated questionnaire consists of 6 questions, each question or item has the following response options: never (6 points), rarely (8 points), sometimes (10 points), very often (11 points) and always (13 points). Headache impact on this scale range (Table 3) from 36 (no headache) to 78 (very severe headache). All checked points are added for the analysis[16].

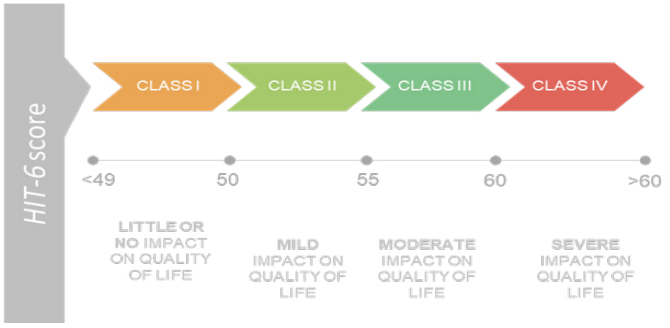

Figure 2: Classes of HIT-6 score

Study design

The study was carried out as a prospective trial. At baseline evaluation, all patients performed diagnostic tests and they began a run-in period without treatment to determinate the number and the intensity of attacks.

The inclusion criteria (Table 4) employed were: (a) aged between 3-17 years;(b) diagnosis of primary headache and/or migraine (including migraine with or without aura; chronic headache; persistent headache); (c) headache/migraine present for at least three months; (d) atleast three migraine attacks per month in the last three months. The exclusion criteria have been: (a) patients with chronic pain of different nature; (b) secondary headache.

Table 2: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
✓ aged between 3-17 years	x patients with chronic pain of different nature
✓ diagnosis of primary headache and/or migraine	x secondary headache
✓ headache/migraine present for at least three months	
✓ at least three migraine attacks per month in the last three months	

At the ground point, all the patients were subjected to the following tests: EEG (if in the family there was a story of epilepsy), eye fundus, blood tests, ORL examination, and neurological examination to rule out other causes of migraine.

Demographic data and medical history were investigated. In this period, one patient was excluded from the study because the EEG showed juvenile epilepsy, not before diagnosed.

During the recruitment visit, after reviewing the results of the exams, patients were asked to fill in a MIDAS questionnaire and an HIT-6 questionnaire.

Treatment with AURASTOP® has been conducted for 3 months, with two sachets per day. Migraine parameters and intake of sachets of AURASTOP® were recorded daily in a diary by parents.

Compliance of patients was monitored weekly by means of exchange of e-mails or phone calls with parents.

At the follow-up visit at the end of the treatment, the patients were asked to complete again a MIDAS and an HIT-6 questionnaire and to evaluate the tolerability and efficacy of the treatment.

Efficacy parameters

The primary efficacy endpoint was determined by the number of days with migraine in 3 months and the Numerical Rating Scale (NRS), in addition to MIDAS score, which measures the headache-related disability. The secondary endpoint was determined by the HIT-6 score, which measures the impact of headaches on a patient's life. Both questionnaires were filled in by the patients' parents at the start of the treatment and at the end of the 3-months treatment.

Statistical analysis

The statistical software (StataCorp. Stata Statistical Software. College Station, TX: StataCorp LLC) were used for the analysis of the collected data. Differences between categories were assessed using the $\chi 2$ and Fisher's exact tests. A statistical significant difference was accepted at a P value < 0.05.

Results and Discussion

Study population

Overall, 42 children overall, 25 females (59.52%) and 17 males (40.48%), were included in the study. The average age of chil-

dren at the time of enrollment was 10.59 ± 3.18 years. The results of the questionnaire at baseline (t1) are compared to the results after the AURASTOP® treatment (t2).

Reduction of headache days

The active treatment was able to reduce the number of headache days in 3 months from 17.28 ± 14.62 days in the pretreatment phase to 4.5 ± 8.86 days after 3 months of treatment (Figure 1). The reduction of headache days from pre- to post- treatment (t-test for paired data) is statically significant ($P < 0.05$)(Table 5).

Table 3: Evolution in the frequency of headache in 3 months with treatment

	Mean	Standard deviation	95% interquantile range
Tot.~post	4.5	8.96	2.6-4.01
Tot.~pre	17.28	14.62	6.9-7.9
Difference	-12.78	2.33	-4.87-(-3.41)

Numerical Rating Scale

The patients experienced reductions in the mean NRS (10 point scale)(Figure 2). This reduction was found statistically significant ($P < 0.05$) from the comparison of pretreatment (7.45 ± 1.74) and post-treatment (3.3 ± 2.26) data(Table 6).

Table 4: Evolution of NRS with treatment

	Mean	Standard deviation	95% interquantile range
Tot.~post	3.31	2.26	2.6-4.01
Tot.~pre	7.45	1.74	6.9-7.9
Difference	-4.14	2.33	-4.87-(-3.41)

MIDAS-score

Comparing pretreatment (46.48 ± 8.35) and posttreatment (9.78 ± 18.16) data, a reduction in mean MIDAS scores was shown. Moreover, if we consider the shifts between the classes of MIDAS score, before and after the treatment, 1/42 patients (2.38%) had worsened, 9/42 patients (21.43%) did not improve 10/42 (23.91%) improved by 1 class , 12/10 patients (28.57%) improved by 2 classes, 10/42 (23.91%) improved by 3 classes (Figure 3). The improvement of disability related to headache has proved statically significant (Fisher's exact test)(Table 7).

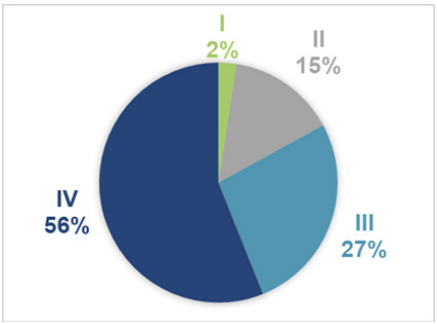

Figure 3: Pie chart of the percentage of patients for each class – MIDAS score, PRE-treatment

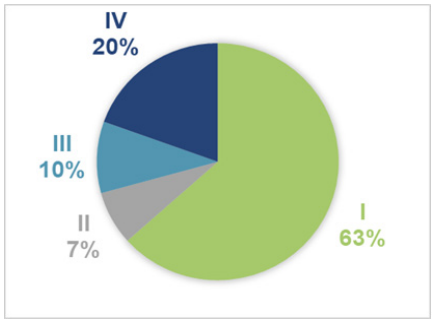

Figure 4: Pie chart of the percentage of patients for each class – MIDAS score, POST-treatment

Table 5: Frequency of variation of class – MIDAS score, POST-treatment

Shift classes MIDAS	No. of patients	Percentage	Cumulative
+3	10	23.8	23.8
+2	12	28.57	52.37
+1	10	23.8	76.17
0	9	21.43	97.62
-1	1	2.38	100

Table 6: Variation MIDAS score PRE treatment vs POST treatment

	Mean	Standard deviation	95% interquantile range
Tot.~post	9.78	18.16	4.12-15.4
Tot.~pre	46.48	8.35	43.87-49.08
Difference	-36.69	15.01	-41.37-(-32.01)

HIT-6 Questionnaire (headache impact test)

The reduction of HIT-6 scores posttreatment (46.48 ± 8.35) in comparison with pretreatment (62.55 ± 5.50) was statistically significant ($P < 0.05$).

Table 7: Variation of HIT-6 score

	Mean	Standard deviation	95% interquantile range
Tot.~post	46.5	8.35	43.87-49.07
Tot.~pre	62.54	5.5	60.83-64.26
Difference	-16.07	7.42	-18.38-(-13.75)

Safety

No significant adverse effects, nor worsening of the patients' the clinical picture were recorded after the assumption of AURASTOP®.

Discussion

Drugs like metoprolol, propranolol, flunarizine, valproic acid, or topiramate have been shown in clinical trials to be effective in reducing migraine symptoms when administered as prophylactic agents in episodic migraine[17,18]. All these drugs have potential side effects, sometime of severe nature. For this reason, many patients look for a natural preventive treatment of migraine.

In fact, some clinical trials have been performed with magnesium, riboflavin (vitamin B2), orubiquinone (ubichinon, coenzyme Q10) mostly as single agents. AURASTOP®, on the other end, innovates by employing a calibrated mix of natu-

ral components acting on different mechanisms of pathogenesis[19-21].

The parents of children suffering from headache are led to use AURASTOP®, because they are unsatisfied with conventional therapies and medications' side effects, or a predilection to be proactive against the disability of their children.

A growing number of parents have recently approached nutraceuticals for headache treatment after trying conventional therapies, which often resulting ineffective or limited by side effects, presuming that natural substances such as vitamins, minerals, and herbal remedies are less toxic than prescription medications.

The combination used in this study is the same used in another study conducted on adults from the Neurological Institute of Brescia, which registered comparable results. The study noted a significant reduction (50%) in the period of aura and the disability of headache, with the number of attacks, the period, the intensity, and the use of painkillers all influenced by the adoption of AURASTOP®[22]. Moreover, the frequency and 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, CSD. An early switching of CSD could modulate aura symptoms and even subsequent migraine[23,24].

Interestingly, all the components included in AURASTOP® demonstrated a selective action onmigraine aura development. For Tanacetum parthenium (and its derivate Parthenolide) the inhibition of nitric oxide synthesis, NF-kB activation, and proinflammatory cytokine synthesis represented key mechanisms[25]. Moreover, Tanacetum parthenium seems to act as a partial agonist of the transient receptor potential ankyrin 1 channel (TRPA1), causing its desensitization and defunctionalization, with a consequent inhibition of calcitonin gene-related peptide (CGRP) release in trigeminovascularsystem actually considered as a key mechanism in the genesis of migraine[26,27]. 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 Griffoniasimpliciofila supplement) entered the kynurenine pathway as a kinurenic acid that was able to act as anendogenous NMDA receptor antagonist, blocking glutamatergic activity. In migraine patients, kynurenine pathway perturbation was related to an aberrant unidirectional metabolization of kinurenic acid into antralic acid (promoting itself free radical production), with a consequent loss of the inhibitory action on glutamatergic acid and its excitatory activity. Thus, low plasmatic levels of kinurenic acid could be considered as an effective proxy of NMDA receptor activity[28]. Finally, magnesium deficiency has been related to CSD, as well as to free radical formation and NMDA modulation of glutamatergic activity[29-31]. 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 of 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.

Conclusion

All these observations are aimed at testing the synergistic effect of AURASTOP® as a symptomatic treatment of migraine aura and related symptoms in childhood as well as the prophylaxis of headache attacks, as already were done in adults. The preliminary results of the study, which is still ongoing, are encouraging and Tanacetum, Parthenium, magnesium and 5-HTP, with their joint action, would seem to have an important role in reducing the pain intensity and the frequency of headaches. AURASTOP® can be used both as a prophylactic treatment at the dose of 1 teaspoon 2 times per day for 2-3 months, resulting in a significant reduction of headache frequency (the treatment can be repeated after a few months in case of need), and as an acute therapy when an attack occurs, in children above 4 years of age, at a dose of 1 pouch.

Authors' contributions

All authors were involved in the study design, interpretation of the results. All authors also confirm accountability for the accuracy and integrity of the work. All authors read and approved the final manuscript.

PF, FDR: Principal investigator. Study conception and design, analysing data and drafting the article.

FDR, ARB: Study conception. Designing and reviewing the article.

FDR, PF: Designing and reviewing the article.

TP, AI: Statistical analysis of the data and reviewing the article.

FDR, LT: Data acquisition and reviewing the article.

FDR: Study conception. Designing and drafting the article.

Compliance with Ethical Statements

Conflict of interest: All authors declare that they have no conflict of interest.

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