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ORIGINAL ARTICLE

Use of nutritional supplements based on melatonin, tryptophan and vitamin B6 (Melamil Triptos®) in children with primary chronic headache, with or without sleep disorders: a pilot study

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ABSTRACT

BACKGROUND: Headache is one of the main complaints in pediatric neurology. Exogenous melatonin has been shown to be useful and safe in improving sleep-wake cycles and sleep quality in children. Tryptophan as well plays a key role in sleep regulation. So far, no studies tried to analyze the effects of a combination of both melatonin and tryptophan in treating chronic headache in children affected also by night-time awakenings.

METHODS: Thirty-four children with a diagnosis of chronic headache (with or without sleep disorders) have been enrolled. The study was articulated in two steps: 1) each child was observed for one month without any intervention; 2) children have been then randomized into two groups: the "ME-group", which received the nutritional supplement melatonin for two months and the "MET-group", which received the nutritional supplements melatonin, tryptophan, and vitamin B6 for two months.

RESULTS: In terms of changes in number of headache events, responders in the ME-group were 91.7% and those in the MET-group were 66.7% (P=0.113). In terms of changes in number of night awakenings, in the ME group, mean number at baseline, after 30 days, and after 60 days were 3.6±3.2, 3.2±3.5, and 2.7±3.4 (P=0.495). In the MET group, mean number of night awakenings was 7.4±8.1, 4.0±4.4, and 3.3±2.9 (P=0.041).

CONCLUSIONS: Using either nutritional supplement for two months can help in decreasing the monthly number of headache episodes and night awakenings. The addition of tryptophan and vitamin B& appears to have stronger influence on night awakenings reduction than melatonin only.

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KEY WORDS: Melatonin; Tryptophan; Headache; Sleep; Sleep initiation and maintenance disorders; Dietary supplements.

Headache is a frequent complaint among children and adolescents and is one of the main reasons for referral to pediatric neurologists. The prevalence of any type of headache ranges from 37% to 51% in children and from 57% to 82% in adolescents.[1] Prevalence of sleep disorders in chronic headache is not well defined, but an increase has been reported in several studies, while insomnia may represent an independent risk factor for headache to become chronic.[2, 3]

Melatonin, which is an endogenously produced indoleamine secreted — usually during darkness — by the pineal gland, regulates the circadian rhythm of sleep. Interestingly, several studies have demonstrated that melatonin has many other important physiological functions including analgesia, anti-inflammatory action and protection against glutamate neurotoxicity.[4] The analgesic effects of melatonin are not yet entirely understood, but might be carried out by interacting with opioid, GABAergic, muscarinic, nicotinic, serotonergic, and α1 and α2-adrenergic receptors located in the CNS.[5, 6] In particular, the serotonin-melatonin pathway has been discovered having a key role in the pathobiology of migraine.[7] Moreover, some studies have demonstrated altered plasma or urine levels of melatonin in patients with different types of headache. While this has still not proven as an effective biomarker for headache, it underscores the relevance of melatonin in its pathogenesis.[7, 8] Melatonin also has an anti-inflammatory effect: it reduces levels of pro-inflammatory molecules and can also decrease tissue damage by scavenging toxic free radicals and limiting transendothelial cell migration and oedema.[4] This antioxidant effect may also be responsible for its protective role against glutamate neurotoxicity.[9] Neuronal hyperexcitability, which can be mediated by glutamate, plays a significant role in the pathogenesis of migraine and aura.[10] Exogenous melatonin has been shown to be useful and safe in improving sleep-wake cycles and therefore sleep quality in children.[4, 11, 12] Besides natural and prolonged-release melatonin, various synthetic analogs have been developed, such as ramelteon, agomelatine and tasimelteon. There is still scarce evidence regarding the use and efficacy of synthetic melatonin receptor agonists and many of them are not approved for the treatment of sleep disorders in Europe.[13] Tryptophan, which is a precursor for melatonin, serotonin, kynuramines and other proteins, plays a key role in sleep regulation by interacting with many different and intertwined biochemical pathways (such as the indole-kynurenine-niacin, the serotonin-melatonin and the tryptamine pathways).[7] Remarkably, it has also been observed that if dietary intake of tryptophan is reduced, the nocturnal melatonin secretion strongly decreases.[14] Tryptophan is also the precursor of indoles as 5-hydroxytryptamine (5-HT) and it has been noted that anomalies of 5-HT1A and 5-HT2A receptors functioning may play a role in the pathogenesis of headache.[10]

While the use of melatonin in headache treatment and prophylaxis has been widely reported in literature,[4, 15-17] to the best of our knowledge, no studies analyzed the effects of a combination of both melatonin and its precursor tryptophan in treating chronic headache in children also affected by night-time awakenings. Both melatonin and tryptophan can cross the blood brain barrier (BBB), and vitamin B6 is pivotal in methionine synthesis, which plays a role in the BBB integrity as well.

Aim of this pilot study was to assess if the use of a combined nutraceutical supplementation based on melatonin, tryptophan, and vitamin B6, may provide a boosted effect in managing night-time awakenings and in decreasing the frequency of headache episodes.

Materials and methods

Study design

This perspective open-label clinical trial involved three Italian centers of excellence regarding the management of children's headaches: 1) Rome, Policlinico Tor Vergata (coordinator Prof. P. Curatolo); 2) Naples, Policlinico Federico II (coordinator Prof. C. Bravaccio); 3) Catania, Policlinico Vittorio Emanuele (coordinator Prof. R. Rizzo).

Population

Thirty-four children (14 boys and 20 girls), aged between 7 and 17 years (mean: 11.5±3.1; median: 11.0), with a diagnosis of chronic headache (with or without sleep disorders) have been enrolled. Enrolment began in February 2018.

All procedures performed involving human participants were in accordance with the ethical standards of our institutional research committee and with the 1964 Helsinki declaration and its later amendments.

After describing the study, the participants, parents and/or guardians gave informed consent

according to procedures approved by our Institutional Review Boards.

The following nutritional supplements were used for the comparison: Melamil Tripo® (Humana® Italia S.p.A.) based on melatonin, tripropan and vitamin B6 and Melamil® (Humana® Italia S.p.A.) containing only melatonin.

Intervention protocol

The study was articulated in 2 steps:

• step 1. Each child was observed for one month without any intervention. Observations were reported by the parents or by the children themselves in a structured and validated diary, which recorded the two investigated parameters: number of night awakenings and number of headache events. The reported numbers constituted the "baseline" (T0);

• step 2. Children have been then randomized into two groups: the "ME-group", which received the nutritional supplement Melatonin for two months and the "MET-group", which received the nutritional supplements melatonin, tryptophan, and vitamin B6 for two months. In both groups, each child received 3 mg of melatonin per day, to be taken at least 30 minutes before going to sleep. For the nutritional supplement melatonin, four drops of the preparation were equivalent to 1 mg of melatonin. For the combined nutraceutical supplement, 0.5 ml were equivalent to 1 mg of melatonin, 20 mg of tryptophan, and 1.4 mg of vitamin B6.

Each child was observed for a period of two months and the observations were reported by the parents or the children themselves in the diary, which recorded number of night awakenings and number of headache events, after 30 (T1) and after 60 days (T2) of nutritional supplement administration. Those children who showed a reduction of at least 50% in one or both measured parameters have been considered as "Responders".

Statistical analysis

Changes in number of headache events and night awakenings among T0, T1 and T2 were evaluated with General Linear Models for repeated measures within subjects (with *post-hoc* Bonferroni correction for multiple comparisons), with Friedman test for repeated measures analysis of variance by ranks, and with paired samples *t*-tests. Comparisons between groups were performed, as appropriate, with two sample *t*-test, Mann-Whitney U Test, and Pearson's χ^2 test. Univariate binary logistic regression models have been developed with responder/non-responder as outcome variable and nutritional supplementation or gender as possible predictive variables. An alpha level of 0.05 was used for all statistical analyses. Results, if not otherwise specified, are given as means±SD. All statistical analyses were performed using SPSS v.23.0 (IBM Corp., Armonk, NY, USA).

Results

Overall, 34 children, have been included in the study: 13 have been enrolled in Rome, 10 in Naples, and 11 in Catania. Four children, three from Rome and one from Catania, did not complete the study and where therefore considered dropouts. In terms of gender, three out of four dropouts where boys.

The 30 children (19 girls and 11 boys) who completed the study presented with a mean age of 11.5±3.2 years.

Out of the 30 children who completed the study, 12 have been randomized into the ME-group and 18 into the MET-group. There were no statistically significant gender differences between the two randomization groups. ME and MET groups did not differ in terms of age.

Table I shows patients' demographic and reports the frequency of headache episodes and awakenings at baseline and after treatment with melatonin at T1 and T2.

Changes in number of headache events

The first goal of the study was to evaluate the effect of the nutritional supplements on primary headache. Mean number of headache events at T0 was 9.0±4.6 for the ME and 9.7±5.0 for the MET-group.

Considering all the 30 children, mean numbers of headache events at baseline (T0), after 30 days (T1), and after 60 days (T2) were 9.4±4.8, 5.7±3.1, and 3.5±2.7, respectively. The

TABLE I.—*Demographic data and frequency of headache episodes and awakenings at baseline and after treatment.*

Pt	Sex	Age (years)	Baseline (30 days)		Group	T1 (day 1-30)		T2 (day 31-60)	
			N. awakenings	N. headache episodes		N. awakenings	N. headache episodes	N. awakenings	N. headache episodes
CT01	M	8	6	10	ME	4	7	3	4
CT02	M	12	7	12	ME	6	15	-	-
CT03	M	10	5	13	ME	5	10	4	5
CT04	F	9	10	15	ME	8	10	5	5
CT05	M	10	4	5	MET	4	5	4	5
CT06	F	9	3	7	MET	3	5	2	4
CT07	F	8	5	7	MET	3	6	3	3
CT08	M	11	10	15	MET	8	8	6	3
CT09	M	9	6	11	MET	5	6	4	4
CT10	F	7	4	8	MET	3	5	3	4
CT11	F	12	5	10	MET	5	9	5	8
NA01	F	9	25	12	MET	4	7	5	5
NA02	M	14	0	12	MET	0	11	0	0
NA03	M	11	0	5	ME	0	0	0	0
NA04	F	13	16	14	MET	17	11	7	11
NA05	F	9	5	8	MET	3	4	6	3
NA06	M	10	0	15	ME	0	3	0	1
NA07	F	7	0	16	MET	0	6	0	4
NA08	F	13	0	14	ME	0	7	0	3
NA09	F	11	0	8	MET	0	8	0	9
NA10	F	7	0	10	ME	0	7	0	5
RM01	F	13	1	5	MET	0	3	0	2
RM02	F	13	-	-	-	-	-	-	-
RM03	M	9	9	0	-	-	-	-	-
RM04	F	16	4	8	ME	6	8	1	3
RM05	F	17	24	23	MET	11	7	10	2
RM06	M	9	4	2	ME	0	1	1	0
RM07	F	16	4	7	MET	0	7	0	7
RM08	M	15	6	3	ME	8	3	8	2
RM09	F	14	2	7	ME	0	2	0	0
RM10	M	15	2	2	MET	1	1	0	1
RM11	F	17	6	6	ME	7	0	10	1
RM12	M	11	20	4	ME	-	-	-	-
RM13	F	17	19	5	MET	5	3	4	2

Pt: patient ID; M: male; F: female; ME: melatonin; MET: melatonin, tryptophan, and vitamin B6.

overall difference was statistically significant (P<0.001).

Considering the 12 patients of ME group, mean number of headache events at baseline (T0), after 30 days (T1), and after 60 days (T2) were 9.0±4.6, 4.8±3.7, and 2.4±2.0, respectively. The overall difference was statistically significant (P<0.001).

Considering the 18 children of MET group, mean number of headache episodes at baseline (T0), after 30 days (T1), and after 60 days (T2) were 9.7±5.0, 6.2±2.6, and 4.3±2.9, respectively. The overall difference was statistically significant (P<0.001).

Between T0 and T2, 76.7% were responders while 23.3% were non-Responders. Responders in the ME-group were 91.7% and those in the MET-group were 66.7%. The difference between these proportions was not statistically significant (P=0.113).

Changes in number of night awakenings

Mean number of awakenings at T0 was 3.6±3.2 for the ME-group and 7.4±8.1 for the MET-group. The higher mean of the MET group was mainly due to four children who presented with more than 16 awakenings.

Considering all the 30 children, mean number

of awakenings at baseline (T0), after 30 days (T1), and after 60 days (T2) were 5.9±6.8, 3.7±4.0, and 3.0±3.1, respectively. The overall difference was statistically significant (P=0.02). The *post-hoc* analysis showed that the significant decrease was mainly due to the difference between T0 and T2. Seven children presented at baseline with zero-night awakenings. Obviously, these subjects could not be considered in a Responders/Non-Responders analysis, as no reduction in number of awakenings was possible. Thus, they have been excluded from this section of the analysis. Out of the 23 children, in 78.3% the number of night awakenings decreased between T0 and T2; 52.2% were Responders and 47.8% were not.

Considering the 12 children of ME group, mean number of awakenings at baseline (T0), after 30 days (T1), and after 60 days (T2) were 3.6±3.2, 3.2±3.5, and 2.7±3.4, respectively. The overall difference was not statistically significant (P=0.495).

As concerned the 18 children of MET group, mean number of night awakenings at baseline (T0), after 30 days (T1), and after 60 days (T2) were 7.4±8.1, 4.0±4.4, and 3.3±2.9, respectively. The overall difference was statistically significant (P=0.041). The *post-hoc* analysis showed that the significant decrease was mainly due to the difference between T0 and T2, as well as T0 and T1. The decrease between T1 and T2 was not statistically significant.

The repeated night awakenings measures were tested also with non-parametric statistics, which confirmed the statistically significant differences in the MET-group (F=15.362; P<0.001) and no statistically significant differences in the ME-group (F=2.138; P=0.343).

Even considering the children with more than 10 awakenings as possible outliers, the significant decrease in mean number of awakenings in the MET-group was confirmed.

Responders in the ME-group were 62.5% and those in the MET-group were 46.7%. The difference between these proportions was not statistically significant.

Discussion

The aim of this pilot study was to evaluate the effectiveness of a nutritional supplement based on melatonin, tryptophan and vitamin B6 (Melamil Tripo®), in children with primary headache with or without sleep disorders and to compare its efficacy to that of melatonin alone (Melamil®).

In relation to headache events, 90% of the children presented some improvement during the two months in which nutritional supplements were used. Considering the mean number of headache events, an important reduction from 9.4 at T0 to 3.5 at T2 was observed. Interestingly, a significant reduction was already present after using nutritional supplements for one month. Reductions were similar in both the ME and the MET group. In addition, 76.7% of all the children improved by at least 50% (Responders) in terms of event decrease. The percentage of Responders was slightly higher and the response quicker in the ME than in the MET-group, however these differences did not reach statistically significance. Gender or age of the child was not associated to treatment response.

Concerning the night awakenings, 78.8% of the children presented an improvement during the two months of nutritional treatment. This is a better outcome compared to literature data, where there is usually reported a lesser reduction or even no reduction in nighttime awakenings in relation to a more significant improvement of sleep duration and overall sleep quality.[4, 18, 19]

A reduction of the mean number of awakenings from 5.9 at T0 to 3.0 at T2 was observed. In this case, two months of supplementations were necessary to observe significant reductions, which - contrariwise - were not recognizable after one month. It is important to highlight that the reduction of night awakenings was statistically significant in the MET-group, but not in the ME-group. Overall, 52.2% of the children decreased their number of night awakenings by at least 50%. The percentage of Responders was slightly higher in the ME-group, but the response was quicker in the MET-group, even though these differences were not statistically significant. Older children and girls had a slightly (non-significant) higher probability of being a Responder.

Overall, 39.1% of the children presented with a 50% decrease in both headache events and night awakenings, with no significant differences between the ME and MET-group.

Limitations of the study

Due to the relatively small sample size and, therefore, the limited power of the study, the results should be considered as preliminary ones rather than as conclusive. Also, the study was an open-label one and did not foresee a control group with no nutritional supplement. Thus, a placebo effect cannot be excluded.[20, 21] Nevertheless, it can be preliminarily maintained that the use for two months of either nutritional supplements can help in decreasing the monthly number of headache episodes and of night awakenings. The combined nutraceutical supplementation appears to have a stronger influence on night awakenings reduction than melatonin only, while the two nutritional supplements seem to be equivalent in reducing the frequency, intensity and duration of headache episodes per month.

Based on our understanding of the available literature,[7, 22, 23] we hypothesize that this could be explained by an increased availability of the amino acid tryptophan in the CNS that, being administered before going to bed, has a lesser competition from other amino acids and proteins in crossing the BBB and can be more easily stripped from its bond with albumin by the carrier.[24] This, in turn, could be responsible for enhancing the serotonin-melatonin pathway and providing a better regulation of sleep-wake cycles.

Conclusions

Using either nutritional supplement for two months can help in decreasing the monthly number of headache episodes and night awakenings. The addition of tryptophan and vitamin B6 appears to have stronger influence on night awakenings reduction than melatonin only.

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Conflicts of interest.—Leonardo Emberti Gialloreti reports a past consultancy fee from Humana. The nutritional supplements were supplied by Humana. There was no involvement of the supplier in the design of the study, or in the collection, analysis, or interpretation of data involved in the publication, nor in the writing of the manuscript, nor the decision to submit it for publication.

Authors' contributions.—Carmela Bravaccio, Renata Rizzo, Paolo Curatolo conceived and planned the study; Gaetano Terrone, Mariangela Gulisano and Michele Tosi carried out the acquisition of data; Leonardo Emberti Gialloreti contributed to the analysis and interpretation of the results; Michele Tosi and Leonardo Emberti Gialloreti contributed in drafting the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript before giving final approval of the version to be published.

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