Journal of Applied Biomedicine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Applied Biomedicine

journal homepage: www.elsevier.com/locate/jab

Original research article

Oral melatonin administration improves the objective and subjective sleep quality, increases 6-sulfatoxymelatonin levels and total antioxidant capacity in patients with fibromyalgia

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ARTICLE INFO

Article history:
Received 8 December 2016
Received in revised form 28 November 2017
Accepted 17 January 2018
Available online xxx

Keywords:
Fibromyalgia
Melatonin
Sleep quality
6-Sulfatoxymelatonin
Antioxidant capacity

ABSTRACT

Background/objective: Chronic pain, sleep disturbances and oxidative stress are implicated in the pathogenesis of fibromyalgia. The aim of this study was to assess the effect of melatonin supplementations on sleep quality, 6-sulfatoxymelatonin (aMT6-s) levels, as well as urinary and serum total antioxidant capacity (TAC) in patients with fibromyalgia.
Methods: Thirty three patients carried out the full study. A baseline period (10 days) was included in the experimental design to collect information about patients' initial status. Then, patients took different doses of melatonin, during 10 consecutive days each. Placebo was given during 10 days either before or between melatonin doses. Objective sleep quality was recorded by actigraphy whereas subjective sleep quality was measured by The Pittsburgh Sleep Quality Index. Quantification of aMT6-s and TAC was achieved by ELISA and colorimetric assay kits, respectively.
Results: Six out of seven sleep parameters evaluated by actigraphy were improved after the intake of melatonin as well as the subjective sleep quality. All the biochemical parameters measured were also elevated after the melatonin administration.
Conclusion: The daily intake of melatonin improved the sleep quality, increased the aMT6-s levels and the total antioxidant capacity in patients with fibromyalgia.

Introduction

The etiology of fibromyalgia (FM) is still unclear (Bellato et al., 2012). It is characterized by chronic widespread musculoskeletal pain. Besides sleep disturbances or poor-quality sleep (Hita-Contreras et al., 2014), anxiety, depression, and lack of concentration and memory (Giacomelli et al., 2013) are also common symptoms in patients with FM. Moreover, different studies have shown disruptions of circadian rhythms of certain biochemical parameters such as: melatonin, cortisol, serotonin or cytokine production (Mahdi et al., 2011). However, it is unknown if these abnormalities are cause or consequence of the disease.

Recently, it has been suggested that oxidative stress is implicated in the pathogenesis of FM (Fatima et al., 2015). Under oxidative stress conditions, excessive reactive oxygen species (ROS) production can damage biomolecules and cellular components (Akbas et al., 2014; Sánchez et al., 2015). In this context, increased ROS levels observed in blood mononuclear cells in patients with FM have been decreased by antioxidant actions (Akkuş et al., 2009; Nazıroğlu et al., 2010; Sartori et al., 2016), which reflect changes in markers of oxidative stress, including the Trolox equivalent antioxidant capacity (TEAC), whose level in serum has been widely used in the assessment of lipid peroxidation (Cordero et al., 2011).

Although pain is the most common symptom associated with FM, and the greatest therapeutic and research efforts have been focused on it, major sleep disturbances are also very common, representing up to 90% of patients. Moreover, a direct negative correlation between sleep and pain has been suggested (Chinn et al., 2016). In this line, it has also been proposed an important complex relationship between pain and sleep disturbance, since pain could disrupt sleep and, at the same time, sleep deprivation could enhance pain sensitivity (Diaz-Piedra et al., 2015; Spaeth et al., 2011).

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https://doi.org/10.1016/j.jab.2018.01.005
1214-021X/

It is known that melatonin is involved in several physiological processes, including the regulation of circadian rhythms, pain, mood, and immune responses (De Zanette et al., 2014), and it is a well-known free radical scavenger and antioxidant (Tan et al., 1993). This indoleamine has been used in several clinical studies in FM patients with successful results (De Zanette et al., 2014; Wilhelmsen et al., 2011). Hence, Citera et al. (2000) have found that pain intensity was reduced and physical parameters were improved 30 days after the administration of 3 mg/day of melatonin. In the same context, other studies have shown that doses of 5 mg/day melatonin and 10 mg/day, administered together with the usual medication of the patient, improved fatigue, mood, sleep quality and pain (De Zanette et al., 2014; Hussain et al., 2011).

Therefore, the purpose of this study was to assess the effect of the intake of different doses of melatonin (3, 6, 9, 12, 15 mg/day) on sleep quality (objective and subjective assessments), the 6-sulfatoxymelatonin (aMT6-s) levels, the main urinary metabolite of melatonin, and the urinary and serum total antioxidant capacity in patients with severe fibromyalgia.

Materials and methods

Participants

Ninety seven patients with FM were initially recruited. Among them, 36 were finally enrolled in the study, according to the inclusion criteria: FM women diagnosed based on the American College of Rheumatology guidelines (Wolfe et al., 2010) aged more than 40 years-old, with >70 total score in Fibromyalgia Impact Questionnaire (FIQ), and not involved in physical/psychological therapies. There were three dropouts throughout the study due to family-related matters and disinterest in the adherence to the protocol of the study. For this reason, 33 out of 36 patients completed the full study. All participants kept their lifestyle habits related to medication, diet, sleep, and exercise throughout the study.

The study was approved by both, the Ethical Committee of the University of Extremadura (Badajoz, Spain) and the Ethical Committee of Servicio Extremeño de Salud, in accordance with the Declaration of Helsinki, the Council of Europe and the Universal Declaration of UNESCO on human rights, biomedicine and human genome. Informed consent was obtained from all participants.

Experimental design

The study had a longitudinal placebo-controlled design with 5 melatonin administration periods of 10 days each, separated by washout periods (10 days each). Before starting with the assay 10 days were left as basal period to collect information about patients' initial status. All the patients took different doses of melatonin (3, 6, 9, 12, 15 mg/day). Each dose was taken as a single pill (Guinama, Puebla de Vallbona, Spain) at night, 30 min before going to bed during 10 consecutive days. Placebo (a rice starch-containing pill) was administered at night (1 pill/day) during 10 days, either before (placebo period) or between (washout periods) the different doses of melatonin (Table 1).

Objective sleep assessment tool: actigraphy

Actigraphic monitoring was used to record and display the temporal patterns of the individuals' activity and rest (Actiwatch, Cambridge Neurotechnology Ltd., Cambridge, UK). Participants wore a wrist activimeter, on the non-dominant wrist that recorded activity throughout the whole assay. When the data collection period finished, the results were analyzed, with the sleep analysis (Cambridge Neurotechnology Ltd.) software package. The parameters analyzed with the software were: sleep efficiency (percentage of sleep time while the subject remains in bed); actual sleep time (assumed sleep minus awake time; determined by algorithms); wake bouts (the number of episodes of high activity during the period of sleep); total nocturnal activity (total pulses of activity during sleep); sleep latency (time from the individual lies down on bed to sleep onset); assumed sleep (the difference between the end and beginning of the period of sleep); immobility (minutes in which the subject has zero mobility).

Subjective sleep assessment tool: Pittsburgh test

The Pittsburgh Sleep Quality Index (PSQI) is a self-report questionnaire developed for measuring the subjective perception of sleep quality and patterns. This questionnaire includes 19 self-rated items divided in 7 components: sleep quality (1 item), sleep latency (2 items), sleep duration (1 item), habitual sleep efficiency (3 items), sleep disturbance (9 items), use of sleeping medication (1 item), and daytime dysfunction (2 items). The global score has a range from 0 to 21. Higher score represents poorer subjective sleep quality (Hita-Contreras et al., 2014). This questionnaire was filled at the end of the different periods: baseline, placebo, melatonin administrations and washout periods.

Urinary 6-sulfatoxymelatonin levels (aMT6-s)

First-void morning urines were collected at the end of basal and placebo periods, and both and at the end of the administration of each different dose of melatonin and washout periods. The samples were stored at −80 °C until biochemical assay. The urinary metabolite aMT6-s was quantified using a commercial enzyme-linked immunoabsorbent assay kit (DRG® Melatonin-Sulfate (EIA-1432), USA) according to the manufacturer's instructions.

To adjust for variation in the dilution of urine, 6-sulfatoxymelatonin was expressed as urinary 6-sulfatoxymelatonin/urine creatinine ratio. Creatinine concentration was determined by means of the Jaffe test.

The total antioxidant capacity in urine samples

First-void morning urines were collected both, at the end of basal and placebo periods, and at the end of the administration of

Table 1
Experimental design.

Period (days) (110 days)	B (10)	P (10)	3 mg (10)	W (10)	6 mg (10)	W (10)	9 mg (10)	W (10)	12 mg (10)	W (10)	15 mg (10)
Melatonin	–	–	x	–	x	–	x	–	x	–	x
Actigraphy	x	x	x	x	x	x	x	x	x	x	x
Pittsburgh test (end of each period)	x	x	x	x	x	x	x	x	x	x	x
Urine collection (end of each period)	x	x	x	x	x	x	x	x	x	x	x
Blood collection	x	–	–	–	–	–	–	–	–	–	x

B, basal period; P, placebo period; W, washout period.

Please cite this article in press as: M.Y. Castaño, et al., Oral melatonin administration improves the objective and subjective sleep quality, increases 6-sulfatoxymelatonin levels and total antioxidant capacity in patients with fibromyalgia, J. Appl. Biomed. (2018), https://doi.org/10.1016/j.jab.2018.01.005