Neurochirurgie 62 (2016) 295–299

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Original article

Effects of melatonin in the treatment of asthenia in aneurysmal subarachnoid hemorrhage

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ARTICLE INFO

Article history:
Received 22 April 2016
Received in revised form 9 June 2016
Accepted 20 June 2016
Available online 16 November 2016

Keywords:
Subarachnoid hemorrhage
Intracranial aneurysm
Asthenia
Melatonin

ABSTRACT

Background and objectives. – Survivors of aneurysmal subarachnoid hemorrhage (aSAH) commonly experience sleep disorders resulting in asthenia. The objective of this prospective study was to determine, in a cohort of patients with treated ruptured intracranial aneurysm (IA), the proportion of asthenia at 2 months, in a cohort of patients treated with melatonin and in a control cohort.
Patients and methods. – Twenty consecutive patients admitted for the treatment of ruptured IA and able to answer a standardized questionnaire were included in the study. After evaluation for fatigue at discharge, we divided our population into 2 cohorts of 10 patients: the first cohort was treated with melatonin for a period of 2 months; the second cohort had no specific treatment for fatigue. The primary endpoint was the proportion of asthenia at 2 months in both groups. Confounding factors, such as depression, autonomy and apathy were evaluated at the same time.
Results. – At discharge, there was no significant difference observed between both groups in terms of mean age and initial clinical status (WFNS, Rankin Scale and Fatigue Severity Scale). At 2 months, the mean FSS score in the control group was of 4.7 ± 1.0 versus 3.8 ± 0.9 in the melatonin group ($P = 0.03$). The mean MADRS score in the control group was of 1.1 ± 1.45 versus 2.7 ± 2.5 in the melatonin group ($P = 0.10$). The mean LARS score in the control group was of -32.5 ± 1.7 versus -31.7 ± 1.9 in the melatonin group ($P = 0.24$).
Discussion. – In a prospective evaluation of post-aSAH fatigue, we suggest that melatonin could decrease fatigue. There is no significant impact on depression and apathy. Further studies would be necessary to improve our comprehension of fatigue physiopathology in a context of aSAH.

1. Introduction

The aneurysmal subarachnoid hemorrhage (aSAH) accounts for up to 5% of all new stroke cases [1,2]. The worldwide incidence of aSAH is estimated at approximately 9 per 100,000 persons/year [1], still responsible for severe consequences for patients. The case-fatality varied between 20% and 62% in population-based studies [3].

Survivors of aSAH commonly experience cognitive sequelae that affect their day-to-day functioning, including activities of daily life, return to work, and quality of life [4]. Sleep and wake disorders in patients who have experienced aSAH may persist several years after aSAH [5]. This could cause asthenia, defined as chronic fatigue not responding to rest [6], resulting in severe daily life disability. Different hypotheses have been proposed to explain asthenia in aSAH: a modulation of neurotransmitter enzymatic activity due to bleeding [5], the alteration of neuronal networks due to ischemia or hydrocephaly [7] or a neuroendocrine dysfunction [8].

To counterbalance the asthenia induced by aSAH, several molecules have been proposed, such as corticoids [9] with no significant impact on quality of life. Melatonin is a pineal hormone, involved in sleep induction and circadian rhythm regulation [10], which has been proposed in reducing fatigue for patients with multiple sclerosis [11] and attempted as supportive care in oncology [12]. Melatonin has proven its efficacy in reducing inflammation in animal models in a context of aSAH [13]. It is also a medicine currently used in insomnia and widely prescribed [14]. We consequently proposed this molecule as a symptomatic treatment of asthenia for aSAH. This treatment has been the standard procedure at our institution for the past several years.

The aim of this prospective study was to determine, in a cohort of patients with treated ruptured IA, the proportion of asthenia at

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http://dx.doi.org/10.1016/j.neuchi.2016.06.010
0028-3770/

2 months, in a cohort of patients treated with melatonin and in a control cohort.

2. Patients and methods

2.1. Study design

This prospective longitudinal study concerned a series of patients with ruptured IA admitted to the neurosurgery department at Rouen University Hospital between January 2014 and February 2015. The primary objective was to compare the proportion of patients with asthenia at 2 months in 2 cohorts of patients, with or without melatonin. Secondary objectives were to evaluate, at 2 months, autonomy, depression and apathy which are sometimes confused with asthenia.

2.2. Population

Inclusion criteria were:

- adult > 18 years old;
- ruptured IA diagnosed on a Willis CT scan and/or angiography;
- exclusion of the AI (surgery or embolization);
- WFNS score [15] ≥ 2;
- no contra-indication to melatonin.

Outflow IA in a context of arterio-venous malformation (AVM) was excluded. We collected demographic data, characteristics of the aneurysm, treatment modalities, a need for external ventricular drainage, and onset of meningitis.

2.3. Clinical endpoints

Fatigue was evaluated according to the Fatigue Severity Scale (FSS) [16,17], one of the most commonly used self-report questionnaires to measure fatigue. The FSS is a self-administered questionnaire with 9 items (questions) investigating the severity of fatigue in different situations during the previous week. Grading of each item ranges from 1 to 7, where 1 indicated a strong disagreement and 7 a strong agreement, and the final score represents the mean value of the 9 items. Asthenia was defined by a FSS > 3, which is a commonly used cut-off point in the literature [16,17]. Two confusing factors of asthenia were evaluated: apathy and depression by a questionnaire.

Apathy was measured with the Lille Apathy Rating Scale (LARS) [18]. The LARS is a questionnaire that comprises 33 queries belonging to nine domains, each corresponding to a clinical manifestation of apathy. Depression was evaluated by using the Montgomery-Åsberg Depression Rating Scale (MADRS) [19], which is a questionnaire used for diagnosis and grading of depression. Autonomy was evaluated by the Rankin modified score [20]. All clinical endpoints were evaluated prospectively by the same investigator, at transfer from the Intensive Care Unit (ICU) to a conventional ward, and at 2 months from initial bleeding. After the ICU, 2 groups were established: a first group treated with extended-release 2 mg of melatonin each evening until the 2 months evaluation; a second group without melatonin. The patients were attributed to each group consecutively. The treatment was initiated after transfer to a conventional ward (day 7). It was administered as recommended, each night, one hour before sleep.

2.4. Statistical analysis

For statistical analysis, NCSS v6.0 was used with a Wilcoxon exact test for categorical data, with non-parametric analyses (Mann–Whitney *U*-test) to compare both groups. The level of statistical significance was set at 0.05.

Table 1
Baseline demographic characteristics.

Patient	Age	Fisher	WFNS	EVD	Aneurysm	Treatment	Melatonin
1	38	1	1	0	ACoA	Clipping	1
2	50	3	2	0	PC	Coiling	1
3	48	1	1	0	ACoA	Clipping	1
4	54	3	1	1	MCA	Clipping	1
5	54	4	2	1	MCA	Clipping	1
6	44	2	2	1	MCA	Clipping	1
7	61	1	1	0	ICA	Coiling	1
8	44	1	1	0	ACoA	Coiling	1
9	78	4	1	1	ICA	Coiling	1
10	62	2	1	0	ACoA	Clipping	1
11	70	2	2	0	ACoA	Clipping	0
12	68	4	2	1	MCA	Clipping	0
13	32	2	2	1	ACoA	Clipping	0
14	55	3	2	1	MCA	Clipping	0
15	46	3	1	0	MCA	Clipping	0
16	48	1	1	0	MCA	Clipping	0
17	59	2	1	1	ICA	Clipping	0
18	22	1	1	1	ICA	Coiling	0
19	50	3	1	1	ACoA	Coiling	0
20	67	2	2	1	ICA	Clipping	0

EVD: external ventricular drainage; MCA: middle cerebral artery; ICA: internal carotid artery; AcoA: anterior communicating artery; PC: posterior circulation.

3. Results

3.1. Population and aneurysmal characteristics

The cohort (Table 1) was composed of 20 patients (17 women; 3 men), with a mean age of 52.5 ± 13.4 years of age, admitted to the neurosurgery department for ruptured IA. The aneurysms were located in the anterior circulation in 19 patients (95%) [middle cerebral artery (MCA) in 7 patients (35%), internal carotid artery (ICA) in 5 patients (25%), anterior communicating artery (AcoA) in 7 patients (35%)], and in posterior circulation in 1 patient (5%). There was no significant difference between both groups in terms of mean age and initial clinical status (WFNS, Rankin and FSS). After intensive care, the mean FSS score in the control group was of 5.9 ± 0.38 versus 5.8 ± 0.44 in the melatonin group ($P = 0.47$). The mean MADRS score in the control group was of 4.1 ± 2.8 versus 8 ± 3.8 in the melatonin group (p = 0.03). The LARS score in the control group was –28.3 ± 2.9 versus –26.5 ± 2.4 in the melatonin group ($P = 0.12$) (Table 2).

Concerning the treatment modalities, 14 patients were operated on, 6 patients had endovascular treatment.

3.2. Outcomes at follow-up

At 2 months evaluation, the mean FSS score (Fig. 1) in the control group was 4.7 ± 1.0 versus 3.8 ± 0.9 in the melatonin group ($P = 0.03$). The mean MADRS score (Fig. 2) in the control group was 1.1 ± 1.45 versus 2.7 ± 2.5 in the melatonin group ($P = 0.10$). The mean LARS score (Fig. 3) in the control group was –32.5 ± 1.7 versus –31.7 ± 1.9 in the melatonin group ($P = 0.24$). The mean Rankin modified score (Fig. 4) in the control group was 0.8 ± 0.4 versus 0.6 ± 0.5 in the melatonin group ($P = 0.37$).

4. Discussion

In our study, we attempted to prove a significant regression of asthenia 2 months after aSAH in our cohort treated with melatonin. We also took into account any confounding factors, such as