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Melatonin for Clinical Improvement in Patients with Ischemic Stroke: A Randomized Clinical Trial

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Abstract

Background: Ischemic stroke is the most frequent form of stroke, which imposes considerable cost and causes disabilities for the patients. Melatonin is proven to have anti-oxidant along with anti-inflammatory effects.
Objectives: The present study aimed to examine the effects of melatonin on clinical features of acute stroke in Iranian patients.
Methods: This randomized clinical trial was conducted on 58 patients who were admitted to Valiasr Hospital and Neurology Center in Arak, Iran, from April 2016 to April 2017. Inclusion criteria were: age ≥ 50 years and diagnosis of acute ischemic stroke. All participants were asked to fill out informed consent forms before entering the study. Through simple randomization, an expert nurse divided cases into two groups of 29 people: Group 1 as the intervention group: ASA 80mg/day + Plavix 75 mg/day + melatonin 3 mg (every night one pill for two months), Group 2 as the control group: ASA 80 mg/day + Plavix 75 mg/day + placebo (every night one pill for two months). Canadian Neurological Stroke Scale (CNSS) was recorded for all cases before and after treatment.
Results: Mean age, sex, circulation, cardiovascular accident incidence time, and symptoms were not significantly different between the two groups. Mean of the CNSS was significantly higher after the treatment in both groups. It improved significantly more in the intervention group than in the control group.
Conclusion: Findings of the present study showed that CNSS improved more in the intervention group than in the control group. Therefore, melatonin administration in patients with ischemic stroke will result in better clinical improvements.

Keywords: Inflammation, Ischemic stroke, Melatonin

1. Background

Stroke, a cerebrovascular disease, is the second cause of death worldwide (1). Ischemic stroke is the most frequent stroke which occurs as the result of thromboembolic occlusion of supplying arteries (1). Despite various studies and trials, there is no effective treatment for protecting against ischemic brain damage (2, 3).

Metabolic failure resulting from blood supply reduction will cause ionic gradient imbalance, intracellular calcium and sodium ions accumulation, and pH reduction (1). Therefore, disturb membrane and mitochondrial functions and the formation of excessive free radicals will happen (1). When pro-apoptosis starts, DNA breakdown and cell death occur (4, 5). Restoring blood flow and ameliorating consequences, such as apoptosis, inflammation, penumbral depolarization, and diaschisis are among the primary therapeutic strategies in stroke (1).

Melatonin (N-acetyl-5-methoxy-tryptamine) is a hormone secreted by different organs (e.g., the pineal gland, retina, and gastrointestinal tract) and it is used as a source of clinical therapy (6, 7). Melatonin is considered to have radical scavenger and anti-oxidant effects (5). The effects of melatonin on neurons have been demonstrated in acute ischemic stroke. Moreover, melatonin has been shown to modulate the postischemic cerebral blood flow and reduce excitotoxicity, neuroinflammation, and ischemia-reperfusion injury (8-10). Administration of melatonin in acute phase will help to reduce infarct size, inflammatory reaction, and oxidative damage (11-13). In rats, it was considered that administration of melatonin will help protecting white and gray matter of the brain against damage and improves neuroplasticity, neurobehavioral and electrophysiological outcomes (9, 10, 14, 15).

2. Objectives

Since there are limited studies evaluating clinical effects of melatonin on the improvement of clinical features in patients with acute stroke, we designed this study to assess the effects of melatonin on clinical features of acute stroke in Iranian patients. In other words, we intended to provide a way to reduce the disability and severity of stroke. Therefore, these patients can have a higher quality of life.

3. Methods

3.1. Study design and participants

This multicentric randomized clinical trial was

conducted on 58 patients with ischemic stroke admitted to Valiasr Hospital and Neurology Center of Arak, Iran (affiliated hospitals of Arak University of Medical Sciences) from April 2016 to April 2017.

Inclusion criteria were: age ≥ 50 years and diagnosis of acute ischemic stroke. The exclusion criteria included: systemic diseases, such as kidney, heart, liver, pulmonary and infectious diseases, loss of consciousness, unwillingness to participate in the study, and incidence of any systemic diseases during the treatment.

3.2. Ethical issue

All participants were asked to fill out informed consent forms before entering the study. The study had been approved by the Ethics Committee of Arak University of Medical Sciences (IRCT number: IRCT2015012917811N6).

3.3. Intervention

Age, sex, education level, job, cardiovascular accident (CVA) incidence time, symptoms, past medical history and social history were recorded for patients. Through simple randomization, an expert nurse divided cases into two groups of 29 people: Intervention Group: "Acetylsalicylic acid" or "Aspirin" 80mg + Plavix 75 mg + melatonin 3 mg (every night one pill for two months), Control Group: ASA 80mg + Plavix 75 mg + placebo (every night one pill for two months).

The placebo was similar to melatonin in shape, color, and taste. The patients and physicians were blinded to the patient's groups. All cases were visited every two weeks by a neurologist and followed up for two months.

3.4. Outcome measurements

Before and at the end of the study, Canadian Neurological Stroke Scale (CNSS) (https://strokengine.ca/en/assessments/canadian-neurological-scale-cns/) was measured for all cases by an independent general practitioner who did not know the patient's groups and was trained to assess the patients. The higher the scores, the better the prognosis is expected. The CNSS difference (after-before) was considered as Δ CNSS.

3.5. Statistical analysis

The collected data was analyzed in SPSS (version 24, SPSS Inc., Chicago, IL, USA). Data was shown in Mean ± SD for continuous and frequencies and percentage for categorical variables. The Chi-squared test, independent sample t-test, and paired t-test were used for data analysis. A *P*-value < 0.05 was considered statistically significant.

4. Results

Sixty cases of ischemic stroke were randomly assigned into two groups. One case in each group withdrew before the beginning of the study. No significant difference was observed regarding age, sex, time of stroke occurrence, and symptoms between the two groups (Table 1).

The CNSS mean was significantly higher after treatment in both groups (Table 2). No significant differences were observed regarding CNSS scores before and after treatment in the two groups (P>0.05). However, according to ΔCNSS, the intervention group improved more than the control group (Table 2).

Table1. Basic characteristics of the patients

	Control group (n=29)	Melatonin group (n=29)	*P*-value
Age (year)	69.3±12.3	73.4±10.9	0.1*
Sex			
Male	15(51.7%)	19(65.5%)	0.2**
Female	14(42.3%)	10(34.5%)	
Occupation			
Employed	16(45.2%)	13(44.8%)	0.1**
Unemployed	13(44.8%)	16(45.2%)	
CVA incidence time			
Before sleep	3(10.7%)	1(3.4%)	
During sleep	5(17.9%)	4(13.8%)	0.6**
After sleep	10(34.4%)	11(37.9%)	
During awakens	11(37.9%)	13(44.8%)	
Circulation			
Anterior circulation	28(96.5%)	24(82.7%)	0.5**
Posterior circulation	1(3.5%)	5(17.3%)	
Symptoms			
Quadri-paresia	1(3.4%)	2(6.8%)	0.5**
Left hemiparesia	11(37.9%)	14(48.2%)	0.4**
Right-hemiparesia	14(48.2%)	12(41.3%)	0.5**
Aphasia	15(51.7%)	17(58.6%)	0.5**
Left facial paresia	3(10.3%)	2(6.8%)	0.6**
Right facial paresia	5(17.2%)	3(10.3%)	0.4**

Table 1. Continued

Vertigo	4(13.7%)	9(33.3%)s	0.1**
Headache	3(10.3%)	8(29.6%)	0.09**
Diplopia	1(3.4%)	1(3.4%)	1**
Loss of consciousness	8(29.6%)	6(20.7%)	0.5**
Seizure	0 (0%)	0 (0%)	-
Incontinency	5(17.2%)	3(10.3%)	0.4**
Social habits			
Smoking	1(3.4%)	0	0.2**
Oral opioid	1(3.4%)	2(6.8%)	
Smoking+ Oral opioid	0	2(6.8%)	
Past medical history			
IHD/HTN	3(10.3%)	4(13.7%)	0.6**
HLP[c]	3(10.3%)	3(10.3%)	
DM	5(17.2%)	10(34.4%)	

*Independent sample t-test, ** Chi-squared test
CVA: cardiovascular accident, DM: diabetes mellitus, IHD: ischemic heart disease, HTN: hypertension, HLP: Hyperlipidemia

Table 2. Canadian Neurological Stroke Scale before and after the treatment in both groups and Δ CNSS in the two groups

	CNSS before treatment	CNSS after treatment	P-value*	Δ CNSS**
Control group	9.3±2.6	11.4±2.7	<0.001	2.1±1.1
Melatonin group	8.8±2.6	12.3±3	<0.001	3.4±1.5

** Independent sample t-test, **Paired t-test, P<0.001, CNSS: Canadian Neurological Stroke Scale

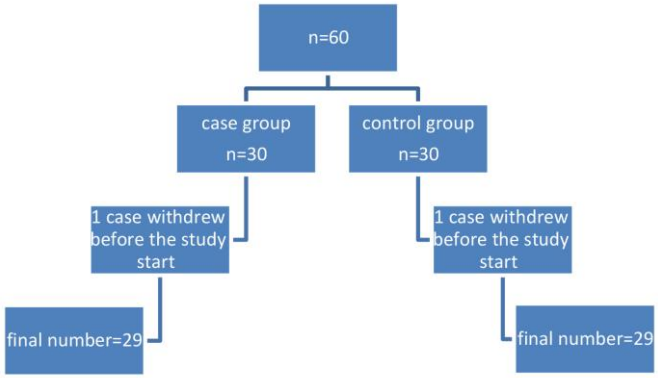

Figure 1. Consort algorithm

5. Discussion

We found that melatonin positively affects ischemic stroke complications. The results of the present research revealed that melatonin causes CNSS improvement more than placebo which may show its neuro-protection effects. The neuroprotective mechanism noted for melatonin is related to free radical scavenging as well as antioxidant effects (16). It also results in lipid peroxidation reduction and blocks oxygen-induced toxicity (17, 18).

Kilic et al. pinealectomized rats three months before Middle Cerebral Artery (MCA) occlusion; and found that melatonin injection before ischemia and reperfusion will reduce infarct volume by up to 40% (19). It was shown that melatonin decreases the inflammatory response, blood-brain barrier permeability, and formation of brain edema in rats (13, 20, 21). In previous animal studies, it was also revealed that melatonin is effective in neuro-protection after hemorrhagic stroke (22-27).

Reduction of brain water content, oxidative stress, early brain injury, lipid peroxidation inhibition, and antioxidant enzymes gene expression increase are among probable mechanisms in hemorrhagic stroke (22-27). Chen et al. found that injection of melatonin (150 mg/kg, i.p.) two h after Subarachnoid Hemorrhage (SAH) causes neural apoptosis inhibition, brain edema reduction, and neurological and survival improvements (28).

Melatonin administration before the MCA occlusion or right after the perfusion was shown to have effects on pH, pCO_2, pO_2, temperature, and blood pressure (8, 29). Nitric oxide production inhibition in neurons and increased activation of NADH-coenzyme Q reductase (Complex I) and cytochrome C oxidase (Complex IV) in mitochondria are among the possible effects of melatonin (30, 31).

These functions will counter energy for cellular function and brain damage decrease (1). The other role of melatonin in the acute phase of experimental model of stroke is inhibition of immune cell infiltration, neuronal degeneration, and DNA damage (1).

Endogenous melatonin deficit after pinealectomization of rats resulted in larger cortical infarction and neuronal damage (16).

On the other hand, reduction of microglial/macrophage activation and immune cells infiltration to the ischemic part of the brain are among melatonin effects in rats after middle cerebral artery occlusion (13).

In summary, administration of melatonin in the acute phase of ischemic stroke could be helpful for the preservation of mitochondrial function, reduction of immune responses, decreases of microglial/macrophage activation, and finally, brain damage reduction.

This study had following limitations. Firstly, it was conducted in one center. Secondly, the sample size was limited. Thirdly, only cases with ischemic stroke were enrolled. Therefore, more multicentric studies, including patients with all types of stroke, is recommended.

6. Conclusion

Melatonin administration in patients with ischemic stroke will lead to better and faster clinical recovery. In other words, stroke patients who use melatonin along with their standard treatment, compared to patients who do not use melatonin, have less neurological deficit and disability, resulting in a better outcome and lifestyle in the future.

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Footnotes

Conflicts of Interest: None.
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