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Research Article

EFFECT OF MELATONIN IN POST-STROKE RECOVERY

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ABSTRACT

Objective: Stroke is the second main cause of death worldwide. Recovery from a stroke differs from person to person. Melatonin is a neuroprotective agent with low adverse effects. The limitation of melatonin studies on human and other clinical bases made us keen to took up this research work to explore its full potential as a neuroprotective agent. The purpose of this research was to evaluate the effect of melatonin in stroke recovery inpatients.

Methods: This was a present prospective observational study carried out at the Department of Neurology of tertiary care hospital over 6 months. The patient data were collected through history interview and from the case sheets. Continuous variables were presented as the minimum, maximum, median, mean, and standard error of the mean (SEM). Categorical variables were presented as frequencies and percentages.

Results: A total of 80 patients were included in this study based on inclusion criteria. A significant difference was not found in the age and gender between the two study groups. There is a statistically significant difference in the percentage of improvement of modified Rankin Scale (mRS), Communication Disability Scale (CDS), and Cognitive Assessment of Stroke Patients (CASP) scores between the study groups.

Conclusion: Our study concluded that patients received melatonin along with first-line treatment which has shown better efficacy in treating post-recovery stroke patients when compared with patients received first-line treatment alone. Melatonin served as an excellent neuroprotectant in patients of acute ischemic stroke with improvement in the motor, speech, and cognitive functions.

Keywords: Stroke, Melatonin, Modified rankin scale, Communication disability scale, Cognitive assessment of stroke patients.

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INTRODUCTION

A stroke or cerebral ischemia is the second main cause of death throughout the world. When cerebral blood flow drops to 25% of its normal value, brain damage occurs. A multiplex of cellular injury events is set in motion during ischemia, consisting of excitotoxicity, reactive oxygen species (ROS) production, and inflammation [1]. A person suffers from a stroke on an average of every 40 s and death is caused by stroke every 4 min. Every year ischemic stroke occurs in about 48% of women and 52% of men. 2.7 million people die from ischemic stroke annually. Stroke is considered an important cause of disability [2].

Recovery from a stroke begins once physicians has stabilized the patients' condition. Recovery is a prolonged process that differs from person to person. It takes days, weeks, months, or even years [3]. A few patients recover completely, while some patients long-term or lifelong disabilities. As reported by National Stroke Association (NSA), 10% of patients recover completely, 25% of patients recover with minor impairments, 40% of patients recover with moderate-to-severe impairments that need special care, and 10% of patients require long-term care. The success of recovery depends on various factors which include the level of damage caused by stroke, how soon recovery is initiated, the presence of comorbidities that affect recovery, and age [4,5].

The primary approach in treating stroke is to restore blood flow with the aim of re-perfusing or reoxygenating the ischemic tissues in a little while probably within minutes to preserve neural tissues that favor functional recovery and survival of individuals. The secondary approach is to refine the consequences of stroke produced by the generation of free radicals during hypoxia/ischemia and reperfusion. Tissue plasminogen activator and thrombolytic agents will be used to achieve the primary goal. Melatonin would be a flawless therapeutic agent due to its antioxidant property and also has a known safety profile that is nontoxic to humans [6,7].

Melatonin is a neuroprotective agent with low adverse effects which were recently shown in many animal studies. It readily crosses the blood-brain barrier (BBB) through a peripheral route of administration [8]. Melatonin exhibits antioxidant, anti-inflammatory, anti-excitotoxicity, and anti-misfolding properties. Melatonin decreases excitotoxicity and cerebral infiltration of immune cells following cerebral hypoxia or ischemia [9]. The limitation of melatonin studies on human and other clinical bases made us keen to took up this research work to explore its full potential as a neuroprotective agent. The purpose of this research was to evaluate the effect of melatonin in stroke recovery inpatients by observing post-treatment changes in the clinical outcomes of motor, speech, and cognitive functions.

METHODS

Study design

The present prospective observational study was carried out at the Department of Neurology of tertiary care hospital, Hyderabad, for 6 months. The study took place from November 2020 to April 2021. All in-patients who presented with acute ischemic stroke and age 18–80 years were allowed to participate in this study. Patients with the following criteria were excluded from the study: (1) Pregnant women; (2) patients coming for long-term therapy; and (3) pediatric and renal impairment. Eighty patients with confirmed acute ischemic stroke based on their MRI reports were enrolled in the study. They were randomized into two study groups, namely, Group A (Test) and Group B (Control). Each group consists of 40 patients. Patients of both the groups were treated with aspirin + enoxaparin + statins as first-line treatment. Patients in Group A treated with melatonin 3 mg once daily at bedtime within 24–48 h of stroke onset along

with first-line treatment. Melatonin is given till the patient's hospital stay. All patient have given consent for involvement in the study. IRB no:- 2021/32/008.

Study outcomes

To evaluate the effect of melatonin on motor, speech and cognitive behaviour of acute ischemic stroke patients. The following scales were used to assess the clinical outcomes of patients: (a) Modified Rankin Scale (mRS) was used to measure the motor function [10]; (b) communication disability scale (CDS) was used to evaluate speech [11]; and (c) cognitive assessment for stroke patients (CASP) was used to assess the cognitive function [12].

Data collection

All patients gave written informed consent before participation. The patient data were collected through history interview and from the case sheets of in-patient then documented in a suitably designed case record form. Collected data includes patients' age, gender, score of mRS, CDS, and CASP.

Statistical analysis

The data were analyzed using Statistical Package for the Social Service (SPSS) Version 20. Continuous variables were presented as the minimum, maximum, median, mean, and standard error of the mean (SEM). Categorical variables were presented as frequencies and percentages. An independent t-test was used to compare the baseline mean scores of two study groups. One-way analysis of variance (ANOVA) was used to compare the mean scores before (baseline) and after treatment (day 7 and day 30). A Chi-square test was carried out for analyzing categorical variables. $p < 0.05$ were considered statistically significant at a 5% level of significance.

RESULTS

Patient demographics

A total of 80 patients were enrolled in this study based on inclusion criteria. The highest frequency of patients was found in the age interval 41–50 years (37%) in Group A and 51–60 years (22%) in Group B. About 60% of males and 40% of females were in Group A, whereas, in Group B, 48% of males and 52% of females. However, significant difference was not found in the age and gender between the two study groups which are shown in Tables 1 and 2 and Figs. 1 and 2.

Comparison of treatment efficacy

The baseline mRS scores of the two study groups were 3.10±0.22 and 2.67±0.21 with no significant difference ($p = 0.1664$). The baseline CDS scores of the two study groups were 1.72±0.18 and 1.57±0.21 with no significant difference ($p = 0.6016$). The baseline CASP scores of the two study groups were 22.60±1.58 and 24.23±1.94 with no significant difference ($p = 0.5189$). This is displayed in Table 3.

After treatment (7th and 30th from the baseline), both the study Groups A and B have shown significant changes in the scores of mRS, CDS, and CASP that are indicated in Tables 4 and 5 and Figs. 3 and 4.

When the percentage of improvement in scores from baseline to day 30 was evaluated, we found that patients receiving melatonin (Group A) shown more changes when compared with Group B who received only first-line treatment that is shown in Table 6. There is a statistically significant difference in the percentage of improvement of mRS, CDS, and CASP score between the study groups. Both treatment patterns were well tolerated by all patients and serious adverse events were not reported during the study period.

Table 1: Age-wise distribution

Age interval (years)	Group A		Group B		p
	n	%	n	%	
21–30	0	0	4	10	
31–40	2	5	7	18	
41–50	15	37	7	18	
51–60	12	30	9	22	0.0731
61–70	5	13	6	15	
71–80	5	13	7	18	
81–90	1	2	0	0	

Table 2: Gender distribution

Group	Male		Female		p
	n	%	n	%	
A	24	60	16	40	0.3699
B	19	48	21	52	

Table 3: Clinical outcomes scores at baseline

Scale	Group	Minimum	Maximum	Median	Mean±SEM	p
mRS	A	0	5	4	3.10±0.22	0.1664
	B	0	5	3	2.67±0.21	
CDS	A	0	5	1	1.72±0.18	0.6016
	B	0	5	1.50	1.57±0.21	
CASP	A	0	36	19	22.60±1.58	0.5189
	B	0	36	25.50	24.23±1.94	

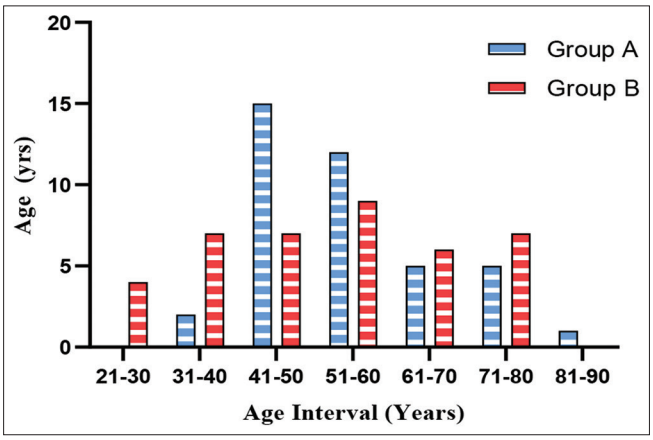

Fig. 1: Age-wise distribution

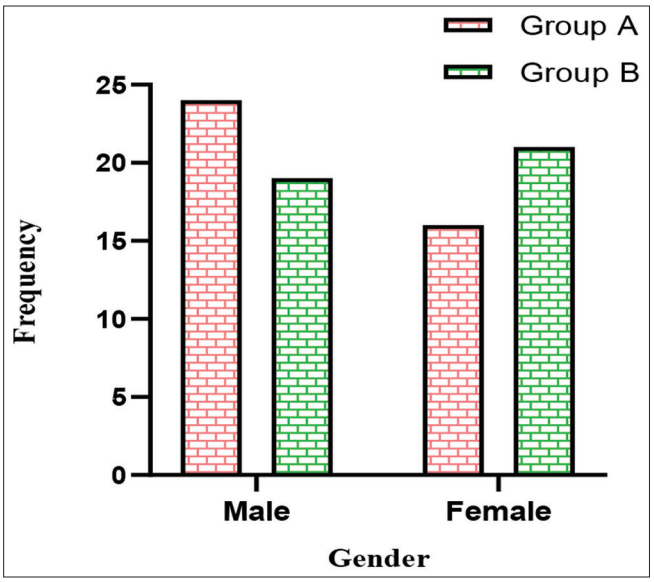

Fig. 2: Gender distribution

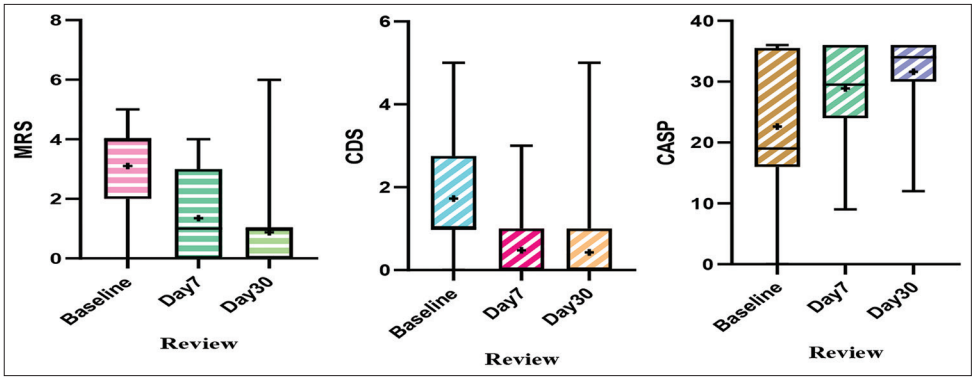

Fig. 3: Clinical outcomes scores before and after treatment in Group A

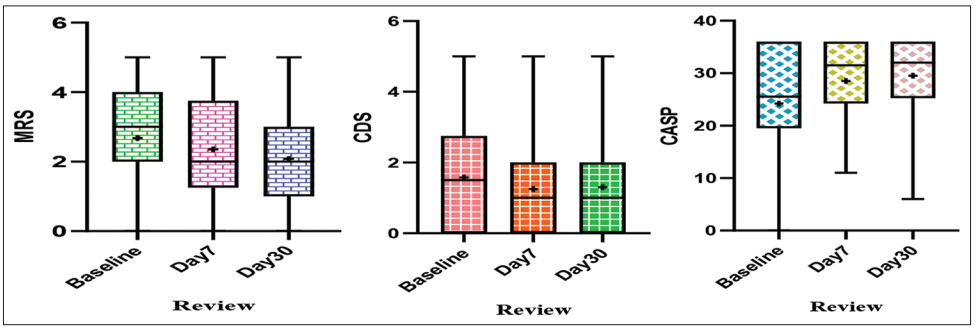

Fig. 4: Clinical outcomes scores before and after treatment in Group B

Table 4: Clinical outcomes scores before and after treatment in Group A

Scale	Review	Minimum	Maximum	Median	Mean±SEM	P value
mRS	Baseline	0	5	4	3.10±0.22	<0.0001
	Day 7	0	4	1	1.35±0.21	
	Day 30	0	6	1	0.87±0.18	
CDS	Baseline	0	5	1	1.72±0.18	<0.0001
	Day 7	0	3	0	0.47±0.11	
	Day 30	0	5	0	0.42±0.14	
CASP	Baseline	0	36	19	22.60±1.58	<0.0001
	Day 7	9	36	29.50	28.88±1.03	
	Day 30	12	36	34	31.63±0.87	

Table 5: Clinical outcomes scores before and after treatment in Group B

Scale	Review	Minimum	Maximum	Median	Mean±SEM	p
mRS	Baseline	0	5	3	2.67±0.21	0.0226
	Day 7	0	5	2	2.35±0.21	
	Day 30	0	5	2	2.07±0.24	
CDS	Baseline	0	5	1.50	1.57±0.21	0.0401
	Day 7	0	5	1	1.25±0.19	
	Day 30	0	5	1	1.30±0.20	
CASP	Baseline	0	36	25.50	24.23±1.94	0.0014
	Day 7	11	36	31.50	28.53±1.30	
	Day 30	6	36	32	29.50±1.14	

Table 6: Comparison of effectiveness of treatment between Group A and Group B

Scale	Group		p
	A	B	
mRS	72	22	<0.0001
CDS	76	17	<0.0001
CASP	40	22	0.0059

DISCUSSION

The brain is a highly complex and active metabolic organ of our body that performs significant functions. Alteration in the normal functioning of brain leads to loss of homeostasis which results in physiological changes in the body [13]. Stroke refers to a range of abnormalities caused by occlusion or hemorrhage of the main arteries supplying blood to brain tissue. Deprivation of oxygen by stroke is a root cause of severe neurological disability [14]. The production of ROS is

distinctly significant during the reperfusion phase in the pathogenesis of cerebral ischemia. Oxidative damage due to the overproduction of reactive free radicals plays a crucial role in the pathogenesis of ischemic brain damage [15]. Many shreds of evidence suggest that oxidative damage does not occur in a single but occurs with complex interactions of excitotoxicity, apoptosis, and inflammation. Moreover, the enormous release of glutamate-produced excitotoxicity generates progressive neuronal death through mitochondrial impairment and functional collapse in cerebral ischemia rats [16].

There are various endogenously occurring bioactive compounds that have neuroprotective properties, melatonin is one among them. Melatonin is chemically N-acetyl-5-methoxytryptamine that is secreted from the pineal gland in the brain. Further, melatonin is secreted from extra-pineal sources including bile, cerebrospinal fluid, the retina, the placenta, the testes, glial cells, and ovarian follicular fluid. Melatonin is amphiphilic that confers the benefit of crossing BBB. Various *in vivo* and *ex vivo* studies propose that melatonin results in functional recovery, improved behavioral outcomes, and reduced inflammatory response in ischemic animals [17,18].

In this study, 80 acute ischemic stroke patients who met the inclusion criteria were enrolled during 6 months study period to evaluate the effect of melatonin in post-stroke recovery patients and also to compare the effect of first-line treatment with melatonin and first-line treatment alone. A stroke occurs in all age groups. However, the risk of stroke doubles between the ages of 55 and 85 [19]. Aging is the non-modifiable risk factor for stroke that is evinced in our study findings. About 56% of patients fall between the above age range. Gender also affects the incidence of stroke. However, the concept of this remains unclear. Few studies suggest that men have been found to experience ischemic strokes more than women. Yet, the mortality rate and severity of stroke are higher in females than males [20]. In the present study, 54% of patients were males that show male predominance.

The motor, speech, and cognitive functions of both the study groups were assessed and compared with the help of mRS for motor function, CDS for speech function, and CASP for cognitive function. Assessment of sensory and motor behaviors is helpful parameters to evaluate the prognosis of stroke patients clinically. Both Group A and Group B patients show significant changes in the scores of mRS, CDS, and CASP between before and after treatment. However, the comparatively higher frequency of changes was seen in Group A patients. Group A patients showed 72% of improvement from the baseline mRS score, whereas patients in Group B showed only 22%. Patients who received melatonin treatment expressed 76% of improvement from the baseline CDS score, but the control group showed only 17%. Several animal studies have shown greater improvement in motor and sensory behavioral scores in melatonin-treated animals than control (vehicle)-treated animals [21]. In the CASP score, 40% of improvement is seen in melatonin-treated patients. On the contrary, 22% of improvement is noticed in Group B patients. Melatonin improves cognitive function by increasing the expression of brain-derived neurotrophic factor (BDNF) in the cortex. cAMP-response element binding (CREB) is a nuclear transcription factor. CREB phosphorylation regulates the transcription of BDNF. The downregulation of the CREB phosphorylation process results in the reduction of BDNF levels. Melatonin reduces the expression of CREB in the prefrontal cortex [22]. Thus, patients who received melatonin along with first-line treatment exhibit significant improvement in the clinical outcomes of post-stroke recovery patients.

CONCLUSION

From the study findings, it was concluded that patients received melatonin along with first-line treatment has shown better efficacy in treating post-recovery stroke patients when compared with patients received first-line treatment alone. Melatonin served as an excellent neuroprotectant in patients of acute ischemic stroke with improvement in the motor, speech and cognitive functions as demonstrated by the scores of modified Rankin scale, communication disability scale, and cognitive assessment for a stroke patient. We also disclose that our results might be biased due to the smaller sample size. Therefore, multi-centric studies with more subjects are necessary to further evaluate outcomes of melatonin in acute ischemic stroke patients.

AUTHORS CONTRIBUTIONS

Sara Shreen: Design and conceptualization of study, Edit and Proof reading, Final approval of manuscript, and Agreement to be accountable. Ayesha samreen: Data collection, Proof reading, and Manuscript Writing. Umra Zahid: Data collection, Proof reading, and Manuscript writing. Aimen Maleeha: Data collection, Manuscript writing, and Proof reading. Nabila Nooreen: Data collection, Manuscript writing, and Proof reading. Dr Mohammed Zoheb: Design and conceptualization of study, Edit and Proof reading, Final approval of manuscript, and Agreement to be accountable.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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