IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 22, Issue 9 Ser.1 (September. 2023), PP 01-05
www.iosrjournals.org

Efficacy & Safety Of Melatonin In Ischemic Stroke: An Interventional Study

Dr. Sivateja Kuruvada*[1,] Dr Srija Yadav Kadari[2], Dr. Sunkoju Madhuri[3], Dr Gummadi Sai Teja[4]

*(Postgraduate[*1], Postgraduate[2], Postgraduate[3], Postgraduate[4]*
Department of General Medicine, Apollo Institute of Medical Sciences, Hyderabad, Telangana, India)

Abstract:
Background*: Stroke is a cerebrovascular accident (CVA), which is a significant reason for morbidity and mortality. Melatonin is produced by the pineal gland to regulate circadian rhythm including light-dark cycles among mammals. It is present in cerebrospinal fluid, bile, ovarian follicular fluid, and the anterior chamber of the eye, suggesting its main role apart from regulating the internal clock. In view of the high prevalence of stroke, and less literature on its effective management, the current study was undertaken.*
Objectives:
1. *To know the effectiveness of Melatonin in stroke patients*
2. *To study the side effect profile of melatonin in stroke patients*

Materials and Methods*: 100 patients with stroke were included. This interventional study was done in the Department of General Medicine at Apollo Institute of Medical Sciences, Hyderabad, Telangana, India. Male and females aged above 18 years with clinical features suggesting acute ischemic stroke (AIS) stroke were included. All patients were given melatonin orally from the time of admission to 270 days. Baseline National Institute of Health Stroke Score (NIHSS) is compared with NIHSS at the end of 180 and 270 days.*
Results: *Most of the patients were aged 61 to 70 years. Most of the patients had moderate stroke at the time of admission as per NIHSS. There is a significant difference in the mean NIHSS from baseline to the end of 180 days and at the end of 270 days. There is a significant reduction in the inflammatory marker interleukin 6 from baseline to the end of 180 and 270 days. Mortality rate was 4 % within 1st 5 days of admission and among 96 patients who were followed up, no patient experienced a repeated episode of stroke in 270 days of treatment. There were no serious side effects except mild sleepiness experienced by 8% of patients.*
Conclusion: *Oral melatonin is effective in reducing the severity of stroke and preventing further stroke episodes during the 1st 270 days. This implies the good cerebroprotective action of melatonin.*
Keywords*: Stroke, Melatonin, Cerebrovascular accident, Embolism, Efficacy, Safety*

Date of Submission: 23-08-2023 Date of Acceptance: 03-09-2023

I. INTRODUCTION

A stroke is a cerebrovascular accident (CVA), which is a significant reason for morbidity and mortality. Strokes can be classified as ischemic (IS), haemorrhagic, or subarachnoid types. Among ischemic stroke (IS) types, TOAST grading is used to classify categories that include cardio embolism large-artery atherosclerosis, small-vessel occlusion, and stroke of unknown aetiology[1]. IS occurs due to a thrombotic or embolic event that leads to a reduction in blood flow to brain. In thrombosis, blood flow to brain is interrupted within the blood vessel due to vessel dysfunction, that occurs secondary to atherosclerotic disease, fibromuscular dysplasia, or any inflammatory condition. In an embolic event, debris from another place blocks blood flow through the affected vessel. The cause affects prognosis and outcomes.[2,3] Stroke was the 2nd most common cause of death globally in 2019, as per the World Health Organization (WHO). It is responsible for 11% of causes of death worldwide[4].

Melatonin is produced by pineal gland to regulate circadian rhythm including light-dark cycles among mammals. It is present in cerebrospinal fluid, bile, ovarian follicular fluid,[5,6] and anterior chamber of the eye,[7-8] suggesting its main role apart from regulating the internal clock. Melatonin was an effective free radical scavenger and antioxidant. Factors that contribute to more production of free radicals include exposure to ultraviolet radiation, ischemia followed by reperfusion and physical or psychological stress.[9] It helps to alleviate oxidative-induced stresses caused by free radicals in the CNS. Neuroprotection caused by melatonin has been explored for the treatment of stroke, which is characterized by aberrant inflammation and excessive production of free radicals.

In view of the high prevalence of stroke, and less literature on its effective management, the current study was undertaken.

Objectives:
1. To know the effectiveness of Melatonin in stroke patients
2. To study the side effect profile of melatonin in stroke patients

II. MATERIAL AND METHODS

Study site: Department of General Medicine, Apollo Institute of Medical Sciences, Hyderabad, Telangana, India
Study duration: Six months: January 2023 to June 2023
Sample size: 100
Type of study: Interventional study
Ethical considerations:
Informed consent was taken from every patient who participated in the study.

Inclusion criteria:
- Male and female subjects aged above 18 years presenting to the emergency department diagnosed to have ischemic stroke as per MRI or CT were included.
- Patients who provided informed consent.

Exclusion criteria:
- Patients with known allergy to melatonin
- Patients with cancer, HIV, connective tissue disorders or cardiovascular disease during the last 3 months
- Pregnant or lactating women.
- Patients with liver or renal disorders

Methodology:

After the admission of patients, informed consent was taken from patients or from their relatives/legally acceptable representatives. NIHSS was assessed at baseline.

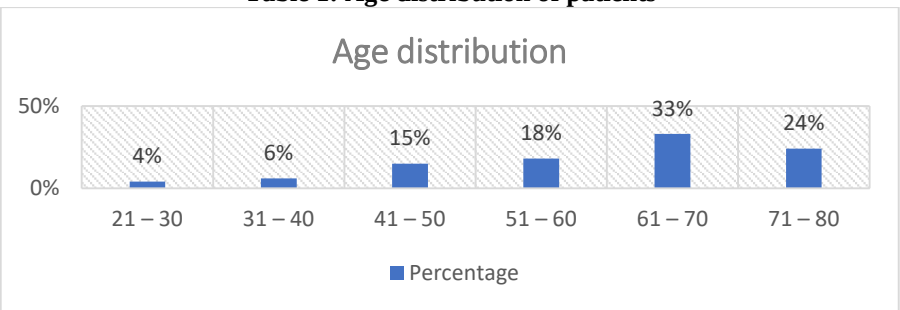
All patients were given extended-release melatonin of dose 10 mg orally every 12 hours for 1 week and then every day once for 173 days.
Patients were asked to come for a check-up at 270 days or 9 months.
The severity of stroke is assessed using the National Institute of Health Stroke Scale (NIHSS).
Function outcome is measured as follows:
The patient is considered to be improved if there is a decrease of NIHSS of 10 points by day 30.
The patient is considered to be deteriorated, if NIHSS increases by more than 4 points during 1st five days of stroke.
NIHSS: Severity of the stroke is assessed as follows:
If the score is 0: There is no stroke.
If the score ranges from 0 to 4: The patient is said to have a minor stroke.
If the score ranges from 5 to 15: The patient is said to have a moderate stroke.
If the score ranges from 21 to 42: The patient is said to have a severe stroke.

Statistical analysis: Data were analyzed using SPSS 23.3 software. Mean, SD, percentages, and frequencies were used. One way ANOVA test was used to compare NIHSS at 3 points of time. P value below 0.05 is considered significant statistically.

III. RESULTS

Age distribution:
Most of the patients were aged 61 to 70 years in the current study, followed by 71 to 80 years.

Table 1: Age distribution of patients



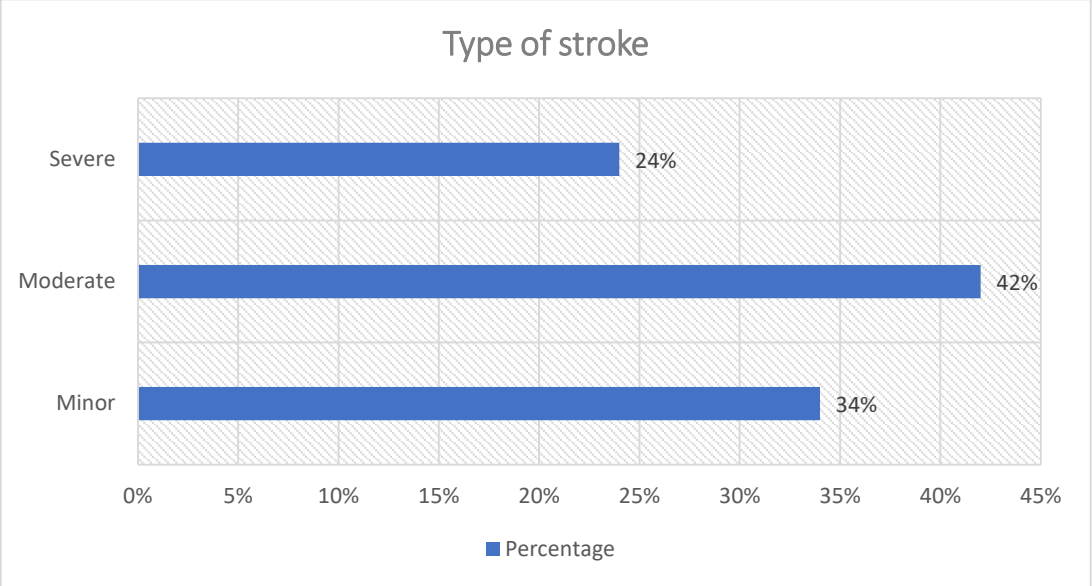
Gender: 56% of cases were males.

Table 1: Gender of patients

Gender	No of patients	% of patients
Males	56	56
Females	44	44

Severity of stroke:
Most of the patients were having moderate stroke as per NIHSS at the time of admission.

Graph 2: Severity of stroke



Mean NIHSS before and after giving melatonin:
There is a significant difference in the mean NIHSS at baseline, at 180 days and at the end of 270 days, as per ANOVA analysis.

Table 2: Mean NIHSS before and after giving melatonin.

NIHSS	Mean and SD of NIHSS	P value
Baseline or at the time of admission	12.4±1.3	0.0001
At 180 days	9.8±0.9	
At 270 days	3.2±0.87	

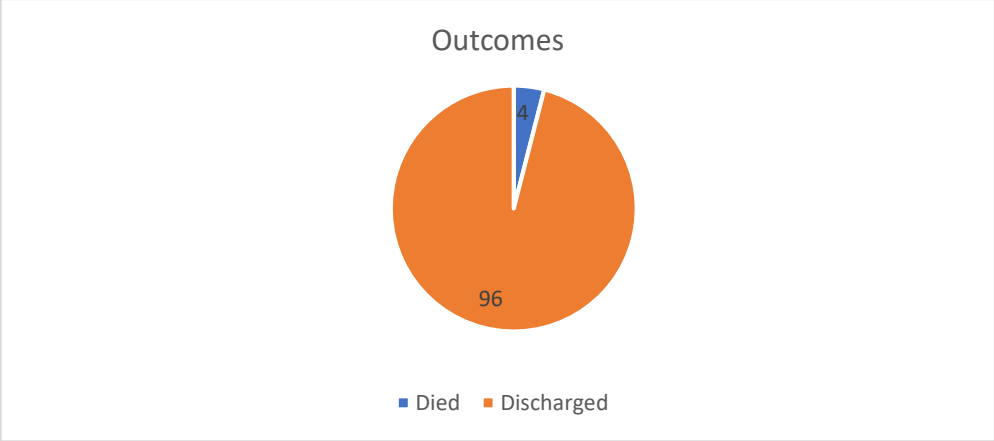
Change in IL6 levels:
There is a significant reduction in IL 6 levels from baseline to the end of 30 and 90 days after treatment with oral melatonin.

Table 3: Mean IL 6 before and after giving melatonin.

NIHSS	Mean and SD of NIHSS	P value
Baseline or at the time of admission	32.4±4.5 pg/ml	0.0001
At 180 days	10.4±3.1 pg/ml	
At 270 days	6.5±4.9 pg/ml	

Outcomes:
4% of patients expired during the 1st 5 days of hospitalization.

Graph 3: Mortality rate of patients



Follow-up: No patient had a repeated episode of stroke among 86 patients who were followed up for 270 days.
Side effects:
No side effects were seen in 88% of patients during 270 days of treatment with melatonin.

Table 4: Side effect profile of Melatonin

Side effects	% of patients
Nil	88
Drowsiness during daytime	9
Vertigo	1
Headache	2

IV. DISCUSSION

In the current study, 100 patients were studied. Most of the patients were males. Most of the patients were aged 61 to 70 years. Most of the patients had moderate stroke. There is a significant difference in the mean NIHSS from baseline to the end of 90 days and at the end of 270 days. There is a significant reduction in the inflammatory marker interleukin 6 (IL 6) from baseline to the end of 180 and 270 days. Mortality rate was 4 % within 1st 5 days of admission and among 96 patients who were followed up, no patient experienced a repeated episode of stroke in 270 days of treatment. There were no serious side effects except mild sleepiness experienced by 8% of patients.

Hao SM et al.[10] did a study to compare the effects in rats. It was found that after 6 daily consecutive treatments of melatonin at 10 mg/kg reduced the infarct volume significantly from 39.6 to 26.2%.

Sadanandan et al.[11] did a review on melatonin-based therapies which have been shown to provide neuroprotective effects in ischemic stroke patients by reducing neuroinflammation and fostering brain tissue restoration.

Liu ZJ et al.[12] did a study on melatonin and concluded that melatonin protects against acute ischemic stroke by affecting microglia polarization toward anti-inflammatory phenotype through STAT pathway.

Azedi F et al.[13] informed that melatonin regulates neuroinflammation IS damage through interactions with microglia in the reperfusion phase.

Kilic C et al.[14] informed that melatonin regulates circadian rhythm proteins after ischemic stroke, playing vital role in cellular survival.

V. CONCLUSION

Oral melatonin is safe and effective in reducing the severity of stroke and preventing further stroke episodes during the 1st 270 days of treatment. This implies the good cerebroprotective action of melatonin.
The study is self-sponsored.
There were no conflicts of interest.

REFERENCES

[1]. Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE. Classification Of Subtype Of Acute Ischemic Stroke. Definitions For Use In A Multicenter Clinical Trial. TOAST. Trial Of Org 10172 In Acute Stroke Treatment. Stroke. 1993 Jan;24(1):35-41. [Pubmed]

[2]. Ntaios G. Embolic Stroke Of Undetermined Source: JACC Review Topic Of The Week. J Am Coll Cardiol. 2020 Jan 28;75(3):333-340. [Pubmed]
[3]. Pierik R, Algra A, Van Dijk E, Erasmus M Et Al. On Behalf Of The Parelsnoer Institute-Cerebrovascular Accident Study Group. Distribution Of Cardioembolic Stroke: A Cohort Study. Cerebrovasc Dis. 2020;49(1):97-104. [Pubmed]
[4]. The Top 10 Causes Of Death [Internet]. Who.Int. [Cited 2023 Aug 07]. Available From: Https://Www.Who.Int/En/News-Room/Fact-Sheets/Detail/The-Top-10-Causes-Of-Death
[5]. Tan D., Manchester L.C., Reiter R.J., Qi W., Hanes M.A., Farley N.J. High Physiological Levels Of Melatonin In The Bile Of Mammals. *Life Sci.* 1999; 65:2523–2529. Doi: 10.1016/S0024-3205(99)00519-6. [Pubmed] [Crossref] [Google Scholar]
[6]. Skinner D.C., Malpaux B. High Melatonin Concentrations In Third Ventricular Cerebrospinal Fluid Are Not Due To Galen Vein Blood Recirculating Through The Choroid Plexus. *Endocrinology*. 1999; 140:4399–4405. Doi: 10.1210/Endo.140.10.7074. [Pubmed] [Crossref] [Google Scholar]
[7]. Yu H.S., Yee R.W., Howes K.A., Reiter R.J. Diurnal Rhythms Of Immunoreactive Melatonin In The Aqueous Humor And Serum Of Male Pigmented Rabbits. *Neurosci. Lett.* 1990; 116:309–314. Doi: 10.1016/0304-3940(90)90092-N. [Pubmed] [Crossref] [Google Scholar]
[8]. Reiter R.J., Tan D.X., Fuentes-Broto L. Melatonin: A Multitasking Molecule. *Prog. Brain Res.* 2010; 181:127–151. Doi: 10.1016/S0079-6123(08)81008-4. [Pubmed] [Crossref] [Google Scholar]
[9]. Cutler R.G. Oxidative Stress: Its Potential Relevance To Human Disease And Longevity Determinants. *AGE*. 1995; 18:91–96. Doi: 10.1007/BF02436084. [Crossref] [Google Scholar]
[10]. Hao SM, Zhong ZG, Qu WM, Huang ZL, Sun FY, Qiu MH. Melatonin Supplementation In The Subacute Phase After Ischemia Alleviates Postischemic Sleep Disturbances In Rats. Brain Behav. 2021 Oct;11(10):E2366. Doi: 10.1002/Brb3.2366. Epub 2021 Sep 14. PMID: 34520636; PMCID: PMC8553311.
[11]. Sadanandan N, Cozene B, Cho J, Park YJ, Saft M, Gonzales-Portillo B, Borlongan CV. Melatonin-A Potent Therapeutic For Stroke And Stroke-Related Dementia. Antioxidants (Basel). 2020 Jul 28;9(8):672. Doi: 10.3390/Antiox9080672. PMID: 32731545; PMCID: PMC7463751.
[12]. Liu ZJ, Ran YY, Qie SY, Gong WJ, Gao FH, Ding ZT, Xi JN. Melatonin Protects Against Ischemic Stroke By Modulating Microglia/Macrophage Polarization Toward Anti-Inflammatory Phenotype Through STAT3 Pathway. CNS Neurosci Ther. 2019 Dec;25(12):1353-1362. Doi: 10.1111/Cns.13261. PMID: 31793209; PMCID: PMC6887673.
[13]. Azedi F, Mehrpour M, Talebi S, Zendedel A, Kazemnejad S, Mousavizadeh K, Beyer C, Zarnani AH, Joghataei MT. Melatonin Regulates Neuroinflammation Ischemic Stroke Damage Through Interactions With Microglia In Reperfusion Phase. Brain Res. 2019 Nov 15; 1723:146401. Doi: 10.1016/J.Brainres.2019.146401. Epub 2019 Aug 21. PMID: 31445031.
[14]. Kılıç E, Çağlayan B, Caglar Beker M. Physiological And Pharmacological Roles Of Melatonin In The Pathophysiological Components Of Cellular Injury After Ischemic Stroke. Turk J Med Sci. 2020 Nov 3;50(SI-2):1655-1664. Doi: 10.3906/Sag-2008-32. PMID: 32962330; PMCID: PMC7672349.