Brief Communication

Melatonin Supplementation May Improve the Outcome of Patients with Hemorrhagic Stroke in the Intensive Care Unit

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ABSTRACT

Objective: Although mechanical ventilation is frequently a life-saving therapy, its use can result in unwanted side effects. It has been well documented that the choice of sedating agent may influence the duration of mechanical ventilation. Melatonin is a sedative and analgesic agent without any respiratory depressant effect which makes it an attractive adjuvant for sedation in the intubated patients. The aim of this study is to evaluate the effect of melatonin on the duration of mechanical ventilation in patients with hemorrhagic stroke. **Methods:** Forty adult intubated patients with hemorrhagic stroke, who were admitted to the Intensive Care Unit (ICU) within 24 h of onset, were enrolled in this randomized double-blind study. Subjects in the melatonin group received 30 mg of melatonin every night throughout the nasogastric tube. Length of ICU stay, mortality, and duration of mechanical ventilation were recorded for all patients. **Findings:** The duration of mechanical ventilation and length of ICU stay were shorter in patients who received melatonin in comparison with the control group, and this difference was statistically significant for the length of ICU stay and marginally significant for the duration of mechanical ventilation. Although not statistically significant, the mortality rate of the control group was 30%, almost double that of the study group (15%). **Conclusion:** Melatonin possesses hypnotic, analgesic, anti-inflammatory, and anti-oxidative properties that distinguish it as an attractive adjuvant in patients under mechanical ventilation. In conclusion, the administration of melatonin may facilitate the weaning process through decreasing the consumption of sedatives with respiratory depressant properties as well as preventing ventilator-associated lung injury.

Keywords: *Hemorrhagic stroke, mechanical ventilation, Melatonin*

Introduction

Spontaneous, nontraumatic intracerebral hemorrhage (ICH) is the second most common cause of stroke following ischemic stroke, which can cause 35%–50% 30-day mortality. Evidence has shown that most patients present with small ICHs, can survive with a good medical care.[1,2] This suggests that an appropriate medical interventions may improve the outcome of these patients.[3] The current data have shown that early initiation of neuroprotective treatment might protect threatened neurons and improve outcome in hemorrhagic stroke.[4] Melatonin is a neurohormone which has generated a great deal of interest as a therapeutic modality for various neurological diseases because of its low toxicity, antioxidative, antiapoptotic, and anti-inflammatory properties. In addition, it has some exclusive properties that are highly desirable in the Intensive Care Unit (ICU).[5,6]

The aim of this study is to evaluate the effect of exogenous melatonin as an adjuvant on the duration of

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mechanical ventilation, length of ICU stay, and mortality in intubated patients with hemorrhagic stroke.

Methods

This study was registered as a clinical trial in IRCT (www.irct.ir) with an allocated number of IRCT2016100530164N1. Forty adult patients with acute, spontaneous ICH, confirmed by cranial computed tomography (CT), who were admitted to the ICU within 24 h of onset, were enrolled in this randomized double-blind study.

Exclusion criteria included evidence of traumatic ICH, contraindications to receiving oral medication, brain tumor, Glasgow coma scale (GCS) score of 8 or more, underlying respiratory disease, renal impairment (estimated glomerular filtration rate <60 ml/min), and pregnancy or breastfeeding.

A full written informed consent was obtained from a legal surrogate, this was because the patients lacked capacity due to being dysphasic or confused. The study protocol was approved by the Ethics Committee for Human Research at Tehran University of Medical Sciences. Patients were allocated to each group using permuted-block randomization method. Subjects in the melatonin group received 30 mg of melatonin (Melatonin, Webber naturals, Canada) every night throughout the nasogastric tube. A sedation and analgesic strategy, using opioid plus benzodiazepine, was chosen as a protocol for all intubated patients. Sedative and analgesic medications were titrated to maintain a light level of sedation according to the Richmond Agitation–Sedation Scale. Risk factors and demographic and clinical characteristics were recorded at the time of enrollment. Length of ICU stay, mortality, and duration of mechanical ventilation were assessed for all patients.

Continuous variables were presented as mean with standard deviation and median with interquartile range boundaries when the data were not normally distributed. Continuous variables were compared between groups using Student's *t*-test or Mann–Whitney U-test. Categorical variables were expressed through frequency in percentage and were compared between two groups using Chi-square test. $P \leq 0.05$ was considered statistically significant. IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA) was applied to conduct the analyses [Figure 1].

Results

From 72 ICH patients, 42 patients who met the inclusion criteria were enrolled in our study. Of this total, 2 patients were excluded from the trial due to the occurrence of pneumothorax after central venus (CV) line insertion. Therefore, the statistical analysis was performed on 40 patients: 20 (50%) subjects in the melatonin group and 20 (50%) as a control group [Figure 1].

There was no significant difference in the baseline characteristics of the included patients except for body mass index [Table 1].

At day 5, GCS score was improved in both groups, but this improvement was more significant for the melatonin group compare with control one [Table 1]. There were no differences between groups regarding the risk factor of ICH [Table 2].

The duration of mechanical ventilation and length of ICU stay were shorter in patients who received melatonin in

Table 1: Demographic data and clinical characteristics of the study groups

Variables	Groups		*P*
	Melatonin (*n*=20)	Control (*n*=20)	
Age (years)	57.7±12.7	52.9±13.7	0.329
Sex (male)	12 (80)	9 (60)	0.232
BMI (kg/m^2)	26.03±1.84	24.6±1.79	0.049
Hb (g/dL)	12.1±1.37	11.2±1.52	0.245
WBC (×103/mm^3)	9.66±2.33	10.3±2.30	0.621
Platelet (×103/mm^3)	195.0±28.9	229.3±35.9	0.061
Urea (mg/dL)	33.9±14.1	25.7±9.27	0.215
Creatinine (mg/dL)	0.96±0.21	0.91±0.15	0.634
INR	1.31±0.25	1.26±0.15	0.659
PTT (second)	35.7±9.05	38.2±4.45	0.439
Ca (mg/dL)	9.29±0.85	8.94±0.23	0.324
Na (mEq/L)	146.1±5.02	141.8±5.24	0.132
K (mEq/L)	4.01±0.20	4.18±0.31	0.22
SOFA score	6.27±0.70	6.64±0.93	0.228
APACHE score	17.60±4.22	16.9±4.73	0.69
GCS-1	6.13±1.24	6.14±0.95	0.982
GCS-5	8.60±1.76	7.07±1.33	0.014

Numerical values are reported as mean±SD and nominal values as *n* (%). Student's *t*-test and Chi-square were used to compare these values, respectively. SD=Standard deviation, BMI=Body mass index, Hb=Hemoglobin, WBC=White blood cell, INR=International normalized ratio, PTT=Partial thromboplastin time, SOFA=Sequential organ failure assessment, APACHE=Acute physiologic assessment and chronic health evaluation, GCS=Glasgow coma scale

Table 2: Comparison of the risk factors for intracerebral hemorrhage in two study groups (*N*=20 in each group)

Risk factors	Groups		*P**
	Melatonin	Control	
Hypertension	3 (15)	5 (25)	0.758
Anticoagulant-induced	6 (30)	5 (25)	0.683
AV malformation or aneurysm	3 (15)	2 (10)	0.348
Unknown	8 (40)	8 (40)	0.998

Data is reported as *n* (%). *Chi-square test. ICH=Intracerebral hemorrhage, AV=Arteriovenous

comparison with the control group, and this difference was statistically significant for the length of ICU stay and marginally significant for the duration of mechanical ventilation ($P = 0.065$) [Table 3].

Table 3: Comparison of duration of mechanical ventilation, length of Intensive Care Unit stay, and in-Intensive Care Unit mortality rate, in two study groups (*N*=20 in each group)

Variables	Groups		*P*
	Melatonin	Control	
Duration of mechanical ventilation (days)	4 (2-16)	12 (4-20)	0.065
Length of ICU stay (days)	8 (6-21)	12 (8-25)	0.041
In ICU mortality	3 (15.0)	6 (30.0)	0.451

Numerical values are reported as median (IQR), and nominal factors as *n* (%). Mann-Whitney U-test and Chi-square test were used to compare these values, respectively. IQR=Interquartile range, ICU=Intensive Care Unit

Although not statistically significant, the mortality rate of the control group was 30%, almost double that of the study group (15%) [Table 3].

Discussion

Melatonin is a neurohormone originated from the amino acid, tryptophan, and is mainly secreted by the pineal gland into the blood stream.[7] The efficacy and safety of exogenous melatonin for the treatment of insomnia have been confirmed in a meta-analysis.[8] This hormone has generated a great deal of interest as a therapeutic modality for various targets in the ICU.[9] Thanks to its antioxidant activity, melatonin has shown protective effects against oxidative injury in different *in vitro* and *in vivo* models of neurodegenerative diseases, not only by neutralizing free radicals but also by upregulating antioxidant and downregulating pro-oxidative and proinflammatory enzymes.[10-12] Efficacy of melatonin on animal models

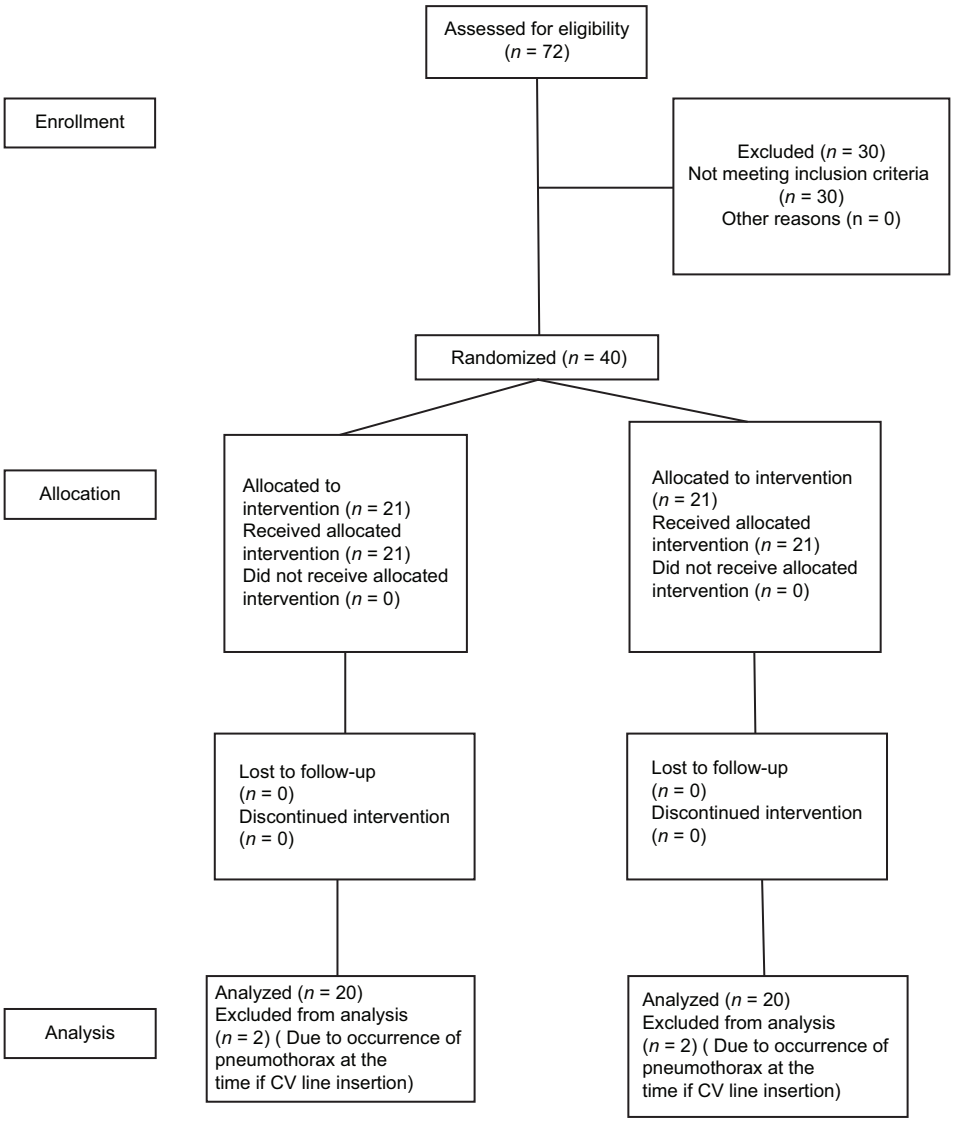

Figure 1: CONSORT flow chart

of stroke has been demonstrated in a meta-analysis.[13] Available clinical data have shown that melatonin is as effective as benzodiazepines in reducing anxiety without inducing any cognitive impairment or adverse effect on psychomotor performance. Moreover, unlike the conventional sedative agents, this hormone does not worsen nocturnal hypoxemia or ventilator responses.[7,14,15] In addition, it has been shown that melatonin is able to treat and prevent the ICU delirium.[16,17]

All of the patients with hemorrhagic stroke and low degrees of consciousness need to be mechanically ventilated. Although mechanical ventilation is frequently a life-saving therapy, its use can result in unwanted side effects, including ventilator associated lung injury, ventilator associated pneumonia, sinusitis, gastrointestinal bleeding, and venous thromboembolism.[18-20] Moreover, investigations have shown that the duration of mechanical ventilation is associated with short and long term mortality.[21]

It has been well documented that the choice of sedating agent may influence the duration of mechanical ventilation. Benzodiazepines and opiates are the most commonly used agents for sedation and analgesia in the ICU. Both of these agents possess some respiratory depressant effect, which can cause the duration of mechanical ventilation to be prolonged.[22-24]

Melatonin is a neuroprotective agent with sedative, hypnotic, and analgesic properties without any respiratory depressant effect which makes it an attractive adjuvant for sedation in the ICU.[7,9]

As shown in Table 2, the duration of mechanical ventilation was shorter in patients who received melatonin in comparison with the control group. According to the literature, it can be hypothesized that the administration of melatonin as an adjuvant with hypnotic properties may have reduced the amount of sedative agents and related adverse effects, including respiratory depression and delirium, which are both risk factors of prolonged weaning. On the other hand, as shown in Table 1, the level of consciousness was raised in melatonin group in comparison with the control one, which can be attributed to the neuroprotective effect of melatonin on stroke.

In a study which was conducted by Frisk *et al*., a decreased melatonin secretion was observed during mechanical ventilation.[25] Dessap *et al*. investigate the relationship between plasma melatonin levels and successful weaning from mechanical ventilation. They concluded that the lower plasma melatonin levels were associated with unsuccessful and prolonged weaning.[26] In an investigation which was operated by Mistraletti *et al*., administration of melatonin as a supplement in critically ill patients was associated with a decrease in the consumption of sedative agents, shortening the duration of mechanical ventilation, improved neurological indicators, and cost reduction.[27]

In addition to the studies mentioned above, it has long been known that one of the complications of mechanical ventilation is ventilator-associated lung injury, which is believed to be caused by free radicals.[28,29] With regard to the extraordinary high antioxidant effect of melatonin, it has been hypothesized that administration of melatonin may be protective against this kind of injury.[30-32] Gitto *et al*. showed that the administration of melatonin in mechanically ventilated newborns reduced the proinflammatory cytokines and improved the clinical outcome.[29]

Melatonin possesses hypnotic, analgesic, anticonvulsive, anti-inflammatory, and anti-oxidative properties that distinguish it as a novel and an attractive adjuvant in patients under mechanical ventilation.[8,9,33] Its sedative and analgesic properties may help patients better tolerate the mechanical ventilation.[8]

Our study encountered some limitations. In this study, the cumulative dose of sedative and analgesic agents were not measured to see to what extent the administration of melatonin could decrease the dose of these agents. In addition, there was no placebo group in this study, which may adversely affect the results and can be mentioned as a limitation of the study. Although it was not statistically meaningful, our study showed that the administration of melatonin may decrease the duration of mechanical ventilation. This observation is too weak to be considered reliable. However, they deserve to be considered as hypotheses-generating observations.

The administration of melatonin may facilitate the weaning process through decreasing the consumption of sedatives with respiratory depressant properties as well as preventing ventilator-associated lung injury.

Authors' Contribution

Mehrnoush Dianatkhah contributed in concept, study design, definition of intellectual content, literature search, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing and manuscript review. Atabak Najafi and Arezoo Ahmadi contributed in concept and study design. Mohammad Sharifzadeh participated in clinical and experimental studies. Hamidreza Sharifnia and Mojtaba Mojtahedzadeh have done the manuscript editing and manuscript review. Farhad Najmeddin contributed

in data analysis. Azadeh Moghaddas has prepared and edited the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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