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Oral Substitution of Melatonin in Critical Care: A Pharmacokinetic Study in Patients with Intracranial Hemorrhage

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ABSTRACT

Background: Intracranial hemorrhage (ICH) is a devastating condition with a high mortality and morbidity rate. Neuroprotective agents protect surrounding brain tissue from the toxic effects of hematoma and can result in better outcomes. There is evidence demonstrating the neuroprotective benefits of melatonin in experimental animal models of ICH. Reduced melatonin levels have been reported in the intensive care unit (ICU) patients. The aim of this study was to evaluate baseline melatonin levels and pharmacokinetic profile of melatonin in ICH patients.

Methods: This was a randomized clinical trial in which 24 patients with non-traumatic ICH were divided into melatonin and control groups. Subjects in the melatonin group received 30 mg of melatonin for 5 days. Another group of 12 healthy volunteers also were recruited for the study. Baseline serum melatonin levels were measured for all groups. For the pharmacokinetic study, sampling intervals were 0.25, 0.5, 0.75, 1.5, 3, 6 and 10 hours after melatonin administration. Samples were analyzed using an HPLC system with fluorescence detection.

Results: Serum melatonin concentrations found to be decreased in all patients. Patients showed a significant increase in levels by the third day but still lower than healthy volunteers. By day 5, the melatonin group reache melatonin levels, statistically similar to healthy volunteers, but the control group didn't reach normal levels even on the seventh day of study.

Conclusion: Our study suggests that monitoring melatonin levels and supplementing with exogenous melatonin can correct the reduced levels. Further studies focused on melatonin administration in ICH patients can be helpful in evaluating clinical outcomes in these patients.

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Introduction

Spontaneous, non-traumatic intracerebral hemorrhage (ICH) is a devastating form of stroke with an overall mortality of 40-50%. This condition also can cause significant disability and still remains a medical concern worldwide (1). In contrast to recent successes in prevention and acute treatment of ischemic stroke, such advances have not occurred in the management of ICH (2). Patients with good medical care have better survival chances which suggest excellent medical care have a direct impact on outcome (3). As recent evidence has implied that secondary contributors of ICH outcome include inflammation, oxidative stress, autophagy, and apoptosis; a rational but still unproven strategy in acute ICH management is that neuroprotective agents can protect surrounding brain tissue from toxic effects of hematoma (3,4).

Melatonin a neurohormone that is the main product of the pineal gland recently has gained additional attention because of its potent antioxidant activity, anti-inflammatory effects,

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and anti-apoptotic properties (5,6). Due to these properties and evidence from animal studies melatonin may be useful in treating pathological events associated with hemorrhagic stroke (7). Several studies reported suppressed melatonin levels in critically ill patients, both in nocturnal peaks and baseline daytime serum concentrations (8). In particular, studies show that melatonin level is correlated with delirium (9), illness severity in septic disease in adults (10), sleep disturbance in traumatic brain injury (TBI) (11), and severe lack of sleep in critically ill patients (12). Impaired melatonin secretion also reported in critically ill and mechanically ventilated patients (13,14), TBI, trauma and medical patients treated at the intensive care unit (ICU) (15).

The exact cause of these lower concentrations is not completely clear; the mechanism behind these disruptions may be as a result of either impaired melatonin production due to any alteration in pineal gland function (16), or consumption of melatonin as a neuroprotective endogenous molecule (15,17,18) because of the higher requirement of antioxidants in these patients (19-21).

Exogenous melatonin supplementation in critical illnesses to correct these decreased levels investigated in previous studies mainly evaluated melatonin effects on sleep (22,23). However, melatonin supplementation in these studies did not directly lead to better sleep (24). Effects of exogenous melatonin to increase total antioxidant capacity in critically ill patients investigated in one study proposed that even in the early phase of critical illness, enteral absorption is enough to reach pharmacological levels (25).

Previous studies on melatonin pharmacokinetic in high-risk patients are limited (25-27), but the increased clinical relevance of melatonin in critical care necessitates further studies (8,28). Substituting melatonin acutely in critical illnesses may improve outcome in these patients (25).

The aim of this study was to investigate melatonin baseline levels in non- traumatic ICH patients, and measuring the pharmacokinetics parameters of exogenous melatonin and evaluating its adverse effects in these patients.

Methods

This was a randomized, single blind, clinical trial in which 24 adult patients with non-traumatic ICH who were admitted to the general ICU within 24 hours of hemorrhage onset recruited in this study and equally divided into melatonin and control groups based on the simple randomization method. Also, 12 healthy volunteers participated in our study as controls for the normal baseline measures.

The sample size was calculated by use of the Open Epi Kelsey statistical software available at http://www.openepi.com/SampleSize/SSCohort.htm with the following parameters and assumptions: a 95% significance level (2-sided), 80% power, and 50% exposure of the sample to melatonin, and an anticipated 90% lower melatonin concentration in unexposed patients.

Exclusion criteria were evidence of traumatic ICH, age under 18, hepatic failure and documented melatonin hypersensitivity. Demographic data were recorded and clinical scores including Acute Physiology And Chronic Health Evaluation (APACHE) II, Sequential Organ Failure Assessment (SOFA) and ICH score (29) were calculated for patients at admission.

All patients received standard treatments based on their clinical situations. Subjects in the melatonin group received 30 mg of melatonin (10 × 3 mg melatonin tablets, Nature Made, CA, USA). Tablets were crushed in mortar then were dissolved in 20 mL of water and administered at 8:00 a.m. through a nasogastric tube for 5 days.

As patients lacked decision-making capacity due to their consciousness state, legal surrogates of subjects were informed about purposes of the study and gave their written voluntary consent to take part in the experiment, which was approved by the Ethics Committee for Human Research at Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1396.2220).

For the measurement of baseline or trough serum melatonin levels, blood samples were collected from all subjects every other day in first 7 days of study (1st, 3rd, 5th, and 7th) at 8:00 am, immediately before melatonin administration in melatonin group. To investigate pharmacokinetic parameters in melatonin group sampling intervals were 0.25, 0.5, 0.75, 1.5, 3, 6 and 10 hours after drug administration on the first day.

To best of our knowledge, no study investigated pharmacokinetic of melatonin as a neuroprotective agent in humans after ICH. We estimated the human dose based on doses used in animal experiments by the following formula (30):

HED = animal dose in mg/kg × (animal weight in kg/human weight in kg)0.33

Average oral bioavailability is low in humans, reported being around 15% across previous studies, while averaging 54% in rats (31).

Ueda et al., administrated 15 mg/kg of oral melatonin in ICH model rat (32). We calculated the bioavailable fraction of this dose to estimate human oral dose. Finally, the calculated amount divided by a factor value of 10 to increase the safety of first human dose (33).

Blood samples were collected from central venous catheters which were placed in the internal jugular vein for patients. Blood samples treated with anticoagulant was centrifuged at 2000 g for 10 min at room temperature and 1 ml of plasma was removed and refrigerated at -70ºC until assayed. Quantitative determination of plasma melatonin concentrations was performed using a modified HPLC method to that described by Muñoz et al., (34).

The intra-assay CV from 5 different injections for each concentration was 14.21% (10 pg/mL), 10.79% (50 pg/

ml), 11.60% (100 pg/ml), and 10.71% (200 pg/ml); and the inter-assay CV from was 13.81%, (10 pg/ml), 11.12% (50 pg/ml), 13.70% (100 pg/ml) and 9.86% (200 pg/ml). Recovery of melatonin from 5 different spiked plasma samples were 90.07 (50 pg/ml), 95.20% (100 pg/ml), and 95.26% (250 pg/ml) and 94.36 (500 pg/ml).

Patients' demographics, laboratory data, and measured scores were compared between the two groups using chi-squared tests, independent t-tests or Mann-Whitney U tests as appropriate. For baseline melatonin interpretation, serum melatonin concentration data were log-transformed prior to analysis, as it was found to be well fitted by a lognormal distribution. Data for different days compared in each group and all groups compared with each other using one way ANOVA test. All statistical analysis performed by using Sigmaplot 11.0 for Windows (Systat Software, Inc. San Jose, CA).

Pharmacokinetic analysis

A non-compartmental model used in this study. Peak concentration (Cmax) and time (Tmax) values were taken directly from observed concentrations. Pharmacokinetic profile for each patient plotted versus time and the elimination rate constant (Ke) was determined by log-linear regression of at least four data points which were in the elimination phase. Half-life calculated by dividing 0.693 by elimination constant. Method of residual was used to determine absorption constant (Ka). The linear trapezoidal method from zero to the last assayed concentration (10 hours after drug administration) used to determine AUC0-tlast, and total AUC calculated by adding C10hr/ke to AUC0-tlast. Dose/AUC total used for calculating the clearance. Apparent volume of distribution calculated by dividing clearance by Ke.

Results

Table 1 shows baseline characteristics in study groups. Patients in Melatonin group had higher baseline SOFA and APACHE II scores and lower Glasgow coma scale (GCS) but none of these differences were statistically significant. Generally, there was no statistically meaningful difference in any of reported factors (P>0.05).

Table 1. Patients' baseline demographic and clinical data.

Characteristics	Melatonin (n=12)	Control (n=12)	P-value
Age (yrs.)	56.41	52	0.449
Sex (M:F)	8:4	10:2	0.889
Body mass index (Kg/m2)	25.72	24.75	0.185
Creatinine (mg/dl)	1.1	1.09	0.521
Urea (mg/dl)	31.33	28.08	0.513
Hemoglubin (g/dl)	10.75	10.5	0.786
GCS	5.33	6	0.219
Intracranial hemorrhage score*	2.08	2	0.424
APACHE II	16	19.03	0.127
SOFA	6.33	7.91	0.068
Mechanical ventilation (Days)	11.5	13.5	0.625
Length of intensive care unit stay (Days)	9.5	11	0.603
Hospital mortality (%)	16%	25%	0.615
Mortality at 1 month (%)	41%	66%	0.437

Abbreviations: APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential organ failure assessment, GCS: Glasgow coma scale
*ICH score was calculated by evaluation of ICH volume in cm^3.

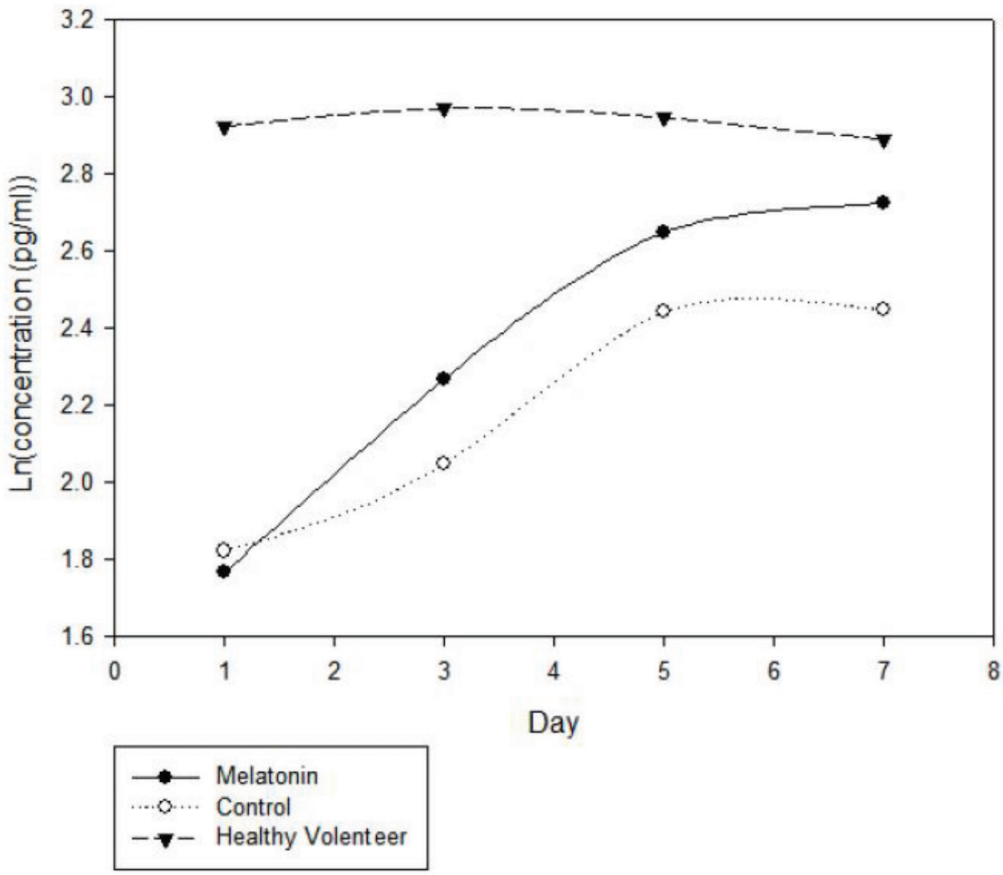
To assess the efficacy of acutely substituting melatonin in ICH patients, melatonin baseline levels compared in groups. In both groups, serum concentrations of melatonin found to be decreased comparing healthy volunteers' levels. Both groups showed a significant increase in baseline levels by the third day of our study but still lower than healthy volunteer. By the day 5, melatonin group reached normal melatonin levels, statistically similar to healthy volunteers, but control group didn't reach normal levels even on the seventh day of our study (Table 2 and Figure 1).

Table 2. Serum melatonin levels.

		Serum Conc. At 8:00 a.m. Mean (Range)	ANOVA P-value		Sig. Difference
1st Day	Melatonin	5.88 (4.18-7.48)	Mel vs HV.	<0.001	Yes
	Control	6.27 (4.67-8.37)	Ctrl vs HV.	<0.001	Yes
	Healthy volunteer	18.95 (14.70 –25.48)	Mel vs Ctrl.	0.432	No
3rd Day	Melatonin	10 (6.61-14.99)	Mel vs HV.	<0.001	Yes
	Control	7.80 (6.33-9.23)	Ctrl vs HV.	<0.001	Yes
	Healthy volunteer	19.49 (11.34-23.09)	Mel vs Ctrl.	<0.001	Yes
5th Day	Melatonin	14.66 (6.38-21.27)	Mel vs HV.	0.068	No
	Control	11.7 (8.52-14.72)	Ctrl vs HV.	<0.001	Yes
	Healthy volunteer	19.45 (18.81-20.40)	Mel vs Ctrl.	<0.001	Yes
7th Day	Melatonin	15.83 (7.55-20.88)	Mel vs HV.	0.206	No
	Control	11.96 (6.32-16.10)	Ctrl vs HV.	<0.001	Yes
	Healthy volunteer	18.52 (13.17-24.10)	Mel vs Ctrl.	<0.001	Yes

ANOVA: Analysis of variance, Mel: melatonin, HV: Healthy volunteer

Figure. 1. Baseline melatonin concentration



Natural logarithm of baseline melatonin concentrations during first 7 days after hemorrhage.

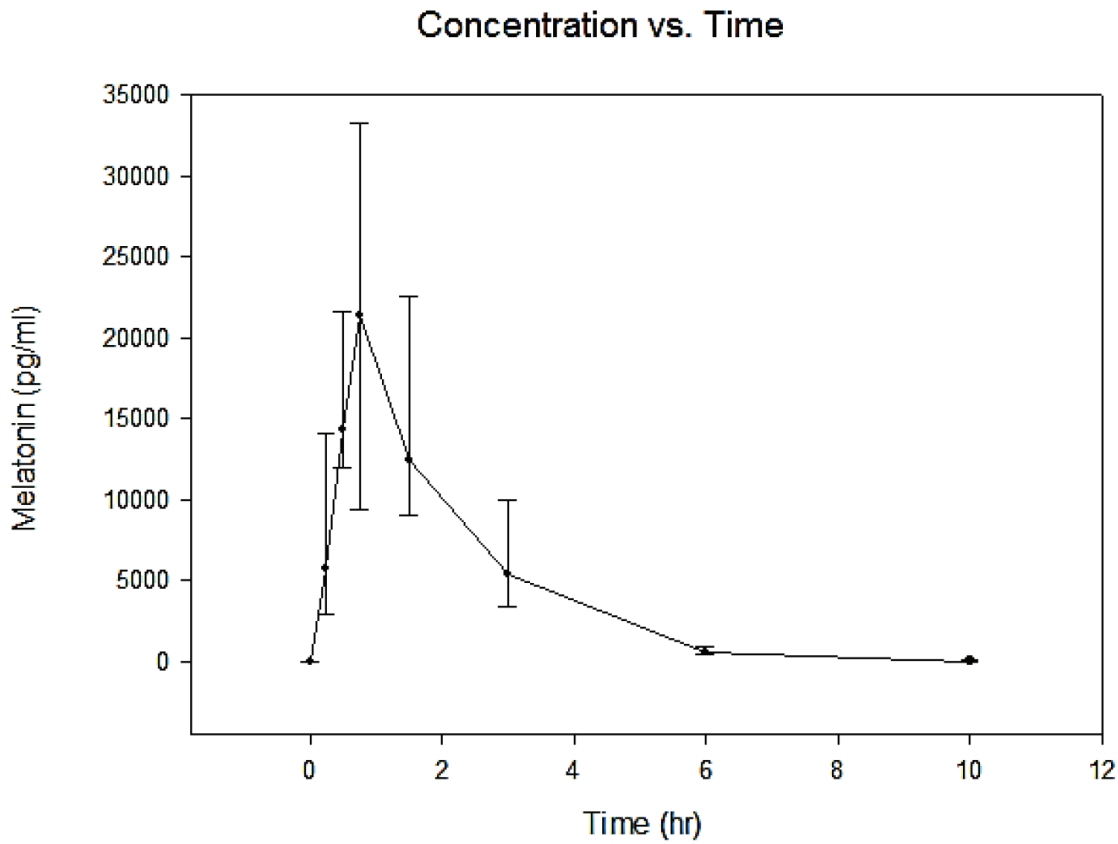
Pharmacokinetic analysis of plasma melatonin concentrations was undertaken in all patients.

Oral melatonin demonstrated first-order absorption and elimination kinetics. Mean t1/2 of oral melatonin was 53.89 min. The mean Cmax and Tmax were 21846.41 pg/mL and 43.75 respectively. The mean ke was 0.772 hr-1. Mean clearance was 670.22 L/hr and the mean Vd/F was 939.92 L. The mean AUC0-∞ was 43613.77 (pg*ml)/hr in this study. The pharmacokinetic parameters of oral melatonin are presented in Table 3, and the pharmacokinetic profile is demonstrated in Figure 2.

Table 3. Pharmacokinetic parameters of patients receiving 30 mg of melatonin.

Value	Unit	Mean	Median	Range
C_{max}	pg/mL	21846.41	19863.89	14955.09-33238.2
T_{max}	min	43.75	45	30-45
K_e	1/hr	0.772	0.766	0.736-0.836
K_a	1/hr	4.88	3.82	1/76-15.44
$T_{1/2}$	min	53.89	54.23	49.74-56.50
V_d/F	L	939.92	963.51	528.69-1247.86
Cl	L/hr	670.22	691.12	402.36-1075.16
$AUC_{0\text{-tlast}}$	$\frac{pg \times ml}{hr}$	43589	39590.94	32772.10-69505.02
$AUC_{tlast\text{-}\infty}$	$\frac{pg \times ml}{hr}$	23.94	24.5	9.76-32.13
$AUC_{0\text{-}\infty}$	$\frac{pg \times ml}{hr}$	43613.77	39615.04	32801.1-65937.15

Figure. 2. Pharmacokinetic profile of melatonin in ICH patients



Discussion

We investigated baseline melatonin levels in 24 non-traumatic ICH patients and found decreased levels in all of them. This decrement was more prominent on the first day and melatonin levels gradually increased during first seven days of the study. Patients who received daily melatonin corrected these levels by the 5th day after hemorrhage onset. However, patients in control group didn't reach normal levels even after the 7th day. Healthy volunteers participated in our study were younger than patients (average age was 33.2 and 54.2 respectively), although melatonin plasma levels tend to decrease with age, this decrement in daytime baseline levels are not significant (35), and probably it did not impact our results.

While decreased melatonin levels were previously reported in critically ill and traumatic brain injury patients (8,15), our study is the first to report reduced levels of melatonin in non-traumatic ICH patients. For developing effective strategies for acute ICH treatment, understanding the pathophysiology of this condition may be helpful. Similar abnormalities related to cerebral blood flow and metabolism reported in traumatic brain injury (TBI) and ICH patients. However, shared mechanisms in these conditions are still unexplained (36). Based on earlier studies, melatonin has beneficial effects in conditions that cerebral hemodynamic parameters like cerebral blood flow are compromised (37). Thus Melatonin supplementation may improve cerebral blood flow in both of these conditions.

Serum melatonin measurement methods are different among previous studies. Radio immune assay (RIA) and enzyme-linked immunosorbent assay (ELISA) methods most commonly employed in them. In our study, we used HPLC with fluorescence detection to obtain higher sensitivity and specificity. Considering the low levels of melatonin in biological specimens, extraction from plasma is an important step. In our study, the average recovery rate was 93.72% which is highly satisfactory compared with the acceptable rate of higher than 70% reported in related studies (38).

Increasing clinical use of melatonin necessitates more information to select appropriate dosing regimen in different conditions. Physiological alterations in critical care patients lead to significant change in pharmacokinetic parameters of the drugs. Understanding these changes help in the optimal use of drugs in this patient population (39). To date pharmacokinetic parameters of melatonin mainly measured in healthy volunteers and results from these studies are inconsistent (27). Few studies evaluated melatonin pharmacokinetic parameters in critically ill patients. Mistraltti et al., reported adequate absorption of 3 mg of orally administrated melatonin in critically ill patients (8). Bellapart et al., investigated the pharmacokinetics of novel dosing regimen by administrating a total dose of 3.5 mg of oral melatonin at night that led to the supra-physiological and sustained serum levels throughout the day without affecting subject's alertness (26).

Bourne et al found improved sleep quality in ICU patients following 10 mg melatonin administration at nights. Their pharmacokinetic analysis suggested that this dose is too high and may negate some of the phase improving effects of nocturnal administration (28).

Generally, critically ill patients demonstrated an accelerated Tmax and extended half-life (8,26,27). However, in the current study, we found Tmax (45 min) and T1/2 (54 min) more similar to healthy subjects reported in the past studies (27). This can be due to our exclusion criteria that patients with impaired renal or hepatic function did not enter into the study. Another possible cause of observed difference may be the different administration time, as our patients received melatonin at mornings (8:00 a.m.), similar to studies that investigated healthy subjects (40–46), in those studies on critically ill patients, subjects took melatonin at nights. Difference between exogenous melatonin metabolism in the day and night hours have not been investigated yet and our data was not sufficient to offer any conclusion.

As expected, we didn't observe any side effect during treatment with melatonin. Supra-physiological concentrations after melatonin administration reported in previous studies (8,26,27). These higher levels may negate some of the circadian effects of melatonin when administrated at nights (26).

This is the first study to evaluate the pharmacokinetic profile of high dose melatonin in ICH patients. Our findings indicate that 30 mg of melatonin which was calculated from animal studies as the first human dose is safe in this population with good absorption even in the acute phase after hemorrhage. However, our study suffers from the small population and lack of clinical evaluation of antioxidant effects of melatonin. Further studies are required to verify our findings.

In conclusion, consistent with previous studies in ICU patients, our findings show reduced levels of melatonin in ICH patients. Exogenous melatonin supplementation is beneficial to correct melatonin plasma concentrations. Melatonin is a safe supplement and even in the acute phase of hemorrhagic stroke, melatonin absorption is adequate. Further studies focused on melatonin administration in ICH patients can be helpful in evaluating clinical outcomes in these patients.

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