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Observation and analysis of clinical efficacy of melatonin on AOPP-induced delirium patients

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Abstract. – OBJECTIVE: To observe the clinical efficacy of melatonin on acute organophosphorus pesticide poisoning (AOPP).

PATIENTS AND METHODS: In this randomized control trial, a total of 59 AOPP patients with subsequent delirium were randomly divided into two groups, the melatonin group (n=29) and the placebo-controlled group (n=30). Patients in the melatonin group (n=29) underwent oral administration of melatonin in addition to the symptomatic treatment, while those in the placebo-controlled group took a placebo in addition to the symptomatic treatment. Before and 12 weeks after treatment, adverse events of participants in both groups were classified according to their scores in the assessment of the Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression-Severity of Illness (CGI-SI) scale, and Treatment Emergent Symptom Scale (TESS).

RESULTS: The excellence rates of patients in the melatonin group and the placebo-controlled group were 82.75% and 30.00%, respectively (χ^2 = 17.054, $p < 0.01$). No adverse events were identified in all participants.

CONCLUSIONS: Melatonin may serve as an effective drug in the treatment of AOPP-induced deliration.

Key Words:
AOPP, Deliration, Melatonin.

Introduction

China is one of the largest countries that manufactures and utilizes organophosphorus pesticide. There are a lot of people suffering from the organophosphorus pesticide poisoning due to inappropriate utilization or suicide of organophosphorus pesticide. Upon poisoning, rapid progression and a high mortality rate were seen in the patients[1,2]. Acute organophosphorus pesticide poisoning, also known as AOPP, is one of the chemical intoxications with the highest incidence rate in China. Delirium, also known as the acute confusional state, is a frequent post-AOPP acute organic brain syndrome characterized by fluctuating dysfunctions in cognition, emotion, attention, consciousness, self-perception, and psychomotor performance[3]. The conventional antipsychotics and benzodiazepines are commonly used drugs in the treatment of delirium. However, their applications were limited due to side effects, such as sedation, extrapyramidal reactions, and anticholinergic responses. Recently, the conventional antipsychotics and benzodiazepines were gradually substituted by the atypical antipsychotics, which has an equivalent efficacy but fewer side effects.

Melatonin (MD)[4], also known as N-acetyl-5-methoxy tryptamine, is a potent free radical scavenger that could pass through the blood-brain barrier. Multiple biological roles of melatonin have been identified in bone marrow stem cell differentiation and macular degeneration disease[5,6]. In this study, we aimed to observe the efficacy of melatonin in 59 patients with AOPP-induced delirium.

Patients and Methods

Patients

According to the inclusion and exclusion criteria, we enrolled a total of 62 patients with AOPP-induced delirium. All patients were admitted to the Emergency Department of Linyi Center Hospital (Shandong, China) between June 2013 and June 2015. We set the inclusion criteria as following: (a) patients aged above 18 years old regardless of the gender; (b) patients meet to the diagnostic criteria of delirium in the American Psychiatric Association's Diagnostic and Statisti-

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cal Manual-IV; (c) patients with a score of Brief Psychiatric Rating Scale (BPRS) > 36 points; (d) patients with a total score of Clinical Global Impression-Severity of Illness (CGI-SI) scale > 4 points. The exclusion criteria: (a) patients aged below 18 years old; (b) patients with a history of psychiatric diseases; (c) patients with a history of administration of antipsychotics within 4 weeks before admission. The research was approved by the Ethical Committee and conducted in accordance with the Declaration of Helsinki and the United National Institutes of Health.

Criteria for Missing Cases

Patients who met the following criteria were considered as missing cases: a) patients who had to withdraw the drugs due to severe adverse events; b) patients who could not fulfill the clinical trial, or decided to suspend the drug administration by themselves, or additionally took in other anti-delirium drugs by themselves; c) patients who failed to continue the clinical trial for other reasons.

Treatments

In this random, control, and non-blind study, 62 patients were divided into the melatonin group (n=31) and the control group (n=31). All patients received the comprehensive treatment upon admission. For patients with oral poisoning, symptomatic treatment was firstly adopted followed by gastric lavage using water or normal saline, catharsis, enema and skin cleaning. For patients with dermal toxicity, the affected skin was firstly rinsed radically using water or soapy water. Subsequently, all patients underwent fluid infusion for symptomatic or supportive treatment. More detail information is included in the AOPP management guideline[7]. Within one week after the patients were enrolled in this trial, they received 8-week therapeutic regimen with one tablet of melatonin (containing 2.9 mg melatonin; Tianjin Wanning Health Product Co., Ltd., Tianjin, China) or placebo before sleep.

Assessment of Clinical Efficacy

During the 8-week observation, patients were scored with BPRS and CGI-SI scales before enrollment and on the 56th day after treatment. The treatment efficacy was assessed according to the reductions in scores of BPRS and CGI-SI (before and after treatment). A reduction rate of BPRS score > 75% was considered as a vast improvement, 50% to 70% as a decided improvement, 25% to 50% as a slight improvement, and < 25% as unchanged or worse. Reduction rate was calculated using the following formula: reduction rate = (Score before treatment – Score after treatment)/(Score before treatment – 18) × 100%.

Safety Evaluation

The traumatic exposure severity scale (TESS) was used to evaluate the adverse events. Laboratory examinations including routine urinalysis, hepatic and renal functions, and electrocardiogram were performed at right before the treatment and again on the second after the treatment.

Statistical Analysis

All data analyses were performed by SPSS 16.0 (SPSS Inc., Chicago, IL, USA). The *t*-test, x^2-test, and one-way analysis of variance were performed for comparisons. The Bonferroni procedure was used as the post-hoc test. $p < 0.05$ suggested that the difference had statistical significance.

Results

Comparisons of General Data and Balance Test

In this study, we enrolled a total of 62 patients with AOPP-induced delirium, in which there were 3 missing cases (2 in melatonin group and 1 in control group) and 59 effective cases. Among the effective cases, there were 35 males and 24 females aged between 18 and 62 years old with an average of (42. 30 ± 7.13) years old. 23 patients were diagnosed with dichlorvos poisoning, 14 were with phorate poisoning, 8 were with parathion poisoning, 9 were with dimethoate poisoning, and 5 were with monocrotophos poisoning. Table I showed that the general condition and baseline indicators between the two group were comparable without a statistically significant difference.

Comparison of Clinical Efficacy Between the Two Groups

As shown in Table II, the improvement rate after treatment was higher in the Melatonin group than in the Control group (82.75% *vs.* 30.00%). The difference between the two groups showed a statistical significance ($\chi^2 = 27.160$, $p < 0.01$).

Comparison of BPRS and CGI-SI Scores Before and After Treatment in Two Groups

As shown in Table III, we found that there was no statistical difference in comparison of BPRS

Table I. Comparisons of general condition and baseline indicators of patients between the two groups.

Item	Melatonin group	Control group	Statistics	*p*
Gender (male/female)	18: 11	17: 13	$\chi^2 = 0.215$	0.898
Age (years)				
18 to 34	9	10		
35 to 49	14	12	$\chi^2 = 1.153$	0.886
50 or above	6	8		
Pesticides (n)				
Dichlorvos	12	11		
Phorate	6	8		
Parathion	4	4	$\chi^2 = 0.216$	0.898
Dimethoate	4	5		
Monocrotophos	3	2		

Table II. Improvement in delirium after treatment in two groups.

Group	n	Unchanged or worse (n)	Slight improvement (n)	Decided improvement (n)	Vast improvement (n)	Improvement rate (%)
Melatonin group	29	2	3	9	15	82.75%
Control group	30	12	9	4	5	30.00%

Note: Compared with the control group, $p < 0.01$.

and CGI-SI scores before treatment between the two groups. After treatment, the scores of BPRS and CGI-SI in both groups were decreased in comparison with those before treatment. The difference between the two groups was statistically significant ($\chi^2 = 15.386$, $p = 0.0001$).

Safety Evaluation

During the trial, no evident adverse events were observed in any participants. In this study, 59 AOPP-induced delirium patients underwent laboratory examinations for routine urinalysis, hepatic and renal functions, and electrocardiogram before and after treatment. The results showed no evident changes except for one participant in the melatonin group: the level of alanine aminotransferase (ALT) was 38 pmol/L before treatment, while after treatment, the level was increased to 68 pmol/L. The patient received no treatment due to no evident discomforts. Fifteen days later, the level of ALT was recovered.

Discussion

In China, AOPP leads to the highest incidence rate in acute intoxications. By inhibiting the activity of cholinesterase, the organophosphorus pesticide can massively aggregate the acetylcholine that could further act on the cholinergic receptor, leading to disorders in the central nervous system (CNS), respiratory system and circulatory system, and muscarinic, nicotinic

Table III. BPRS and CGI-SI scores before and after treatment.

Group	71	BPRS score		CGI-SI score	
		Before treatment	After treatment	Before treatment	After treatment
Melatonin group	29	49.96 ± 12.14	23.58 ± 5.53[1,2]	4.97 ± 0.87	2.00 ± 0.80[1,2]
Control group	30	50.12 ± 11.40	30.20 ± 7.05U	5.00 ± 0.78	2.83 ± 0.87[1]

[1]Compared with the scores before treatment in the same group, $p < 0.01$; [2]Compared with the scores of control group after treatment, $p < 0.01$.

and CNS-symptoms. Delirium developed from AOPP is an acute organic brain syndrome, and can significantly increase the mortality rate and the medical cost of patients[8,9]. Thus, active treatment of AOPP-induced delirium is of great significance.

Currently, comprehensive intervention including elimination of susceptible and inducible factors, symptomatic and supportive treatment, prophylaxis of complications, medication, and intensive care was used as the major treatment of AOPP-induced delirium[10]. Medication (haloperidol, risperidone, aripiprazole, and olanzapine) with antipsychotics was the major method in the management of AOPP-induced delirium. However, none of these drugs were recommended by the US Food and Drug Administration (FDA) for treatment of delirium, because of their side effects, such as somnolence, increased risk of cerebrovascular diseases, prolonged QT interval and extrapyramidal symptoms[11,12]. Recently, case reports and small-scale clinical studies have revealed that exogenous supplementation of melatonin could be used for prophylaxis and treatment of postoperative delirium. In 2002, Hanania and Kitain [11] reported 2 cases with successful treatment and prophylaxis of delirium after surgery of femoral neck fracture through oral administration of melatonin. In this report, a 53-year-old male patient experienced severe delirium after surgery and gained poor efficacy after medication with benzodiazepines and antipsychotics (droperidol). However, after administration of 2 mg sustained-release melatonin, the symptoms of delirium disappeared with significant improvement in sleep. In the other case, an 81-year-old male patient who had experienced the delirium after orthopedic surgery three years ago underwent debridement in this hospital. To avoid delirium, 2 mg melatonin was given every day for 3 days after surgery, and no delirium was found during the hospitalization.

In this study, we used the melatonin to treat AOPP-induced delirium and gained promising efficacy. The results showed that there was a statistically significant difference in comparison of the improvement rates between the melatonin group (82.75%) and the control group (30.00%). Also, no significant variations were identified in the comparison of the results of laboratory examination of patients in both groups before and after treatment. Melatonin is a hormone secreted by the pineal gland. In 1958, melatonin was first isolated and purified from the bovine pineal gland (Aaron B. Lerner, James D. Case, Yoshiyata Takahashi, Teh H. Lee, Wataru Mori. Isolation of melatonin, the pineal gland factor that lightens melanocytes. J Am Chem Soc 1958; 80. pp. 2587-2587). They found that injection of this hormone into a frog would make the skin color shallow, and this hormone was named as melatonin. Melatonin has a variety of functions, such as regulating the development of the reproductive system, biological clock, and neuro-immune response[13,14]. The following mechanism is potentially involved in the treatment of AOPP-induced delirium by melatonin: (a) anti-free radical effect: as a potent free radical scavenger, melatonin is twice as active as vitamin E, four times as glutathione, and 14 times as mannitol. The antioxidative effect of melatonin is dependent on the 5-methoxyl group that has a synergistic effect with the acetyl on the side chain. After elimination of one hydroxyl radical, melatonin would be transformed into a cationic compound that could form N1-acetyl-N2-formyl-5-methoxy-kynuramine (AFMK) with a more potent antioxidative effect than melatonin[15]. (b) Antagonist effect on the neurotoxicity of Aβ: clinical data have shown that Aβ is the common pathway of various factors contributing to AOPP-induced delirium, and, is considered as the key component in development and progression of AOPP-induced delirium. Aβ derives from the amyloid precursor protein (APP). The APP can be processed through diversified proteolysis mechanisms. Peptide hydrolysis at α site of APP could alter the steric configuration, thereby blocking the formation of Aβ. Studies *in vitro* have confirmed that melatonin can bind with the α site, resulting in the hydrolysis of the peptide. In addition, melatonin could also destruct the β sheet in Aβ to decrease the aggregation and facilitate the elimination of Aβ, thus minimizing the neurotoxicity of Aβ[11]. Besides, melatonin could reduce the free radicals directly produced by Aβ or by an increase in the intracellular level of Ca^{2+}, thus weakening the neurotoxicity of Aβ[16]. (c) Reduction in hyperphosphorylation of tau protein: as one of the pathological features in AOPP-induced delirium, neurofibrillary tangles contains hyperphosphorylated tau protein. Latest studies have indicated that melatonin can effectively alleviate the hyperphosphorylation of tau protein in AOPP-induced delirium, but the specific mechanism may be correlated with the direct regulation of activities of protein kinase and protein phosphatase[17].

Conclusions

Antipsychotic medication is the preferred choice in the treatment of AOPP-induced delirium. However, it also causes many complications and poor drug tolerance in some patients. Our study showed that melatonin can effectively manage the mental status of AOPP-induced delirium patients with high safety and convenience in clinical application. Thus, melatonin can serve as a first-line drug and an option for physicians in the treatment of AOPP-induced delirium.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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