Effect of Dexmedetomidine-Induced Sleep Balance Treatment on the Chronic Refractory Primary Insomnia Patients

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Abstract: *Aim*: To pilot study the therapeutic effect of dexmedetomidine-induced sleep balance treatment (DISBT) on the chronic refractory primary insomnia patients.

Methods: Forty-two patients with chronic refractory primary insomnia were randomly divided into two groups by random number table. Patients in DISBT group were given DISBT for 3 days, while patients in the control group were given conventional treatment for 3 day. Pittsburgh sleep quality index (PSQI), the hyperarousal scale (HAS), and Hamilton anxiety scale (HAMA) were evaluated and compared between the pre-treatment and post-1-week-treatment. Sleep architecture and electroencephalogram (EEG) spectrum were also recorded and compared pre-treatment and post-treatment.

Results: The scores of PSQI and HAMA in both groups after treatment were lower than those before treatment ($P < 0.05$), DISBT group-reduced degree were higher than those of the control group ($P < 0.05$). Sleep architecture of Stage 2 sleep proportion, EEG spectrum beta, and gamma relative power value in DISBT group were lower than those before treatment ($P < 0.05$), Stage 3 sleep proportion and delta relative power value were higher than those before treatment ($P < 0.05$); Sleep architecture of Stage 2 sleep proportion, beta, and gamma relative power value in control group were higher than those before treatment ($P < 0.05$); rapid eye movement sleep, Stage 3 sleep proportion, and delta relative power value were lower than those before treatment ($P < 0.05$). The total scores of the hyperarousal scale (HAS) in both groups after treatment were lower than those before treatment ($P < 0.05$), DISBT group-reduced degree were higher than those of the control group ($P < 0.05$), the extreme score, introspectiveness score, react score of HAS in control group after treatment had no statistical significance compared to those before treatment ($P > 0.05$), the extreme score, introspectiveness score, react score of HAS in DISBT group after treatment were lower than those before treatment ($P < 0.05$).

Conclusion: DISBT effectively reduced the insomnia patient cortex hyperarousal level, corrected disorder of sleep-awakening pathways and eased up insomnia symptom. It is an effective method for chronic refractory primary insomnia.

Keywords: Dexmedetomidine, primary insomnia, hyperarousal.

According to the survey, the incidence of chronic primary insomnia in the adults is about 3–5% [1]; the chronic primary insomnia causes patients decline in productivity, rising accident rate, and a big consummation of medical resources [2]. Currently, it is believed that the patients with chronic primary insomnia have cerebral cortical hyperarousal [1, 3]. Dexmedetomidine can reduce the cerebral cortical hyperarousal level in patients with insomnia by changing the activity of LC-Noradrenergic system and other arousal pathways of ascending reticular activating system (RAS), and can help to restore the sleeping–awakening system in balance and improve the symptoms of insomnia. The effect of traditional drug treatment for some insomnia patients is poor, This part of patient was stubborn insomnia. This study used Dexmedetomidine lower stubborn insomnia patients' arousal level to improve sleep. Primary insomnia patients have the clinical features such as falling asleep difficulty, sleep maintenance difficulties and sleep quality, [4] and the objective index of PSG performs in prolonged sleep latency, reduced deep sleep, and increased light sleep [5]. The cerebral cortex hyperarousal is considered as a physiological characteristic in primary insomnia patients, and the important mechanism for the pathogenesis of primary insomnia patients [1, 3]. So the insomnia symptoms can be effectively improved by reducing the cerebral cortex excessive arousal level [6, 7]. The cerebral cortex hyperarousal can be found in some susceptible population, who has brain awakening–sleep pathway disorders because of conduced factors in daily life, and manifests as a high activation state of the arousal system no matter it is day time or night time. So patients are unable to sleep even if they are fatigue due to the lack of sleep in long term [7, 8]. The brain arousal system is composed mainly by the ascending

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RAS. Of which, the LC-Norepinephrine is the important pathway of the ascending RAS, and plays an important role in regulating the body's sleep and wake state [9, 10]. The cerebral cortex hyperarousal manifests mainly as a risen ratio of the high-frequency brain waves in EEG spectrum (Beta and Gamma bands) and a declined ratio of the low-frequency brain waves (Delta band) [11, 12]. The cerebral cortex hyperarousal is in out-of-inhibition state. Such also makes insomnia patients present a highly alert state during the day time, although they have the symptoms of fatigue and sleepy, they cannot fall asleep, and cannot control themselves to have various negative intrusive thoughts. The subjective characteristic of patients can be well reflected by the hyperarousal measurement table [13]. Nowadays, the treatment of chronic primary insomnia includes medication and cognitive–behavioral treatment. The cognitive–behavioral treatment has an exact effect on chronic insomnia, but has a slow onset, therefore has a significant impact on patients' compliance [14]. Medication treatment takes mainly benzodiazepine receptor-related drug, which impacts the ventrolateral preoptic (VLPO) area to impose sleep, but has a weak inhibition on the awakening system that has an abnormal hyperactivity. When benzodiazepine receptor-related drugs act on the VLPO area, although patients are asleep, their awakening system activity is not weakened, and the cerebral cortical activity is not correspondingly reduced, thus the normal 'on–off' module sleep–wake trigger structure occurs disorders [15, 16].

Dexmedetomidine is α_2-adrenoceptor agonist, It can impact on the LC-Norepinephrine and other awakening pathway activity to regulate the body wakefulness [17].

OBJECTS AND METHODS

Research Subjects

Among the patients with chronic intractable primary insomnia recruited by our hospital (Third Military Medical University, Daping Hospital) from February 2012 to June 2012, 42 cases were selected. It's a randomized controlled study. After admission, patients were randomly numbered and divided into two groups: (1) control group, including six males and 15 females; (2) DISBT group, including seven males and 14 females. After getting the approval of the hospital's ethics committee and the written informed consent of patients, they were administrated DISBT. Patients' medical history were inquired once after their admission in hospital, executed routine physical examination and laboratory examinations to exclude relevant physical illnesses and mental illnesses.

Admission Criteria

(1) Meet the diagnostic criteria and the exclusion criteria for chronic primary insomnia in 'Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)' established by the American Psychiatric Association [18]. (2) Before admission, ensure that all patients have received conventional treatment based on 'China insomnia definition, diagnosis and medication treatment consensus' [19] (hereinafter referred to as 'the consensus'), ensure that all patients have taken more than two kinds of treatment medication, and ensure that all patients have been treated for more than 3 months, but have got poor effect or no effect; patients'Pittsburgh score was more than nine points before admission, and the patients were diagnosed as chronic intractable primary insomnia. (3) There was no history of head injury or epilepsy, and there was no abnormal electroencephalogram (EEG).

Exclusion Criteria

(1) Patients with heart block, severe ventricular dysfunction, severe liver and kidney dysfunction, or other serious physical illnesses. (2) Patients with excessively high or low blood pressure: SBP > 150 mmHg or SBP < 110 mmHg (1 mmHg = 0.133 kPa); bradycardia (fewer than 60 beats/min); diabetes with poor glycemic control (fasting glucose > 6.1 $mmol \cdot L^{-1}$). (3) Apnea hypopnea index > 30. (4) Patients allergic to dexmedetomidine. (5) Patients with lower level than primary school in education or those unable to understand the rating scale used before and after the treatment. (6) Female patients during pregnancy or lactation or having pregnancy plans recently.

Therapeutic Scheme

(A)control group was given: (1) looking for the possible causes of insomnia and correcting the inadequate sleep hygiene habits; (2) giving cognitive–behavioral therapy; (3) giving benzodiazepine receptor agonistic medication(zopiclone) treatment for 3 days.

(B) DISBIT group was given injection dexmedetomidine at 9:00 am after 8 hours of fasting. Baseline respiration, pulse, blood pressure, heart rate ECG and blood oxygen saturation were recorded. Injection dexmedetomidine produced by Sichuan Guorui Pharmaceutical Inc, trade name is LeWeiJia, approval number: National drug approval H20110097)

by using the micro-injection pump, which has a target-controlled infusion function; the initial dose is 0.5-1.0 μg·kg−1·h−1, with a duration of 10 min; then, adjust the maintenance dose to 0.2 μg·kg−1·h−1, with a duration of 30-50 min; keep the patients inhale continuously low flow oxygen, observe closely patients' situation during the injection, wake up the patients every 15 min to ask about their feelings; if witness patients with persistent heart rate <60 beats/min or systolic blood pressure <100 mmHg, and, after symptomatic treatment, if there is no improvement or there are other serious adverse events occurring (such as arrhythmia, allergic shock, vomiting, etc.), immediately stop the treatment. Administrate DISBT treatment once every day, for 2-3 days consecutively.

Efficacy Assessment

The efficacy assessment comprehends one evaluation index, two assessment scales, and the monitoring of the polysomnography as the following:

1. PSQI (Pittsburgh sleep quality index) [20]: execute the sleep quality assessment of patients 1 week before and after the treatment. PSQI includes five ratings and 19 self-assessments, of which, the five ratings and the 19th self-assessment are not counted in the cumulative score, and the rest 18 items counted in the cumulative score are divided into seven factors, which are sopite duration, sleep duration, sleep efficiency, sleep quality, sleep disorders, sleep medication, and daytime function. Each item scores from 0 to 3 points, the cumulative score of each item is the total score of PSQI; the higher the score, the worse the quality of sleep. The assessment of patients is completed by a physician blinded to the grouping situation.

2. HAS (The Hyperarousal Scale) [13]: execute the subjective hyperarousal state of patients 1 week before and after the treatment. HAS is divided into 26 items to evaluate the daytime wakefulness of patients with insomnia, of which the summation limit, the response factor, and the self-reflection factor are most closely related to the brain cortex over-activity. Each item scores from 0 to 3 points; the higher the score, the higher the arousal level. The assessment of patients is completed by a physician blinded to the grouping situation.

3. Hamilton anxiety scale (HAMA) [21]: a senior psychiatric physician blinded to the grouping situation executes the assessment of patients with the HAMA 1 week before and after the treatment.

4. Polysomnography: use the Australian Condi E-type Polysomnography (PSG) to monitor the patients during the whole night before and after the treatment. EEG electrodes are set according to the International 10–20 system standard; sleep stages are determined in accordance with the standards of '2007 The AASM Manual for the Scoring of Sleep and Associated Events Rules, Terminology and Technical Specifications' [22]. The profusion software was used to carry on a preliminary analysis of sleep architecture toward the monitoring data, and adopt the manual analysis to correct and determine each stage. The sleep structure indicators include sleep phase 1, sleep phase 2, sleep phase 3, and REM sleep (rapid eye movement sleep). Use METLAB7.6(R2008a) software to execute the spectral analysis on the EEG C3-M2 channel data; the data acquisition time is the first three NREM, eliminate the interference of post-sleep awakening and body movement, and take the fast Fourier transformation; the EEG spectral includes six bands, which are Delta (0.5–3.75 Hz), Theta (3.75–6.75 Hz), Alpha (6.75–12.50 Hz), Sigma (12.50–14.75 Hz), Beta (14.75–30 Hz), Gamma (30–60 Hz), and calculate the relative power values of each band, which is to say the band relative power value = a band power value (μV^2/Hz)/the gross band power (μV^2/Hz). The EEG spectrum and sleep staging are analyzed by a technician blinded to the grouping situation.

Treatment Adverse Reactions Assessment

Treatment adverse reaction assessment (TESS) to assess the patients before and after treatment, to observe the adverse reactions due to the treatment. TESS which includes a number of laboratory tests results and common adverse symptoms is the most widely used adverse reactions scale.

Statistical Analysis

SPSS version 17.0 is used for data analysis. Results are mentioned as mean+_ SD. The paired samples *t*-test to compare the situation before and after the treatment, use the independent sample *t*-test to compare the difference between the groups, and the

Table 1: Baseline Characteristics Between Two Groups

Item	DISBT group (21 cases)	Control group (21 cases)	$t/\chi^2/Z$	*P*
Sex (male/female) (case)	7/14	6/15	0.111	0.739
Age (year)	49.86 ± 9.31	48.27 ± 9.00	0.556	0.581
Education (year)	10.57 ± 2.94	10.62 ± 2.71	−0.55	0.957
Duration (month)	75.24 (79.50)[a]	65.76 (70.00)[a]	−0.378	0.705
Insomnia severity (PSQI score)	16.81 ± 3.33	17.33 ± 3.01	−0.535	0.595

[a]For non-normal distribution, express for median (interquartile range).

count data uses χ^2 test; the median (interquartile range) to indicate the non-normally distributed data; the comparison of groups uses the rank sum test, $P < 0.05$ is considered statistically significant.

RESULTS

Baseline Characteristics Between Two Groups

Comparing the two groups of patients in age, sex ratio, years of education, insomnia severity, and the course of disease, the differences were not statistically significant ($P > 0.05$) and were comparable (see Table **1**).

Comparison of the PSQI 7 Factors Between Two Groups Before and After Treatment

Comparing each factor scores between the two groups before the treatment, the difference was not statistically significant ($P > 0.05$). The sleep latency, sleep time, sleep efficiency, and the total scores of both groups have decreased comparing to those before the treatment; the difference was statistically significant ($P < 0.05$); after treatment, the difference scores of DISBT group have decreased more obviously than those of the control group; the difference was statistically significant ($P < 0.05$). The sleep quality, sleep disorders, and daytime function scores of DISBT group after treatment have decreased comparing to those before treatment; the difference was statistically significant ($P<0.05$); comparing the sleep quality, sleep disorders, and daytime function scores of the control group after treatment with those before treatment, the difference was not statistically significant ($P > 0.05$), as shown in Table **2**.

Comparison of the HAS Between Two Groups Before and After Treatment

Comparing the HAS between two groups before and after treatment, all differences were not statistically significant ($P > 0.05$). The total score of the control group after treatment has decreased comparing to that before treatment ($P < 0.05$); comparing the extreme score, introspectiveness score, and react score of the control group after treatment with that before treatment, the difference was not statistically significant ($P > 0.05$). The extreme score, introspectiveness score, and

Table 2: Comparison of the PSQI 7 Factors Between Two Groups Before and After Treatment ($\bar{x} \pm s$)

Items	Pre-treatment				Post-1-week-treatment			
	DISBT group	Control group	*t*	*P*	DISBT group	Control group	*t*	*P*
Sleep quality	2.76 ± 0.43	2.81 ± 0.40	−0.368	0.715	2.10 ± 0.54[a]	2.52 ± 0.68	−2.264	0.029
Sleep latency	2.81 ± 0.40	2.86 ± 0.36	−0.405	0.688	1.76 ± 0.44[a]	2.10 ± 0.54[a]	−2.203	0.033
Sleep time	2.57 ± 0.60	2.76 ± 0.54	−1.085	0.285	1.52 ± 0.68[a]	1.95 ± 0.59[a]	−2.183	0.035
Sleep efficiency	2.48 ± 0.81	2.86 ± 0.48	−1.850	0.072	1.38 ± 0.86[a]	2.00 ± 0.84[a]	−2.358	0.023
Sleep disorders	1.90 ± 0.89	2.00 ± 0.77	−0.370	0.713	1.43 ± 0.51[a]	1.86 ± 0.79	−2.087	0.043
Sleep drugs	1.81 ± 1.40	1.67 ± 1.32	0.341	0.735	1.67 ± 1.32	1.71 ± 1.23	−0.121	0.904
Daytime function	2.48 ± 0.68	2.38 ± 0.80	0.414	0.681	1.81 ± 0.75[a]	2.33 ± 0.80	−2.196	0.034
Total	16.81 ± 3.33	17.33 ± 3.01	−0.535	0.595	11.67 ± 2.69[a]	14.48 ± 3.03[a]	−3.180	0.003

[a]Each factors post-1-week-treatment compared to those before treatment, $P < 0.05$.

Table 3: Comparison of the HAS Between Two Groups Before and After Treatment ($\bar{x} \pm s$)

Items	Pre-treatment				Post-1-week-treatment			
	DISBT group	Control group	*t*	*P*	DISBT group	Control group	*t*	*P*
Extreme score	4.71 ± 1.19	5.62 ± 2.01	−1.774	0.84	3.14 ± 1.42[a]	4.67 ± 2.01	−2.836	0.007
Introspectiveness score	12.95 ± 1.12	12.90 ± 1.18	0.134	0.894	10.38 ± 1.68[a]	12.57 ± 1.29	−4.729	<0.001
React score	6.38 ± 1.40	6.52 ± 1.36	−0.335	0.739	5.05 ± 1.56[a]	6.38 ± 1.40	−2.914	0.006
Total	49.95 ± 3.09	50.33 ± 2.82	−0.418	0.679	43.67 ± 4.19[a]	48.14 ± 3.30[a]	−3.845	<0.001

[a]Each factors post-1-week-treatment compared to those before treatment, $P < 0.05$.

react score of DISBT group after treatment have decreased comparing to those before treatment; all differences were statistically significant ($P < 0.05$); the total score of DISBT group after treatment has decreased obviously comparing to that of the control group; the difference was statistically significant ($P < 0.05$), as shown in Table **3**.

Comparison of EEG Spectrum and Sleep Architecture Between Two Groups Before and After Treatment

Comparing all the bands in the EEG spectrum and each stage of sleep ratio before treatment, the difference was not statistically significant ($P > 0.05$) (see Tables **4** and **5**). After treatment, Delta band relative power value and the third sleeping stage proportion in DISBT group have increased comparing to those before treatment ($P < 0.05$). Theta, Alpha, Beta, and Gamma band relative power values and the second sleeping stage proportion have decreased comparing to those before treatment ($P < 0.05$); Delta band relative power value, the third sleeping stage proportion, and REM proportion have decreased comparing to those before treatment, and the difference was statistically significant ($P < 0.05$). Sigma, Beta, and Gamma band relative power values and the second sleeping stage proportion have increased comparing to those before treatment, and the difference was statistically significant ($P < 0.05$).

Table 4: Comparison of EEG Spectrum Between Two Groups Before and After Treatment ($\bar{x} \pm s$)

Items (%)	Pre-treatment				Post-treatment			
	DISBT group	Control group	*t*	*P*	DISBT group	Control group	*t*	*P*
Delta	74.43 ± 5.35	74.06 ± 4.64	−0.238	0.813	82.57 ± 2.48[a]	67.62 ± 5.96[a]	10.623	<0.001
Theta	8.50 ± 2.95	9.02 ± 2.63	0.601	0.551	6.35 ± 1.60[a]	10.49 ± 2.80	−5.861	<0.001
Alpha	5.62 ± 1.87	6.06 ± 1.26	0.904	0.371	3.98 ± 0.81[a]	7.04 ± 1.85	−6.925	<0.001
Sigma	1.36 ± 0.47	1.46 ± 0.43	0.735	0.466	0.86 ± 0.19[a]	1.77 ± 0.56[a]	−7.039	<0.001
Beta	8.19 ± 2.08	7.79 ± 2.80	−0.527	0.601	4.72 ± 1.49[a]	10.77 ± 3.94[a]	−6.574	<0.001
Gamma	1.88 ± 0.62	1.51 ± 0.81	−1.646	0.108	1.47 ± 0.67[a]	2.27 ± 0.73[a]	−3.718	0.001

Table 5: Comparison of Sleep Architecture Between Two Groups Before and After Treatment ($\bar{x} \pm s$)

Items (%)	Pre-treatment				Post-treatment			
	DISBT group	Control group	*t*	*P*	DISBT group	Control group	*t*	*P*
REM sleep	15.68 ± 8.16	15.57 ± 7.36	0.046	0.963	16.21 ± 6.21	12.08 ± 5.92[a]	2.207	0.033
Stage 1 sleep	11.81 ± 7.69	9.54 ± 5.85	1.077	0.288	8.90 ± 4.88	7.48 ± 4.66	0.963	0.341
Stage 2 sleep	66.34 ± 11.69	65.32 ± 10.85	0.292	0.772	58.90 ± 10.25[a]	75.86 ± 9.33[a]	−5.611	<0.001
Stage 3 sleep	7.11 ± 5.70	10.58 ± 7.51	−1.690	0.099	16.19 ± 7.86[a]	5.12 ± 3.67[a]	5.844	<0.001

[a]Each sleep stages post-treatment compared to those before treatment, $P < 0.05$.

Table 6: Comparison of HAMA **Between Two Groups Before and After Treatment ($\bar{x} \pm s$)**

Items	Pre-treatment				Post-1-week-treatment			
	DISBT group	Control group	*t*	*P*	DISBT group	Control group	*t*	*P*
Psychic anxiety	8.14 ± 1.28	8.24 ± 1.81	−0.197	0.845	6.14 ± 1.06[a]	7.19 ± 1.83[a]	−2.266	0.029
Somatic anxiety	3.48 ± 2.34	3.67 ± 1.53	−0.313	0.756	2.29 ± 1.42[a]	3.19 ± 1.44[a]	−2.054	0.047
Total	11.57 ± 2.64	11.95 ± 2.01	−0.486	0.630	8.43 ± 1.47[a]	10.38 ± 2.16[a]	−3.430	0.001

[a]Each factors post-1-week-treatment compared to those before treatment, $P < 0.05$.

Comparison of HAMA Between Two Groups Before and After Treatment

Comparing the HAMA between two groups before treatment, the difference was not statistically significant ($P > 0.05$) (see Table **6**). The HAMA of both groups after treatment has decreased comparing to that before treatment; the difference was statistically significant ($P < 0.05$); the HAMA of DISBT group after treatment has significantly decreased comparing to that of the control group after treatment; the difference was statistically significant ($P < 0.05$).

Adverse Reactions

After DISBT treatment, one patient (4.76%) has complained of dizziness, one (4.76%) has chest distress, one (4.76%) has complained of discomfort on the medication injection site. After symptomatic treatment, all problems have been alleviated quickly. The total adverse reaction rate was 14.3% (3 cases), and we did not find any other side effect.

DISCUSSIONS

The results of this study show that, after treatment, the patients in control group have their sleep efficiency increased and their sleep time prolonged, but it manifests mainly on the light sleeping stage 2. The sleep architecture did not tend to be normal. After treatment, due to the cerebral cortical arousal level of the control group not decreased and the significantly prolonged sleep time in light sleeping stage 2, the ratio of fast waves in EEG spectrum is increased and slow waves decreased. The increased dealing of sensory perception and memory extension from the increased fast waves have interfered patients' sleep continuity and stability [11]. So patients have experienced non-restorative sleep. PSQI indicates only the improvement of the sleep time, sleep latency and sleep efficiency factor, while the sleep quality and sleep disorder factors are not significantly improved. The hyperarousal total score has decreased comparing to that before treatment, but it is only because of the declined sleep disorder factors in the scale. The cerebral cortex over-activity most related scores like the extreme score, introspectiveness score, and reactive score were not significantly reduced.

It is reported that Dexmedetomidine can regulate sleep [23, 24]. Dexmedetomidine is able to induce a unique 'wake-up' sedative and hypnotic effect, which means at the same time to obtain a valid clinical sedative and hypnotic effect. Patients can be easily awakened and can regain consciousness to communicate with others and cooperate to conduct a simple check up, and can get asleep again within seconds to minutes when the external stimulation disappears [25]. In addition, when Dexmedetomidine – induced sleep, the changes in patients' respiration and cardiovascular system are similar to those of the spontaneous sleep [26, 27]. So it has a high security. As α_2-adrenoceptor agonist, Dexmedetomidine can impact on the LC-Norepinephrine through adreno-autoreceptors to regulate the body wakefulness; Dexmedetomidine can also regulate other awakening pathway activity by other adrenoceptors on other nerve terminals [17]. Studies have shown that after using Dexmedetomidine, the BOLD signal of subjects has changed similarly to that in physiological sleep; animal tests have shown that when Dexmedetomidine – induced sleep, the changes of c-Fos in various cerebral nucleuses are similar with those in physiological sleep, both in quantity and quality (i.e. continent in VLPO area increases; tuberomammillary nucleus [TMN] and LC decrease) [26]. Therefore, it is speculated that Dexmedetomidine can possibly impact on both awaking system and sleep system, reduce overall the cerebral cortex hyperarousal level in patients, and correct quickly the disordered sleep–awakening pathway of patients. The results of this study show that after treatment, patients' sleep structure of DISBT group tends to get normal, EEG spectral analysis shows that the fast wave proportion has reduced, slow wave proportion has increased, the cerebral cortex awakening level of patients has significantly decreased,

and the PSQI results are better than that in the control group.

The results of this study show that after treatment, the HAMA scores of patients in DISBT group have decreased more significantly than those in the control group, and it is possibly related to Dexmedetomidine that inhibits the release of norepinephrine and regulates 5-serotonin and other neurotransmitters through the activation of α_2-adrenoceptors [28]. In addition, the discomfort experience of the night time symptoms of insomnia and daytime dysfunction has formed a chronic stress to patients, and therefore results in a state of anxiety. Dexmedetomidine can ease the stressing state of insomnia patients, and thereby reduce their anxiety symptoms. It is also believed that insomnia and anxiety have a comorbidity mechanism of hyperarousal [29-32]. So Dexmedetomidine can ease insomnia and anxiety symptoms by reducing the cerebral cortex hyperarousal.

In short, DISBT treatment has offered a safe and effective treatment option for patients with chronic refractory insomnia. Regarding the small sample size and short clinical observation time of this study, it is still lacking a long-term observation efficacy. In future studies, it is expected to expand the sample size, observe a long-term clinical efficacy as well as to evaluate the best treatment numbers, best medication dosage, and treatment time point so as to explore the research.

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