Feasibility of Patient-Controlled Sleep with Dexmedetomidine in Treating Chronic Intractable Insomnia

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Background: Patient-controlled analgesia (PCA) is an “on-demand” system which allows patients to self-administer intravenous medications in small bolus doses. Based on the principles of PCA, we developed Patient-Controlled Sleep (PCSL) for chronic intractable insomnia where the traditional analgesics in PCA were replaced with dexmedetomidine (Dex), an alpha-2 agonist widely used for premedication, sedation, anxiolysis and analgesia. The purpose of this study was to assess the feasibility of the new method for the treatment of chronic intractable insomnia.

Patients and Methods: Patients with chronic intractable insomnia undergoing PCSL (n=20) were evaluated with the Pittsburgh Sleep Quality Index (PSQI), Symptom Checklist 90 (SCL-90), Hamilton Anxiety Scale (HAMA) and Hamilton Depression Scale (HAMD) before and after the treatment. The patient characteristics, overall outcomes and related side effects were also assessed.

Results: Fifteen patients completed the treatment protocol. The duration of PCSL varied from a few days to four months, and the dosage of Dex gradually decreased without eliciting signs or symptoms of tolerance or physical dependence. The sleep quality improvement occurred immediately after the therapy in 12/15 patients, and of which, 7/12 patients achieved continuously improved sleep quality in follow-up.

Conclusion: PCSL with Dex might be a potential treatment for patients with chronic intractable insomnia. However, it is an off-label use, and the potential side effects of dexmedetomidine with long-term use needs further evaluation.

Keywords: insomnia, dexmedetomidine, Patient-Controlled Sleep, biomimetic sleep

Introduction

Insomnia is one of the most frequent sleep disorders in the world with an estimated prevalence ranging from 8~20% in adults.^{1,2} The absence of sleep is associated with significant health and economic burdens, reduced work efficiency and quality of life.³ Common pharmaceutical treatments of insomnia, based on the use of benzodiazepines and non-benzodiazepine hypnotics,⁴ can cause residual effects, withdrawal reactions, tolerance, abuse potential and physical dependence.⁵ Further, these drugs alter sleep structure and reduce the depth of non-rapid eye movement sleep.⁶ These various safety concerns have limited their prolonged use. For patients with chronic intractable insomnia, who have not responded to conventional treatments such as pharmacotherapy, physical therapy (Transcranial Magnetic

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Stimulation, etc.) and cognitive behavioral therapy (CBT), an alternative treatment option that promotes sleep via a different mechanism of action is needed.

In the 1970s, analgesic researchers began to test instruments that would allow post-operative patients to self-administer small doses of opioid drugs when they felt the need for them.⁷ This would be termed patient-controlled analgesia (PCA), consisting of a microprocessor-controlled infusion pump that has been successfully used to meet analgesic requirements. Patient-controlled sedation (PCS) was first adapted for controlled anxiolysis using diazepam by Galletly and associates in 1989 and afterwards for peri-operative sedation using either midazolam or propofol.^{8,9} It is a method to meet patients' highly individual needs for sedative therapy.¹⁰ However, drugs applied in PCS, primarily midazolam and propofol, can induce tolerance and pharmacological dependence when used over long periods of time; therefore, it is not appropriate for the treatment for chronic insomnia.

Dexmedetomidine (Dex) was initially approved by the United States Food and Drug Administration (FDA) in 1999 for the short-term sedation of intubated and mechanically ventilated patients.¹¹ Recent studies have shown that Dex infusion modestly ameliorated the subjective sleep quality in post-operative and intensive care unit (ICU) patients.¹² Dex induces a state mimicking natural sleep accompanied by an increase in slow-wave activity,¹³ with the unique aspect that patients remain easily rousable and respiration is minimally affected. Moreover, withdrawal symptoms seem to be lacking in the setting of prolonged use.¹⁴

Based on the above background, we began a pilot project to examine a new concept: Patient-Controlled Sleep (PCSL), a technology that allows patients with chronic intractable insomnia to intermittently trigger measurable doses of Dex through a patient-controlled device to produce and maintain natural sleep.

Patients and Methods

Ethical Approval

The single-center, single-arm, pilot study was approved by the Institutional Review Board (IRB) of the Aviation General Hospital of China Medical University (HK2015-03-01), and registered on Chinese Clinical Trial Registry (ChiCTR2000035041). The study protocol was conducted in accordance with the Declaration of Helsinki.¹⁵ All participants provided written informed consent to participate

in the study. They were fully aware of the off-label use, unclear outcomes, and possible side effects, such as nausea, vomiting, dizziness, bradycardia, infection, and unforeseen adverse events.

Participants

The study was performed at our center between May 2015 to March 2019. Eligible Participants fulfilled the diagnostic criteria for insomnia (the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders), including severe difficulties initiating sleep, maintaining sleep, and/or early morning awakenings with no ability of return to sleep; have insomnia duration of at least three times a week for at least 3 months; and complain of impaired daytime functioning.¹⁶ In addition, these patients had been diagnosed and treated by the sleep medicine specialist prior to being referred our center. They were not sensitive to hypnotics (or have a history of abuse of hypnotics), and also failed to respond to physical therapy and CBTi. The following exclusion criteria were used: presence of sleep apnea defined as apnea-hypopnea index greater than 15 or periodic limb movements during sleep; working night shifts and unable or unwilling to discontinue this work pattern; having a serious somatic condition preventing further participation; unwillingness or inability to gradually stop taking sleep medication. The flow diagram of the therapeutic process is shown in Figure 1.

Dex Titration

Patients preparing for Dex titration were asked to fast for 6 hours, but clear liquids were allowed up to 2h before

Figure 1 Flow diagram of therapeutic process.

titration. Height and weight were assessed for body mass index (BMI) calculation. Upon arrival into the post-anesthetic care unit (PACU), patients were placed in the supine position. A dedicated intravenous cannula was inserted by a certified registered nurse anesthetist (CRNA) and an infusion of saline solution (500 mL) was commenced. Patients were monitored using an electrocardiogram, pulse oximetry, non-invasive blood pressure and end-tidal carbon dioxide monitoring devices during the procedure. Two hundred mcg of Dex (Yangtze River Pharmaceutical Group Co., Ltd., Jiangsu, China) was diluted with 0.9% normal saline to 50 mL in a syringe (the final drug concentration was 4 mcg/mL), and connected to a Constant Speed Syringe Pump (Kelly Med™ Syringe Pump, KL-605T, Beijing, China), that was then infused via the intravenous cannula. The titration protocol was designed by an experienced anesthesiologist (An JX), and the operation and evaluation were performed and recorded by an attending anesthesiologist (Fang QW). The constant speed syringe pump was operated by the anesthesiologist with a basal rate of 0.1 mL/h (0.4 mcg/h), a bolus dose of 2.5 mL (10 mcg), and a lockout interval of 10 minutes. The degree of sedation was evaluated every 5–10 min before the start of the next bolus. The evaluation was conducted according to the Modified Observer's Assessment of Alertness/Sedation (MOAAS) Scale, which was based on the assessment of responsiveness in the original Observer's Assessment of Alertness/Sedation Scale.^{17,18} Finally, patients were escorted back to the ward by the nurse after awakening and reaching the discharge criteria of the PACU.

Rescue Protocol

Blood pressure (BP) was controlled within 30% of baseline. If the BP went outside that target range, it was increased with phenylephrine or decreased with nitroglycerin. If the heart rate (HR) dropped below 45 bpm, anisodamine was administered; atropine and isoproterenol were available if the previous treatment was ineffective. Further medical management was at the discretion of the anesthesiologist.

Administration of PCSL

After Dex titration, patients were excluded if they complained of being uncomfortable or experienced side effects, such as transient hypertension, bradycardia or hypotension. Those patients who tolerated the treatment were included as candidates to continue PCSL. The Patient-controlled device (Rehn Medtech Co., Ltd., Jiangsu, China) protocols were

800 mcg Dex diluted to 200 mL (the final drug concentration was 4 mcg/mL). The device was set up to deliver a continuous infusion of 0.1 mL/h (0.4 mcg/h), a maximum dose of 30 mL/h (120 mcg/h) and a bolus of 1–3 mL (4–12 mcg), with a 10-minute lockout interval, according to the Dex titration data generated in the PACU. The loading dose was usually twenty-five percent of the sleeping doses. To request sleep, patients could press a button on a hand-held device to send a signal to the microprocessor controlling the syringe driver, which delivers a pre-determined dose of Dex via an intravenous cannula. Additionally, the PCSL device enables patients to self-administer by pressing the button whenever they wake up during the night. HR and peripheral arterial oxygen saturation (SpO₂) were monitored overnight by specially trained nurses during sleep in a sound-insulated ward. BP and respiratory rate (RR) were monitored 1 h after PCSL administration. The rescue protocol was the same as described in the rescue protocol section.

Adverse Events Assessment

Adverse effects were also recorded by a physician (Wang Y) throughout the treatment period, such as nausea, vomiting, dizziness, headache, tinnitus, itching, dyspnea, respiratory depression, fluctuation of BP, and HR reduction.

Assessment of Sleep

The Pittsburgh Sleep Quality Index (PSQI) is a self-reported questionnaire to assess sleep quality over a 1-month time interval. PSQI has 19 individual items and reflects seven different dimensions of sleep, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficacy, sleep disturbances, sleep medication, and daytime dysfunction. The sum of seven components generates a global PSQI score ranging from 0 to 21, with a higher score representing poorer subjective sleep quality.¹⁹ PSQI was assessed in three different periods: before the first treatment, the first morning after the last treatment, and 6 months after the last treatment.

Psychometric Evaluation

Chinese versions of the Symptom Checklist 90 (SCL-90), Hamilton Depression Scale (HAMD) and Hamilton Anxiety Scale (HAMA) were collected during three different time periods: before the first treatment, first morning after the last treatment, and 6 months after the last treatment. SCL-90 scores ≥ 160 are considered as existing mild

psychological problems; therefore, this study used “1” to indicate a score ≥ 160 , and “0” to indicate a score < 160 .

Follow-Up

Patients were recalled for follow-up clinical visits 6 months after the last treatment. The score of PSQI, SCL-90, HAMD and HAMA were collected by telephone enquiries and online questionnaires. Follow-up interviews were performed by two physicians who were not involved in the clinical procedure. All personal information were recorded at the Case Record Form (CRF) and be kept strictly confidential for research purposes only. The research team members will be responsible for maintaining personal data.

Statistical Analysis

Statistical analyses were performed with Statistical Package for Social Sciences (SPSS) 22.0. Variables with normal distributions were expressed as mean $\pm$ standard deviation (SD). Categorical data were presented as percentages. Comparisons of differences before and after treatment were with paired *t*-tests. Comparisons of differences between groups were examined with an independent sample *t*-test. A *p*-value of < 0.05 was considered to be statistically significant.

Results

Characteristics of the Patients

Patients' characteristics for all 20 cases are shown in [Tables 1 and 2](#). There were 12 (60%) females and 8 (40%) males, mean age was 49.60 (± 11.32) years, and the duration of insomnia was on average 8.46 (± 8.31) years. The clinical laboratory tests of patients before treatment were listed in [Supplemental Table 1](#). The previous psychiatric diagnoses were presented in [Supplemental Table 2](#). All of the participants had previously received treatment for insomnia.

Dex Titration

All 20 patients accepted Dex titration. The depth of sedation (MOAAS decreasing from 5 to 2) was associated with increasing dosage of Dex. As shown in [Figure 2](#), the mean dosages of Dex required to achieve MOAAS levels 4, 3 or 2, which are similar to drowsy, light sleep and deep sleep, were 21.54 (± 11.44) mcg, 34.69 (± 16.16) mcg and 54.31 (± 31.96) mcg, respectively.

During this process, HR significantly decreased ($*P < 0.05$) from 66.30 (± 10.25) to 58.20 (± 6.43) as the MOAAS decreased from 5 to 4, with a decreasing amplitude of 11.61 (± 6.14) %. During decreasing values of MOAAS from 4, 3, to 2, the HR remained stable although

Table 1 Patient Characteristics

Patient No.	Age (Year)	Gender	Duration of Insomnia (Years)	Weight (kg)	BMI (kg/m ²)	HR (BPM)	BSP (mmHg)	BDP (mmHg)
1	41	F	0.25	58	22.4	72	120	70
2	46	F	10	51	21.1	70	120	70
3	67	M	1	73	23.9	55	130	75
4	57	F	12	69	25.1	80	108	67
5	49	M	10	N/A	N/A	78	130	80
6	56	M	10	74.5	25.8	71	135	75
7	46	F	3	50	20.8	60	95	60
8	69	M	20	65	24.5	78	125	76
9	57	M	1	65	25.4	78	140	60
10	41	F	6	54	22.8	64	93	59
11	35	F	10	48	17.8	78	99	59
12	61	F	5	64	24.7	60	127	71
13	46	F	10	65	23.6	72	130	82
14	57	F	2	65	25.4	60	132	75
15	41	M	30	68	24.4	71	138	88
16	27	M	1.5	76	N/A	78	130	78
17	40	M	5	74	23.7	63	118	75
18	66	F	26	62	24.3	78	111	67
19	49	F	2.5	66	21.0	56	110	55
20	41	F	4	59	23.0	56	127	69

Abbreviations: BDP, baseline diastolic pressure; BMI, body mass index; BPM, beats per minute; BSP, baseline systolic pressure; HR, heart rate; M, male; N, normal; N/A, not available; F, female.

Table 2 Patient General Characteristics

Variables	Patients
Age (years)	49.60±11.32
Gender, n (%)	
Male	40
Female	60
BMI (kg/m ²)	23.31±2.14
Baseline heart rate (BPM)	68.90±8.80
Baseline systolic pressure (mmHg)	120.90±14.00
Baseline diastolic pressure (mmHg)	70.55±8.73
Duration of insomnia (years)	8.46±8.31

Abbreviations: BMI, body mass index; BPM, beats per minute.

the dosage of Dex was increasing. Although SBP/DBP decreased slightly from 118.10 (±17.72)/69.60 (±12.09) mmHg to 112.80 (±20.86)/66.20 (±11.47) mmHg as the sedation level changed from 5 to 2, these changes were not statistically significant. In addition, no statistically significant changes in SpO₂ and RR were recorded during Dex titration. Further details are provided in [Figure 3](#).

Discontinuation of PCSL

Five of the 20 patients received no further treatment for various reasons after the Dex titration. Among them, three patients (Patient #3, 12 and 13) suffered heart rate decreases below 50 bpm, one patient (Patient #9) had a blood pressure fluctuation over 20% of the baseline, yet none of these side effects required medication treatment, and one patient (Patient #8) voluntarily gave up treatment due to the perception of inefficacy. No patient developed fever, sepsis or other systemic toxic effects.

Figure 2 Dosage of dexmedetomidine (Dex) required in different sedation level measured by Modified Observer's Assessment of Alertness/Sedation (MOAAS).

Outcomes

Fifteen (ten women, five men) of the 20 participants adhered to the treatment protocol. Vital signs, results of the physical, electrocardiographic, and clinical laboratory examinations did not vary before and after treatment. The sleep assessments for all fifteen patients are shown in [Table 3](#). The PSQI score significantly decreased (**P*<0.05) from 14.33 (± 3.66) to 8.40 (± 6.15) after treatment. The follow-up score was 10.26 (± 6.13), which is also significantly decreased (**P*<0.05) than pre-treatment. Among these fifteen, three patients (Patient # 14, 15, 16) failed to sleep at night after PCSL, twelve patients had improved sleep quality after PCSL. The treatment time of patients varied from several days to four months. During the final follow-up, five patients (Patient # 2, 5, 6, 11, 19) achieved improved sleep quality during treatment, but insomnia recurred after cessation of treatment. Seven patients (Patient # 1, 4, 7, 10, 17, 18, 20) had lower PQSI scores 6 months after the treatment than before, among which, the PQSI score of three patients (Patient # 1, 10, 17) was below 5 and their sleep quality was significantly improved, and rarely needed additional hypnotics for insomnia.

As shown in [Table 4](#), all patients were in a state of anxiety or depression, and six of them had mild psychological problems before treatment. HAMA significantly decreased (**P*<0.05) from 17.00 (±9.99) to 11.27 (±8.40) after treatment. The follow-up score was 10.46 (± 8.26). Anxiety assessed by the HAMA at the follow-up was significantly reduced (**P*<0.05) compared to the pre-treatment. The HAMD score was 14.33 (± 3.66) pre-treatment, 8.40 (± 6.15) post-treatment, and 12.31 (±9.89) in follow-up periods. HAMD scores of patients in the post-treatment and follow-up periods were significantly lower than pre-treatment (**P*<0.05).

Interestingly, patient #17 received treatment for four months. This patient required 3 to 4 different kinds of hypnotics, including clonazepam, zolpidem, oxazepam, and continued these hypnotics at the time of initiation of PCSL. Between the first to ninth treatments, the dosage of hypnotics was gradually reduced and at the ninth treatment, clonazepam and zolpidem were discontinued. After the sixteenth treatment, oxazepam was also stopped completely. Although the dosage of Dex required for sleep increased with the initial withdrawal of the hypnotic drugs, following discontinuation of all hypnotics the Dex dose gradually decreased. After treatment, the score of PSQI, HAMA and HAMD was significantly reduced. Further details are provided in [Figure 4](#).

Figure 3 The vital signs change during different sedation levels. Trajectory of the change in the (A) heart rate (HR) in beats per minute, (B) systolic blood pressure (SBP) and diastolic blood pressure (DSB) in mmHg, (C) peripheral arterial oxygen saturation (SpO₂) and (D) respiratory rate (RR) in breaths per minute according to the sedation level measured by Modified Observer's Assessment of Alertness/Sedation (MOAAS) (* $P < 0.05$).

Discussion

Our study suggests that PCSL is feasible for the treatment of chronic intractable insomnia when introduced specifically as two separate processes: Dex titration followed by PCSL administration. The first process is used as a preliminary experience for PCSL administration. The titration process showed that the dosage of Dex varied widely among patients, which may be due to the difference in liver metabolic activity or differences in expression at the level of the alpha-2 adrenergic receptors or other factors. Considering this individual variability, it is important to obtain the appropriate dosage for patients with the initial titration stage to set the parameters for PCSL. Additionally, five of the twenty patients received no further treatment for side effects or other reasons after Dex titration. The most frequently reported adverse effects associated with Dex in published reports include hypotension, hypertension and bradycardia, which are closely related to the loading dose and infusion rate. So, it is necessary to select

patients carefully and to determine appropriate dosage of Dex regarding safety.

This finding demonstrates that PCSL can improve the subjective assessment of sleep immediately after therapy in 12/15 patients with chronic intractable insomnia, and 7/12 patients achieved continuously improved sleep quality in our follow-up. Dex exerts its hypnotic action through selective activation of central pre- and post-synaptic alpha-2 adrenergic receptors in the locus coeruleus. It inhibits locus coeruleus-derived noradrenergic neurotransmission to the ventrolateral preoptic nucleus (VLPO), thus disinhibiting the VLPO and provoking an inhibition of cortical arousal nuclei.²⁰ Akeju et al posited that the altered arousal states induced with the administration of Dex neurophysiologically approximates natural sleep and he termed this "biomimetic" sleep.²¹ This seems to be a more appropriate term to define this method, i.e., Patient-controlled Biomimetic Sleep.

The mechanism for long-term recovery from chronic intractable insomnia after PCSL is still unclear. One possible mechanism may be attributed to Dex's neuroprotective

Table 3 Effect of Patient-Controlled Sleep

Patient No.	No. of Treatments	Pre-Treatment PSQI	Post-Treatment PSQI	6 Months Follow-Up PSQI
1	100	15	6	4
2	6	16	3	11
4	12	9	3	7
5	6	10	9	11
6	7	12	4	12
7	5	14	8	8
10	14	14	0	0
11	7	9	6	8
14	6	15	13	15
15	5	19	19	19
16	7	21	21	21
17	117	15	12	4
18	30	16	7	10
19	5	19	16	19
20	30	11	5	5

Abbreviation: PSQI, Pittsburgh Sleep Quality Index.

effects. Sleep deprivation can lead to neuronal injury and waste products accumulating in the brain.^{22,23} Animal experiments have shown that Dex can attenuate neuroapoptosis,²⁴ exerting a protective effect on neuronal injury,²⁵ and thereby protecting cognitive function.²⁶ In addition, the glymphatic system is a cerebrospinal fluid-

interstitial fluid exchange system dependent on the water channel aquaporin-4 that is normally polarized on astrocyte end-feet. This is proposed to account for the clearance of abnormal proteins (eg, β -amyloid) and metabolites (eg, lactate) from the brain.²⁷ Noradrenaline (NE) is a key neurotransmitter to regulate the function of the glymphatic system. Dex can decrease NE release, producing a substantial decrease in the volume of the interstitial (extracellular) space, allowing streams of water to pass through them increasing the clearance of waste products in the brain.²⁸ Another possible mechanism could be that comfortable sleep after PCSL helps patients to restore their sleep homeostasis.

Dex has a distribution half-life of about 6 minutes and an elimination half-life of approximately 2 hours.²⁹ It is metabolized in the liver by glucuronization and CYP2A6 hydroxylation and then excreted primarily in the urine. Research shows that Dex could inhibit CYP-450 isoenzyme 3A4 and interfere with the metabolism of some drugs, such as valdecoxib and tacrolimus.^{30,31} Therefore, in clinical application, attention should be paid to the possible drug-drug interactions or adverse reactions caused by the combination of Dex with these and other drugs.

Three patients treated with PCSL did not achieve satisfactory clinical efficacy. Among them, one patient with insomnia was caused by jugular vein thrombosis, which may lead to tinnitus and cerebral blood insufficiency, and

Table 4 Psychometric Evaluation

Patient No.	Pre-Treatment			Post-Treatment			6 Months Follow-Up		
	HAMA (Score)	HAMD (Score)	SCL-9	HAMA (Score)	HAMD (Score)	SCL-90	HAMA (Score)	HAMD (Score)	SCL-90
1	16	20	1	6	10	0	5	13	0
2	20	23	1	13	11	1	14	16	1
4	7	8	0	7	6	0	7	6	0
5	2	10	0	3	10	0	N/A	N/A	N/A
6	16	16	0	13	16	0	N/A	N/A	N/A
7	18	30	1	10	23	0	13	23	1
10	14	5	0	3	5	0	1	1	0
11	35	22	1	20	20	1	23	21	1
14	8	8	0	8	8	0	5	8	0
15	24	14	1	20	15	1	26	14	1
16	24	38	1	25	32	1	20	36	1
17	37	32	1	28	24	1	8	6	0
18	16	7	0	3	6	0	2	4	0
19	12	13	0	8	10	0	10	10	0
20	6	35	0	2	7	0	2	2	0

Abbreviations: HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; N/A, not available; SCL-90, Symptom Checklist 90.

Figure 4 The dosage of dexmedetomidine (Dex) applied over the number of treatments in Patient #17.

we speculated that PCSL was not effective because the patient's insomnia resulted from complications of jugular vein thrombosis. The other two patients who failed to achieve the desired effect may not have received an adequate dose of Dex; however, the parameters were determined by titration. We speculate that there may be a diurnal difference in the dosage of Dex required by the body, and the titration obtained during the day may be different from that required at night. A re-application of the Dex titration may be helpful in resetting or determining parameters.

Individuals suffering from insomnia are more likely to report emotional distress, including anxiety disorders and depression, and recurrent health problems.³² Recently, genomic studies have also demonstrated a genetic correlation between insomnia and psychiatric traits, and identified a causal effect of insomnia on depression.^{33,34} Most of the included patients were noted to be suffering with both anxiety and depression, which was alleviated after PCSL. It is possible that the sedative effect of Dex may be useful in relieving the anxiety and depression that accompanies insomnia. It is also possible that psychological problems could be reduced after sleep quality is improved.

PCSL requires a procedure in a post-anesthesia care unit staffed by a team of health-care professionals and an inpatient stay. These resource and cost requirements limit access compared to other conventional treatments.

Nevertheless, for patients with chronic intractable insomnia, who were unsuccessfully treated with currently available therapeutic methods, PCSL could serve as a new treatment option. Patients' demands are used to trigger a suitable infusion bolus dose for achieving an individually stable effective dose. The pharmacokinetic properties of Dex, particularly its rapid re-distribution,²⁹ and pharmacological effect that produces biomimetic sleep makes it suitable for PCSL. However, the available literature describing safety, dosing, and interactions, especially with long-term use, remains limited. Physicians will need to more rigorously evaluate the risks of long-term use.

Limitations

This study has a small sample size. Therefore, large-scale multi-center clinical studies should be conducted to provide more robust evidence to assess long-term efficacy. Secondly, the data of actigraphy and polysomnography were not recorded at the CRF nor processed statistically. Thirdly, questionnaires to evaluate life quality and lifestyle changes, eg, The MOS item short form health survey (SF-36), were not administered. Fourthly, there are few reports with small subject numbers describing the safety of dexmedetomidine with long-term use. The potential side effects of long-term use of Dex are undetermined and may be a possible safety concern.

Conclusions

To the best of our knowledge, this is the first report to present that Dex PCSL might be a potential treatment for patients with chronic intractable insomnia who respond well to Dex. However, it is an off-label use and the long-term efficacy needs further evaluation.

Data Sharing Statement

All relevant data are within the paper and its supporting information files.

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Disclosure

The authors report no conflicts of interest in this work.

References

- Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev*. 2002;6(2):97–111. doi:10.1053/smr.2002.0186
- Fan TT, Chen WH, Shi L, et al. Objective sleep duration is associated with cognitive deficits in primary insomnia: BDNF may play a role. *Sleep*. 2019;42.
- Equihua-Benitez AC, Guzman-Vasquez K, Drucker-Colin R. Understanding sleep-wake mechanisms and drug discovery. *Expert Opin Drug Discov*. 2017;12(7):643–657. doi:10.1080/17460441.2017.1329818
- Brietzke E, Vazquez GH, Kang MJY, Soares CN. Pharmacological treatment for insomnia in patients with major depressive disorder. *Expert Opin Pharmacother*. 2019;20:1341–1349.
- Terzano MG, Rossi M, Palomba V, Smerieri A, Parrino L. New drugs for insomnia: comparative tolerability of zopiclone, zolpidem and zaleplon. *Drug Saf*. 2003;26(4):261–282. doi:10.2165/00002018-200326040-00004
- Manconi M, Ferri R, Miano S, et al. Sleep architecture in insomniacs with severe benzodiazepine abuse. *Clin Neurophysiol*. 2017;128(6):875–881. doi:10.1016/j.clinph.2017.03.009
- Lehmann KA. New developments in patient-controlled postoperative analgesia. *Ann Med*. 1995;27:271–282.
- Cook LB, Lockwood GG, Moore CM. True patient-controlled sedation. *Anaesthesia*. 2007;48(12):1039–1044. doi:10.1111/j.1365-2044.1993.tb07521.x
- Rudkin GE, Osborne GA, Finn BP, Jarvis DA, Vickers D. Intraoperative patient-controlled sedation. Comparison of patient-controlled propofol with patient-controlled midazolam. *Anaesthesia*. 1992;47(5):376–381. doi:10.1111/j.1365-2044.1992.tb02216.x
- Chlan LL. Engaging critically ill patients in symptom management: thinking outside the box! *Am J Crit Care*. 2016;25(4):293–300. doi:10.4037/ajcc2016932
- Gerlach AT, Murphy CV, Dasta JF. An updated focused review of dexmedetomidine in adults. *Ann Pharmacother*. 2009;43(12):2064–2074. doi:10.1345/aph.1M310
- Wu XH, Cui F, Zhang C. Low-dose dexmedetomidine improves sleep quality pattern in elderly patients after noncardiac surgery in the intensive care unit: a pilot randomized controlled trial. *Anesthesiology*. 2016;125:979–991. doi:10.1097/ALN.0000000000001325
- Huopponen E, Maksimow A, Lapinlampi P. Electroencephalogram spindle activity during dexmedetomidine sedation and physiological sleep. *Acta Anaesthesiol Scand*. 2008;52(2):289–294. doi:10.1111/j.1399-6576.2007.01537.x
- Weerink MAS, Struys MMRF, Hannivoort LN. Clinical pharmacokinetics and pharmacodynamics of dexmedetomidine. *Clin Pharmacokinet*. 2017;56(8):893–913. doi:10.1007/s40262-017-0507-7
- World Medical Association. World medical association declaration of helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191–2194. doi:10.1001/jama.2013.281053
- Riemann D, Spiegelhalter K, Feige B. The hyperarousal model of insomnia: a review of the concept and its evidence. *Sleep Med Rev*. 2010;14(1):19–31. doi:10.1016/j.smr.2009.04.002
- Chernik DA, Gillings D, Laine H. Validity and reliability of the observer's assessment of alertness/sedation scale: study with intravenous midazolam. *J Clin Psychopharmacol*. 1990;10:244–251.
- Koelsch S, Heinke W, Sammler D, Olthoff D. Auditory processing during deep propofol sedation and recovery from unconsciousness. *Clin Neurophysiol*. 2006;117(8):1746–1759. doi:10.1016/j.clinph.2006.05.009
- Tsai PS, Wang SY, Wang MY. Psychometric evaluation of the Chinese version of the Pittsburgh Sleep Quality Index (CPSQI) in primary insomnia and control subjects. *Qual Life Res*. 2005;14(8):1943–1952. doi:10.1007/s11136-005-4346-x
- Guldenmund P, Vanhaudenhuyse A, Sanders RD. Brain functional connectivity differentiates dexmedetomidine from propofol and natural sleep. *Br J Anaesth*. 2017;119(4):674–684. doi:10.1093/bja/aex257
- Akeju O, Hobbs LE, Gao L, et al. Dexmedetomidine promotes biomimetic non-rapid eye movement stage 3 sleep in humans: a pilot study. *Clin Neurophysiol*. 2018;129(1):69–78. doi:10.1016/j.clinph.2017.10.005
- Alkadhi K, Zagaar M, Alhaider I. Neurobiological consequences of sleep deprivation. *Curr Neuropharmacol*. 2013;11(3):231–249. doi:10.2174/1570159X11311030001
- Shokri-Kojori E, Wang GJ, Wiers CE. β -Amyloid accumulation in the human brain after one night of sleep deprivation. *Proc Natl Acad Sci U S A*. 2018;115(17):4483–4488. doi:10.1073/pnas.1721694115
- Lv J, Wei Y, Chen Y. Dexmedetomidine attenuates propofol-induced neuroapoptosis partly via the activation of the PI3K/Akt/GSK3 β pathway in the hippocampus of neonatal rats. *Environ Toxicol Pharmacol*. 2017;52:121–128. doi:10.1016/j.etap.2017.03.017
- Ma D, Hossain M, Rajakumaraswamy N. Dexmedetomidine produces its neuroprotective effect via the α 2A-adrenoceptor subtype. *Eur J Pharmacol*. 2004;502(1–2):87–97. doi:10.1016/j.ejphar.2004.08.044
- Sanders RD, Xu J, Shu Y. Dexmedetomidine attenuates isoflurane-induced neurocognitive impairment in neonatal rats. *Anesthesiology*. 2009;110(5):1077–1085. doi:10.1097/ALN.0b013e31819daedd
- Xie L, Kang H, Xu Q. Sleep drives metabolite clearance from the adult brain. *Science*. 2013;342(6156):373–377. doi:10.1126/science.1241224
- Fuxe K, Agnati LF, Marcoli M, Borroto-Escuela DO. Volume transmission in central dopamine and noradrenaline neurons and its astroglial targets. *Neurochem Res*. 2015;40(12):2600–2614. doi:10.1007/s11064-015-1574-5
- Nguyen V, Tiemann D, Park E, Salehi A. α -2 agonists. *Anesthesiol Clin*. 2017;35(2):233–245. doi:10.1016/j.anclin.2017.01.009

30. Hu J, Lv BF, Guo WJ, et al. Effects of dexmedetomidine on the pharmacokinetics of parecoxib and its metabolite valdecoxib in beagles by UPLC-MS/MS. *Biomed Res Int*. 2020;1563874.
31. Stiehl SR, Squires JE, Bucuvalas JC, et al. Tacrolimus interaction with dexmedetomidine—a case report. *Pediatr Transplant*. 2016;20(1):155–157. doi:10.1111/ptr.12618
32. Morgan K, Dixon S, Mathers N, Thompson J, Tomeny M. Psychological treatment for insomnia in the regulation of long-term hypnotic drug use. *Health Technol Assess*. 2004;8(8):1–68. doi:10.3310/hta8080
33. Jansen PR, Watanabe K, Stringer S. Genome-wide analysis of insomnia in 1,331,010 individuals identifies new risk loci and functional pathways. *Nat Genet*. 2019;51(3):394–403. doi:10.1038/s41588-018-0333-3
34. Lane JM, Jones SE, Dashti HS. Biological and clinical insights from genetics of insomnia symptoms. *Nat Genet*. 2019;51(3):387–393. doi:10.1038/s41588-019-0361-7

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