ANESTHESIOLOGY

Oral Dexmedetomidine Promotes Non-rapid Eye Movement Stage 2 Sleep in Humans

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Dexmedetomidine is an alpha-2 adrenergic agonist sedative that is approved for intravenous use
- A continuous infusion of dexmedetomidine promotes non–rapid eye movement stage 2 sleep neurophysiology
- A single nighttime loading dose of intravenous dexmedetomidine in healthy volunteers promotes non–rapid eye movement stage 3 sleep neurophysiology

What This Article Tells Us That Is New

- The hypothesis that oral dexmedetomidine would promote non–rapid eye movement stage 2 sleep was tested in a single-center, randomized, double-blind, crossover trial in 15 healthy volunteers
- Oral dexmedetomidine increased the duration of non–rapid eye movement stage 2 sleep by 63 (95% CI, 19 to 107) min
- Oral dexmedetomidine may impair sleep-dependent motor memory consolidation

ABSTRACT

Background: The administration of dexmedetomidine is limited to highly monitored care settings because it is only available for use in humans as intravenous medication. An oral formulation of dexmedetomidine may broaden its use to all care settings. The authors investigated the effect of a capsule-based solid oral dosage formulation of dexmedetomidine on sleep polysomnography.

Methods: The authors performed a single-site, placebo-controlled, randomized, crossover, double-blind phase II study of a solid oral dosage formulation of dexmedetomidine (700 mcg; n = 15). The primary outcome was polysomnography sleep quality. Secondary outcomes included performance on the motor sequence task and psychomotor vigilance task administered to each subject at night and in the morning to assess motor memory consolidation and psychomotor function, respectively. Sleep questionnaires were also administered.

Results: Oral dexmedetomidine increased the duration of non-rapid eye movement (non-REM) stage 2 sleep by 63 (95% CI, 19 to 107) min ($P = 0.010$) and decreased the duration of rapid eye movement (REM) sleep by 42 (5 to 78) min ($P = 0.031$). Overnight motor sequence task performance improved after placebo sleep (7.9%; $P = 0.003$) but not after oral dexmedetomidine–induced sleep (–0.8%; $P = 0.900$). In exploratory analyses, we found a positive correlation between spindle density during non-REM stage 2 sleep and improvement in the overnight test performance (Spearman rho = 0.57; $P = 0.028$; n = 15) for placebo but not oral dexmedetomidine (Spearman rho = 0.04; $P = 0.899$; n = 15). Group differences in overnight motor sequence task performance, psychomotor vigilance task metrics, and sleep questionnaires did not meet the threshold for statistical significance.

Conclusions: These results demonstrate that the nighttime administration of a solid oral dosage formulation of dexmedetomidine is associated with increased non-REM 2 sleep and decreased REM sleep. Spindle density during dexmedetomidine sleep was not associated with overnight improvement in the motor sequence task.

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Dexmedetomidine is an alpha-2 adrenergic agonist sedative medication that patterns the activity of various arousal nuclei similar to sleep.[1–7] We recently demonstrated that a single nighttime loading dose of intravenous dexmedetomidine in healthy volunteers promoted non–rapid eye movement (non-REM) stage 3 sleep.[8] This result suggested that continuous infusions of dexmedetomidine may not be necessary for sleep promotion and that dexmedetomidine could be developed as an oral sleep-enhancing medication. We note that a continuous infusion of dexmedetomidine in humans produces electroencephalogram spindle (13 to 16 Hz) and slow-delta (0.1 to 4 Hz) oscillations that approximate non-REM stage 2 sleep.[9–13] However, dexmedetomidine-induced non-REM stage 2 and non-REM stage 3 sleep may depend on the pharmacokinetic profile

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associated with the route of administration or the timing of drug administration (*i.e.*, nighttime *vs.* daytime).

Dexmedetomidine is widely used in intensive care units as a sedative agent and as a pharmacologic aid to reduce the incidence and duration of delirium.[14–18] The administration of dexmedetomidine is limited to highly monitored care settings because it is only available for use as an intravenous medication. An oral formulation may broaden the use and benefits of dexmedetomidine to patients in general medical and surgical units. An oral formulation of dexmedetomidine may also provide evidence to support its use in patients with sleep onset or maintenance disorders. We note that the intravenous formulation of dexmedetomidine has been administered preoperatively as an oral anxiolytic solution.[19] However, whether an oral dosage formulation of dexmedetomidine has a sedative or sleep-promoting effect in humans is not clear.

Therefore, we investigated the effect of a capsule-based solid oral dosage formulation of dexmedetomidine in a phase II (n = 15) polysomnography study. Because oral dexmedetomidine is expected to more closely approximate a continuous infusion compared to a loading dose, we hypothesized that it would increase the duration of non-REM stage 2 sleep. Sleep spindles, a characteristic electroencephalogram feature of non-REM stage 2 sleep,[11,20] have been associated with improved motor sequence task performance (sleep-dependent memory consolidation).[20] Therefore, we also hypothesized that the solid oral dosage formulation of dexmedetomidine would be associated with improved performance on the motor sequence task. Finally, we hypothesized that dexmedetomidine would not affect performance on the psychomotor vigilance task.

Materials and Methods

Ethics Statement

The Partners Human Research Committee (Boston, Massachusetts) approved this human research study conducted at the Massachusetts General Hospital, Boston, Massachusetts (2016P000269), and it was registered on clinicaltrials.gov (NCT02818569) on June 29, 2016 (Principal Investigator: Oluwaseun Akeju). This study was conducted under a Food and Drug Administration (Silver Spring, Maryland) investigator-initiated Investigational New Drug Application (IND129461). A Data and Safety Monitoring Board was charged with the safety of study volunteers and the scientific goals of the study being met.

Subject Selection

A phase I dose-finding study (n =15) was first performed. The primary endpoint for the phase I study was hemodynamic stability. Our Data and Safety Monitoring Board approved the use of 700 mcg for this phase II sleep study. The maximum mean ± SD plasma concentration of this dose of oral dexmedetomidine was 0.38 ± 0.44 ng/ml.[21] This occurred 120 min after drug administration. The mean plasma concentration at the last sampling timepoint, which occurred 420 min after drug administration, was 0.14 ± 0.20 ng/ml. Subjects were recruited for this phase II study between July 2017 and April 2018. A study flyer was disseminated through the Partners Public Affairs (Boston, Massachusetts) distribution list. Potential study participants contacted a clinical research coordinator, who administered a questionnaire to confirm that the study inclusion and exclusion criteria were met. The following information was also verified by self-report: regular sleep-wake cycles, absence of naps or consumption of alcohol or caffeinated beverages before sleep, drug-free, and nonsmoking status. Before potential enrollment, subjects underwent a complete medical history and standard preanesthesia assessment. Other procedures included a toxicology screen to rule out prohibited drug use, a pregnancy test for females, and an electrocardiogram to rule out cardiac conduction abnormalities. None of the subjects had any known history of sleep disorders or any physical or psychiatric illness. Written informed consent was obtained from a total of 16 right-handed subjects during the screening visit. One subject withdrew from participation before any experimental study visits due to scheduling conflicts. All subjects were American Society of Anesthesiologists (Schaumburg, Illinois) Physical Status I.

Drug Allocation

Dexmedetomidine hydrochloride, United States Pharmacopeia, purchased from Jiangsu Hengrui Medicine Company Limited (China), was weighed in a laminar flow hood and packaged in oral capsules with an inert excipient. The placebo capsule contained only the inert excipient (lactose powder). The order of drug administration was determined by a computer-generated randomization schedule generated by the clinical trials pharmacist. Allocation concealment was ensured by the fact that dexmedetomidine and placebo capsules could not be distinguished based on appearance. The randomization key associated with each participant trial identification number remained with the clinical trial pharmacist for the duration of the study. All trial medications were labeled as "dexmedetomidine or placebo" to preserve the integrity of randomization assignments. The study nurse taking care of the subject administered the medications.

Polysomnography

This was a single-site, placebo-controlled, double-blind, randomized, controlled, crossover study to assess the effect of a 700-mcg capsule-based solid oral dosage formulation of dexmedetomidine (n = 15) on objective and subjective measures of sleep quality. Study subjects were instructed to arrive at Massachusetts General Hospital at 17:00 h to

prepare for overnight polysomnography recording. Data were recorded using the Somté PSG (Compumedics, USA). Electroencephalogram (six channels: two frontal, two central, two occipital), electrooculogram, and electromyogram were placed according to the American Academy of Sleep Medicine (Darien, Illinois) practice standards. Each study subject underwent three polysomnography study visits, with the first visit serving to acclimate subjects to the sleep environment and polysomnography recording equipment. A urine toxicology screen was performed at each of three study visits to rule out the use of prohibited substances. Additionally, a urine pregnancy test was performed to rule out pregnancy in all female subjects.

After the acclimation night, subjects were randomly assigned to receive dexmedetomidine or placebo. We employed a placebo-dexmedetomidine/dexmedetomidine-placebo (two periods, two treatments) design. Thus, all subjects received dexmedetomidine and placebo but on separate study visits. Our randomization procedure resulted in seven subjects in the placebo-dexmedetomidine group, and eight subjects were in the dexmedetomidine-placebo group. The experimental overnight polysomnography visits were separated by at least a 48-h washout period. This washout period was based on the pharmacokinetic properties of dexmedetomidine. Immediately before lights-out, subjects were required to perform the PM motor sequence task (training) followed by the PM psychomotor vigilance task (training). Drug administration followed by lights-out occurred at 21:00 h. Trained nursing staff monitored video surveillance, heart rate, and oxygen saturation levels overnight. Subjects were instructed to silence their electronic devices, and the use of cell phones throughout the night was strictly prohibited. Lights-on occurred at 07:00 h the next morning. Immediately after lights-on, subjects were required to perform the AM motor sequence task (testing) followed by the AM psychomotor vigilance task (testing). Polysomnography data were scored using validated automated sleep scoring software.[22] Sleep spindles were manually picked from a central electroencephalogram channel during non-REM stage 2 sleep in the spectral domain by a blinded investigator (S.M.).[23] This approach is sensitive to sleep spindles that are not easily discerned in the time domain (*i.e.*, due to low power).[23]

Motor Sequence Task

The motor sequence task has previously been described.[24,25] The motor sequence task involves pressing four keys with the fingers of the left hand, repeating a five-digit sequence quickly and accurately for 30 s (fig. 1A). We employed different sequences (*e.g.*, 4-1-3-2-4 and 1-4-2-3-1) for each sleep visit, and their order was counterbalanced within groups. There is no known transfer of learning between sequences on this task.[26] The sequence was displayed at the top of the screen, and dots appeared beneath it with each keystroke. During both training (evening) and testing (morning) sessions, participants alternated tapping and rest periods of 30 s each for a total of 12 tapping trials. Motor sequence task performance was measured as the number of correctly typed five-digit sequences per trial. The primary dependent measure for the motor sequence task was overnight improvement, which is calculated as the percent improvement in correct sequences from the average of the last three training trials to the average of the first three test trials.[25,27]

Psychomotor Vigilance Task

The psychomotor vigilance task was also administered. The psychomotor vigilance task is a computerized reaction task that measures the response times to visual stimuli. These stimuli were presented at random intervals (2 to 10 s) for 10 min. Subjects were trained on the psychomotor vigilance task before the onset of sleep and then tested in the morning. The primary dependent measures for the psychomotor vigilance task were the number of responses that were longer than 400 ms (lapse 400) and the mean response times.

Statistical Analysis

An *a priori* sample size calculation was not performed. Our sample size was approved by the Food and Drug Administration after they weighed potential risks and benefits and the results of our previous study. Data from the acclimation night visits were not analyzed. We analyzed differences between training and testing motor sequence task (psychomotor vigilance task) measures using the two-sample paired *t* test. For group-level inferences, we analyzed polysomnography, sleep questionnaire, motor sequence task, and psychomotor vigilance task difference data using a statistical approach for the placebo-dexmedetomidine/dexmedetomidine-placebo (two periods, two treatments) design. We first obtained an individual paired difference for each metric. The paired differences were then used in a two-sample *t* test to test the difference between the periods, which is equivalent to the treatment effect.

We computed Spearman rho correlation between overnight motor sequence task improvement and spindle density (and spindle count) before and after data imputation (n = 2 data points were imputed for the dexmedetomidine and placebo visits, respectively). Imputed data are expectations conditional on the nonmissing data. The mean and covariance matrix, which was estimated using the restricted maximum likelihood approach, was used for the imputation calculation. Data imputation and all analyses were performed using JMP, Pro 14 (SAS Institute Inc., USA). All tests were two-sided with alpha = 0.05.

Results

Polysomnography

Oral Dexmedetomidine Biased the Sleep Architecture toward non-REM Stage 2 Sleep. All subjects were required to lie in bed for 10 h. One subject's sleep data for the placebo visit

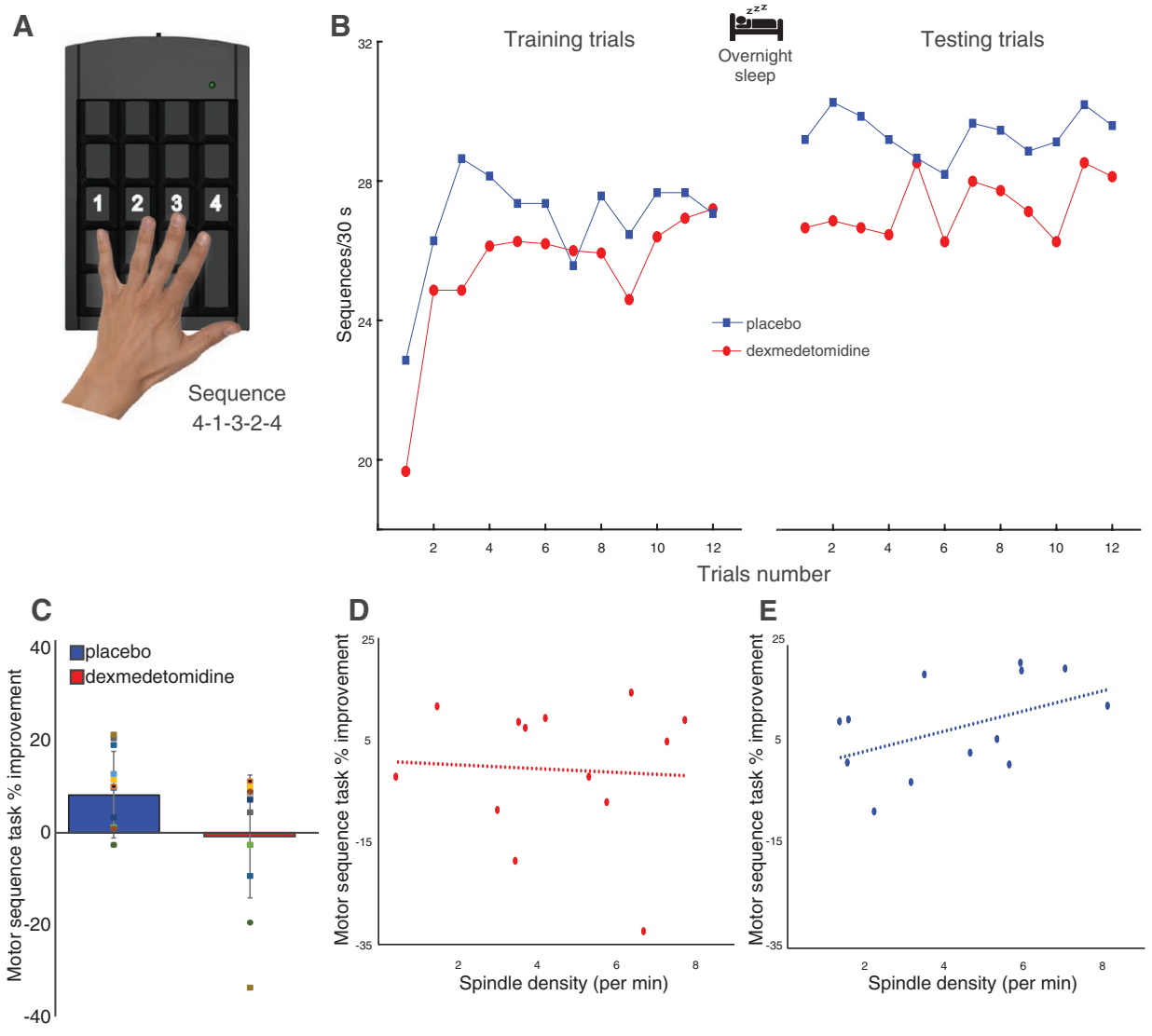

Fig. 1. Motor sequence task performance. (*A*) The motor sequence task involves typing a five-digit sequence (4-1-3-2-4) as quickly and correctly as possible for 12 rounds of 30-s intervals. (*B*) Motor sequence task performance during both the placebo and dexmedetomidine study visits. Placebo visits showed visibly improved overnight performance (average of first three testing sequences – average of last three training sequences), whereas oral dexmedetomidine immediate performance appeared similar between training and testing sessions. (*C*) Improvement in motor sequence task performance (%) met our threshold for statistical significance for the placebo ($P = 0.003$) but not for the dexmedetomidine ($P = 0.900$) study visits. There were no statistically significant differences in immediate ($P = 0.078$) performance between groups. (*D*) Spindle density during non-REM stage 2 sleep and overnight motor sequence task improvement after oral dexmedetomidine were not correlated (Spearman rho = 0.1, $P = 0.748$, n = 13; Spearman rho = 0.1, $P = 0.820$, n = 15 after data imputation). (*E*) We confirmed the previously described[25,27] positive correlation between spindle density during non-REM stage 2 sleep and overnight motor sequence task improvement after placebo (Spearman rho = 0.54, $P = 0.058$, n = 13; Spearman rho = 0.57, $P = 0.028$, n = 15 after data imputation). MST, motor sequence task.

was excluded from sleep stage analyses due to poor signal quality. Poor electrode contact was encountered several hours after sleep onset in a different subject during their placebo study visit, and in another subject during their oral dexmedetomidine study visit. Total time in bed and sleep times were similar between the groups (table 1). However, dexmedetomidine increased non-REM stage 2 sleep by 63 (95% CI, 19 to 107) min ($P = 0.010$) and decreased rapid eye movement (REM) sleep by 42 (5, 78) min ($P = 0.031$). We analyzed the effect of oral dexmedetomidine on total sleep time (defined as the sum of all sleep stages) and found that it significantly increased the percentage of total sleep

Table 1. Sleep Metrics Derived from Polysomnography

	Placebo (mean ± SD)	Dexmedetomidine (mean ± SD)	Diff (95% CI)	*P* Value
Total dark time, min	600 ± 0.3	600 ± 0.4	0.1 (–0.5, 0.2)	0.422
Total sleep time, min	523 ± 40	544 ± 33	–16 (–43, 11)	0.207
Sleep efficiency, %	87 ± 7	91 ± 5	–3 (–7, 2)	0.211
Wake after sleep onset, min	53 ± 39	42 ± 29	5 (–19, 29)	0.639
Wake duration, min	77 ± 40	56 ± 33	16 (–11, 43)	0.212
Non–rapid eye movement stage 1, min	24 ± 13	24 ± 19	0.3 (–10, 11)	0.953
Non–rapid eye movement stage 2, min	256 ± 46	326 ± 69	–63 (–107, –19)	0.010
Non–rapid eye movement stage 3, min	122 ± 32	108 ± 34	5 (–7, 18)	0.362
Rapid eye movement stage, min	120 ± 27	86 ± 53	42 (5, 78)	0.031
Non–rapid eye movement stage 1 total sleep time, %	5 ± 3	5 ± 4	0.2 (–2, 2)	0.881
Non–rapid eye movement stage 2 total sleep time, %	49 ± 6	60 ± 11	–10 (–16, –4)	0.005
Non–rapid eye movement stage 3 total sleep time, %	24 ± 6	20 ± 6	2 (–0.2, 4)	0.071
Rapid eye movement stage total sleep time, %	23 ± 6	16 ± 11	8 (1, 15)	0.026

Diff, differences in the mean of the groups.

time spent in non-REM stage 2 sleep by 10% (4, 16%; P = 0.005) and decreased REM sleep by 8% (1, 15%; P = 0.026). These data are summarized in table 1. We did not find any significant differences in standard measures of sleep latency (table 2) or measures of sleep stage switching (table 3). We assessed sleep stage switching using the number of stage shifts (switch) and number of shifts to a lighter stage (sleep fragmentation). We did not find significant differences in subjective measures of sleep quality (table 4).

Oral Dexmedetomidine Did Not Improve Overnight Motor Sequence Task Performance. The number of correct motor sequence task responses after dexmedetomidine sleep remained stable from a mean of 26.8 (STD ± 4.3) responses at training to a mean of 26.7 ± 6.1 correct responses at testing (fig. 1B). This mean difference of –0.1 (95% CI, –2 to 1.8) correct responses represented a 0.8% decrease in performance that did not meet our threshold for statistical significance (P = 0.900). In contrast, overnight test performance after placebo sleep increased from a mean of 27.5 ± 6.2 correct responses at training to a mean of 29.8 ± 7.4 correct responses at testing (fig. 1B). This mean difference 2.3 (0.9, 3.7) represented a 7.9% increase in performance that met our threshold for statistical significance (P = 0.003). These data are illustrated in figure 1B.

We found that oral dexmedetomidine was associated with a reduction in overnight motor sequence task performance of 9.3% (–1.4, 19.9%) compared to placebo (fig. 1C). However, this group level difference did not meet our threshold for statistical significance (P = 0.078).

Non–Rapid Eye Movement Sleep Stage 2 Spindle Density and Motor Sequence Task Performance. In exploratory analyses, spindle density during non-REM stage 2 sleep and overnight motor sequence task improvement (fig. 1D) after oral dexmedetomidine were not correlated (Spearman rho = 0.1, P = 0.748, n = 13; Spearman rho = 0.1, P = 0.820, n = 15 after data imputation). Similarly, total spindle count during non-REM stage 2 sleep and overnight motor sequence task improvement after oral dexmedetomidine were not correlated (Spearman rho = 0.04, P = 0.887, n = 13; Spearman rho = 0.04, P = 0.899, n = 15 after data imputation). We confirmed the previously described[25,27] positive correlation between spindle density during non-REM stage 2 sleep and overnight motor sequence task improvement (fig. 1E) after placebo (Spearman rho = 0.54,

Table 2. Sleep Latencies Derived from Polysomnography

	Placebo (mean ± SD)	Dexmedetomidine (mean ± SD)	Diff (95% CI)	*P* Value
Sleep latency, min	23.8 ± 18.4	12.6 ± 7.5	11.1 (–2.6 , 24.7)	0.101
Wake duration, min	77.0 ± 40.2	55.6 ± 32.5	16 (–10.9 , 42.9)	0.212
Sleep latency to non–rapid eye movement stage 1, min	24.8 ± 18.6	13.0 ± 7.4	10.6 (–3.2 , 24.4)	0.117
Sleep latency to non–rapid eye movement stage 2, min	28.3 ± 18.4	21.0 ± 12.8	5.5 (–8.4 , 19.4)	0.395
Sleep latency to non–rapid eye movement stage 3, min	49.5 ± 27.0	34.8 ± 21.4	–10.7 (–2 , 23.4)	0.089
Sleep latency to rapid eye movement stage, min	70.6 ± 56.6	74.3 ± 88.4	–7.4 (–96.1 , 81.2)	0.837

Diff, differences in the mean of the groups.

Table 3. Sleep Fragmentation and Switch Derived from Polysomnography

	Placebo (mean ± SD)	Dexmedetomidine (mean ± SD)	Diff (95% CI)	*P* Value
Switch	173.9 ± 44.7	170.2 ± 64.0	5.8 (–26.3 , 38)	0.690
Switch index per min	0.3 ± 0.1	0.3 ± 0.1	0.02 (–0.03 , 0.1)	0.404
Sleep fragmentation	59.1 ± 15.5	58.7 ± 20.4	1.9 (–10.7 , 14.5)	0.746
Sleep fragmentation index per min	0.1 ± 0.01	0.1 ± 0.04	0.0 (–0.02 , 0.03)	0.588

Diff, differences in the mean of the groups; Sleep fragmentation, number of shifts to a lighter stage; Switch, number of stage shifts.

$P = 0.058$, n = 13; Spearman rho = 0.57, $P = 0.028$, n = 15 after data imputation). We also found a positive correlation between the total spindle count during non-REM stage 2 sleep and overnight motor sequence task improvement after placebo (r = 0.51, $P = 0.074$, n = 13; Spearman rho = 0.57, $P = 0.0287$, n = 15 after data imputation).

Psychomotor Vigilance Was Preserved after Dexmedetomidine-induced Sleep

Lapse 400. We previously demonstrated that lapse 400 was impaired after zolpidem extended-release sleep.[8] Lapse 400 after placebo sleep increased from a mean of 6.5 ± 7 lapses during the training performance to a mean of 12.3 ± 13.2 lapses during the testing performance (fig. 2A). This mean difference of 5.8 (0.5, 11.1) lapses met our threshold for statistical significance ($P = 0.036$). Lapse 400 after dexmedetomidine-induced sleep increased from a mean of 5.8 ± 5 lapses during the training performance to a mean of 14.5 ± 15.5 lapses during the testing performance (fig. 2A). This mean difference of 8.6 (1.7, 15.7) lapses met our threshold for statistical significance ($P = 0.009$).

To make inferences on group differences, we analyzed AM–PM change scores using an appropriate statistical approach for our crossover design. The mean difference of 2.4 (–3.9, 8.7) in the AM–PM change scores at the group level did not meet our threshold for statistical significance ($P = 0.398$).

Reaction Time. Reaction time after placebo sleep increased from a mean of 281.3 ± 36.5 ms during training to a mean of 306.5 ± 53.8 ms during testing (fig. 2B). This mean difference of 25.1 (6.3, 43.9) ms met our threshold for statistical significance ($P = 0.012$). Reaction time after dexmedetomidine-induced sleep increased from a mean of 284.7 ± 35.5 ms during training to a mean of 319.9 ± 70 ms during testing (fig. 2B). This mean difference of 35.2 (8.5, 62) ms met our threshold for statistical significance ($P = 0.014$).

To make inferences on group differences, we analyzed AM–PM change scores using an appropriate statistical approach for our crossover design. The mean difference of 7.1 (–15.2, 29.3) in the AM–PM change scores at the group level did not meet our threshold for statistical significance ($P = 0.501$).

No serious adverse events were reported during this study.

Discussion

In this investigation, we studied the effect of a capsule-based solid oral dosage formulation of dexmedetomidine on objective and subjective measures of sleep quality. Our major finding was that oral dexmedetomidine increased the duration of non-REM stage 2 sleep and decreased the duration of REM sleep. Non-REM stage 2 sleep spindle density and total spindle count have previously been positively correlated with overnight motor sequence task improvement.[24,25,27] We confirmed these previously reported positive correlations with data from the placebo study arm. However, we did not find a positive correlation between oral dexmedetomidine-induced

Table 4. Sleep Metrics Derived from Questionnaire

	Placebo (mean ± SD)	Dexmedetomidine (mean ± SD)	Diff (95% CI)	*P* Value
Total sleep, min	521.3 ± 62.2	531.6 ± 59.5	–16.9 (–44.2 , 10.5)	0.203
Sleep latency, min	36.3 ± 27.3	33 ± 24.4	5.9 (–10.3 , 22.2)	0.435
Times awakened, No.	3.7 ± 3	3.2 ± 2.6	0.9 (–1.1 , 3.1)	0.315
Total time awake, min	23 ± 21.3	24 ± 21	–2.5 (–12.1 , 17.1)	0.719
Overall sleepiness (1, awake; 7, not awake)	2.6 ± 1.1	2.6 ± 1.2	–0.1 (–0.8 , 1)	0.826
Quality of sleep (1, bad; 4, excellent)	2.5 ± 0.8	2.6 ± 0.6	–0.3 (–0.8 , 0.2)	0.230

Diff, differences in the mean of the groups.

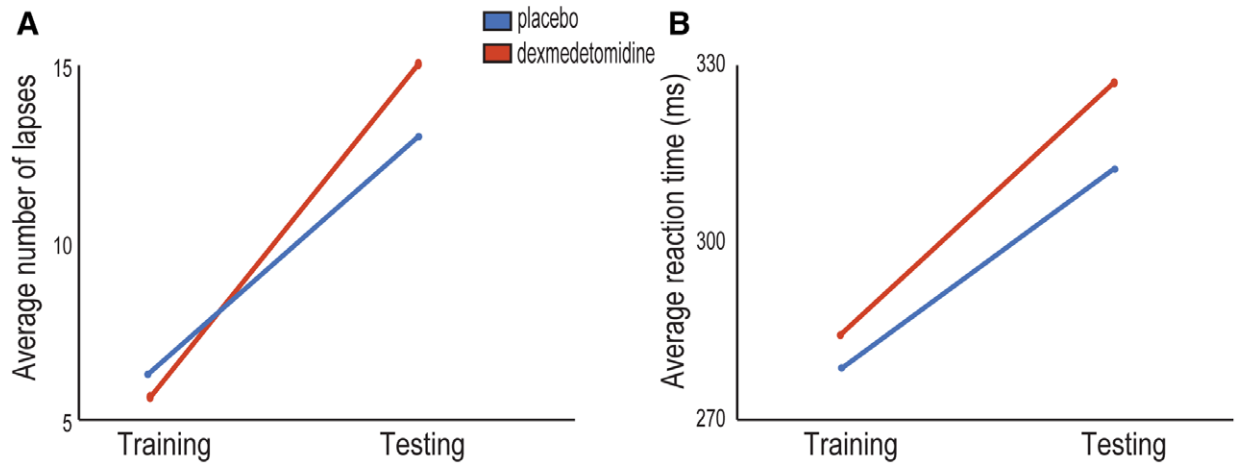

Fig. 2. Psychomotor vigilance task performance. (*A*) Testing lapse 400 during the placebo study visit was increased from training lapse 400 ($P = 0.036$). Testing lapse 400 during the dexmedetomidine study visit was also increased from training lapse 400 ($P = 0.009$). There was no statistically significant difference in testing lapse 400 between groups after controlling for training lapse 400 ($P = 0.281$). (*B*) The average testing reaction time during the placebo study visit was increased from the average training reaction times ($P = 0.012$). The average testing reaction time during the dexmedetomidine study visit was also increased from the average training reaction time ($P = 0.014$). There was no statistically significant difference between the average testing reaction times between groups after controlling for the average training reaction times ($P = 0.295$).

non-REM stage 2 spindle density or total spindle count and overnight motor sequence task performance. Differences in motor sequence task findings may have been secondary to impaired sleep-dependent memory or slower than usual reaction times (*i.e.*, residual drug effect on psychomotor function). Because our psychomotor vigilance task measures of psychomotor function did not significantly differ between groups, we conjecture that oral dexmedetomidine impaired sleep-dependent memory consolidation.

Our finding that dexmedetomidine promoted non-REM stage 2 sleep and preserved sleep cycling is consistent with laboratory[1–5] and human studies[8–11,13,28–31] that suggest dexmedetomidine modulates non-REM sleep circuitry. Sleep spindles, along with K-complexes, are a neurophysiologic feature of non-REM stage 2 sleep.[11,20] Sleep spindles are transient time-domain (~0.5 to 2 s) oscillations that are generated in the thalamus.[20,32] They require intact thalamocortical and corticothalamic circuits for synchronization and propagation to cortical regions,[20,33] and may act to prime neural networks for synaptic plastic processes by inducing calcium influx.[34] Sleep spindles have been suggested to mediate the overnight consolidation of declarative and procedural memory.[35–38] Sleep spindles are also associated with learning potential and intelligence,[39,40] and sleep spindle abnormalities have been identified in several neurocognitive disorders affecting cognition.[27,41,42] However, the mere manifestation of sleep spindles may not be sufficient for improvement in overnight motor sequence task performance.

The lack of a positive correlation between oral dexmedetomidine spindle density or total spindle count with overnight motor sequence task performance suggests that oral dexmedetomidine may have impaired the slow oscillation-spindle-ripple cross-frequency coupling dynamic that is important for sleep-dependent motor memory consolidation. The two-stage memory model assumes that new memories are transiently encoded to temporary storage represented by the hippocampus and surrounding structures before being transferred to long-term storage represented by the cortex.[25,34] Transfer of memory from temporary to long-term storage is postulated to occur during non-REM sleep.[25,34] This process is dependent on cross-frequency coupling between thalamocortical spindles and hippocampal sharp-wave ripples (*i.e.*, sharp-wave ripples are nested on the trough of thalamocortical spindles).[25,34,43] Spindle-ripple cross-frequency coupling is regulated by the on and off phases of cortical slow oscillations.[25,34,43] Thus the cortical slow oscillation regulates the hippocampal to cortical redistribution of memory.[34,43]

The clinical implication of our finding is that oral dexmedetomidine may be further investigated and developed as a non-REM sleep—promoting sedative medication. However, whether the mortality,[44] cognitive,[44] and delirium sparing benefits[14–18] of intravenous dexmedetomidine will be realized with a solid oral dosage formulation is unclear. The inhaled and intravenous anesthetic drugs in common clinical use significantly affect brain neurophysiology,[9,45–47] likely explaining why sleep disturbance is a hallmark of the postoperative period. Thus, future investigations are

necessary to make clear the putative benefits of oral dexmedetomidine in the postoperative period, critical illness, and patients with primary and secondary sleep disorders. Limitations of our study include the small sample size, healthy study population, and administration of a single dose of oral dexmedetomidine. Thus, future larger studies are necessary to enable insights, in various study populations, on the effect of repeated drug administration. These studies may also enable insights into whether oral dexmedetomidine has longer-term effects on sleep architecture (*i.e.*, rebound REM sleep), and whether these effects are clinically relevant.

Our results demonstrate the feasibility of developing oral solid dosage formulations of dexmedetomidine as non–rapid eye movement sleep—promoting sedative medications. Refinements to drug formulation and dosing may enable more precise sleep stage targeting.

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Competing Interests

Dr. Akeju has received speaker's honoraria from Masimo Corporation (Irvine, California) and is listed as an inventor on pending patents on electroencephalogram monitoring and oral dexmedetomidine that are assigned to Massachusetts General Hospital, Boston, Massachusetts. The other authors declare no competing interests.

Reproducible Science

Full protocol available at: oluwaseun.akeju@mgh.harvard.edu. Raw data available at: oluwaseun.akeju@mgh.harvard.edu.

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