



## SLEEP DURATION ENHANCEMENT: EFFECTS OF MAGNESIUM SULFATE DERMAL SPRAY IN A NORMAL PERSON

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Article Received on 10/12/2018

Article Revised on 30/12/2018

Article Accepted on 20/01/2019

### ABSTRACT

**Importance:** Sleep deprivation or prolonged sleep has significant deleterious health effects on the cardiovascular system related to disturbances in autonomic nervous system (ANS) function. Magnesium sulfate ( $MgSO_4$ ) is an inexpensive natural element which reduces blood pressure (BP) through its effects on ANS and its probable influence on sleep duration with transdermal application, needs scientific recognition. **Objective:** To document that  $MgSO_4$  dermal spray can extend sleep duration safely and efficaciously by its transdermal effects on the ANS.

**Design, Setting, and Participants:** Single person statistically-controlled data of the corresponding author. Home setting. **Main Outcomes and Measures:** Self-measurement of systolic (S), diastolic (D) BP and heart-rate (H-R) before sleep and on immediate natural awakening the following morning during the control phase of regular sleep (N=54). During the test phase (N=48) BP/H-R were immediately measured pre-sleep (before spraying  $MgSO_4$ ) and on immediate natural awakening the following morning. **Results:** Sleep duration <300 minutes with natural sleep and with  $MgSO_4$  spray aided-sleep occurred respectively in 50% and 0% of occasions and  $\geq 420$  minutes sleep in 13% and 79% of occasions. Significantly higher SBP, DBP, and H-R noted post regular sleep. Post  $MgSO_4$  aided-sleep had similar BP findings but without significant changes in H-R. With increasing sleep durations, natural sleep had a significant increase in SBP and H-R but  $MgSO_4$  spray aided-sleep showed a significant decrease in SBP and DBP without significant H-R changes. **Conclusions and Relevance:** Transdermal application of  $MgSO_4$  spray definitively increases sleep duration safely and efficaciously. Any interested person can self-investigate the deleterious cardiovascular health effects of curtailed/prolonged sleep by daily self-recording sleep duration, BP and H-R pre-sleep and on natural awakening the following morning.

**KEYWORDS:** Sleep duration enhancement; magnesium sulfate dermal spray; self-detect; cardiovascular health; blood pressure; heart-rate.

### INTRODUCTION

Only 48% of US adult population reports a habitual sleep time within the recommended 7-9 hours/night sleep duration.<sup>[1]</sup> Habitual sleep duration of 7-8 hours/night prevents premature death among adults.<sup>[2,3]</sup> An average sleep duration in 30% of workers is < 6 hours/night.<sup>[4]</sup> It is well known that sleep loss induces accidents in transportation and other industries from decreased vigilance and falling asleep while working/driving.<sup>[5]</sup> Physicians who sleep <6 hours after post-nighttime surgical procedures have an increased complications rate.<sup>[6]</sup> Elite European football players have reduced sleep quantity, quality and reduced perceived recovery following night matches.<sup>[7]</sup> Heading the ball under such conditions could lead to sports-related minimal traumatic

brain injuries which increase the risk of subsequent injury by about 50% for such players.<sup>[8]</sup> Thus preventive, safe and efficacious strategies to augment sleep are needed to reduce the potential disease burden of this important public health problem.

$MgSO_4$  given intravenously has known analgesic,<sup>[9,10]</sup> anesthetic,<sup>[11]</sup> and muscle relaxant<sup>[12,13]</sup> effects and thus has the potential for aiding sleep. We have previously shown that  $MgSO_4$  spray improves autonomic function useful in BP reduction and decreasing muscle tension especially when used together with Electrical Twitch-Obtaining Intramuscular Stimulation (ETOIMS).<sup>[14]</sup>

The corresponding author routinely performs self-ETOIMS as preventive neuromusculoskeletal system health care management. She has had chronic work-stress related sleep deficiency for 6 months habitually sleeping <5 hours. On applying MgSO<sub>4</sub> spray during self-ETOIMS to facilitate twitch elicitation,<sup>[15]</sup> serendipitously it was noted that her sleep duration improved significantly. In patients with chronic lower back pain, relaxing muscles using heat-wrap therapy led to electroencephalographically documented improved sleep during the night. This results from acute muscle relaxation with reduced nociceptive information load on the central nervous system.<sup>[16]</sup>

We thus aim to show that dermal MgSO<sub>4</sub> spray can improve sleep quality and duration safely and efficaciously due to its ability to reduce muscle tension, decrease sympathetic tone and activate the parasympathetic function of the ANS.

## METHODS AND MATERIALS

The corresponding author was the test subject which significantly decreases the study's internal validity from potential researcher bias. However, collecting data daily over many weeks late at night and on awakening related to a sleep study, if subjected to a randomized control trial (RCT) with many patients is considerably expensive and fraught with inevitable delays for even starting the study. Also, funded RCT is not possible as there is no prior data on the use of MgSO<sub>4</sub> as a sleep-aid. We thus used the statistical process control (SPC) method that obviates the need for cost-prohibitive, time-consuming RCTs.<sup>[17,18]</sup> SPC results cannot occur by chance and we subjected the consecutive data input and statistical analysis to a blinded person. We were thus able to expeditiously and inexpensively obtain valuable clinical information on MgSO<sub>4</sub> spray effects on sleep duration and BP.

There were two phases in the study. In the control phase (1/2/17- 2/24/17), the work-associated sleep-deprived corresponding author then in her late sixties, recorded the mean of 3 sitting BP and H-R measurements using an automated sphygmomanometer before and on awakening from regular sleep the following morning.

The second phase of the study (4/15/17-6/1/17) involved using MgSO<sub>4</sub> spray before sleep. The same protocol was used but pre-sleep BP recordings were made just before MgSO<sub>4</sub> spray. Sleep durations were recorded.

The skin was not specially prepared for the experiment, however there were no oily skin creams or lotions on it. The spray was applied once to bilateral paraspinal muscles starting from hairline to include the entire expanse of neck, shoulder slopes over trapezius muscles, inter-scapular area, middle back to low back (to include latissimus dorsi muscle), gluteus maximus, thigh and leg muscles circumferentially in the same fashion as an ETOIMS treatment. These areas were sufficiently

covered using 8-10 presses on spray bottle/body side. The spray dried within 2 minutes. Sleep onset occurred in 10-15 minutes.

## RESULTS

The outcome measures were sleep duration, BP and H-R measured pre-sleep and on awakening, serum and RBC magnesium levels for both phases of the study.

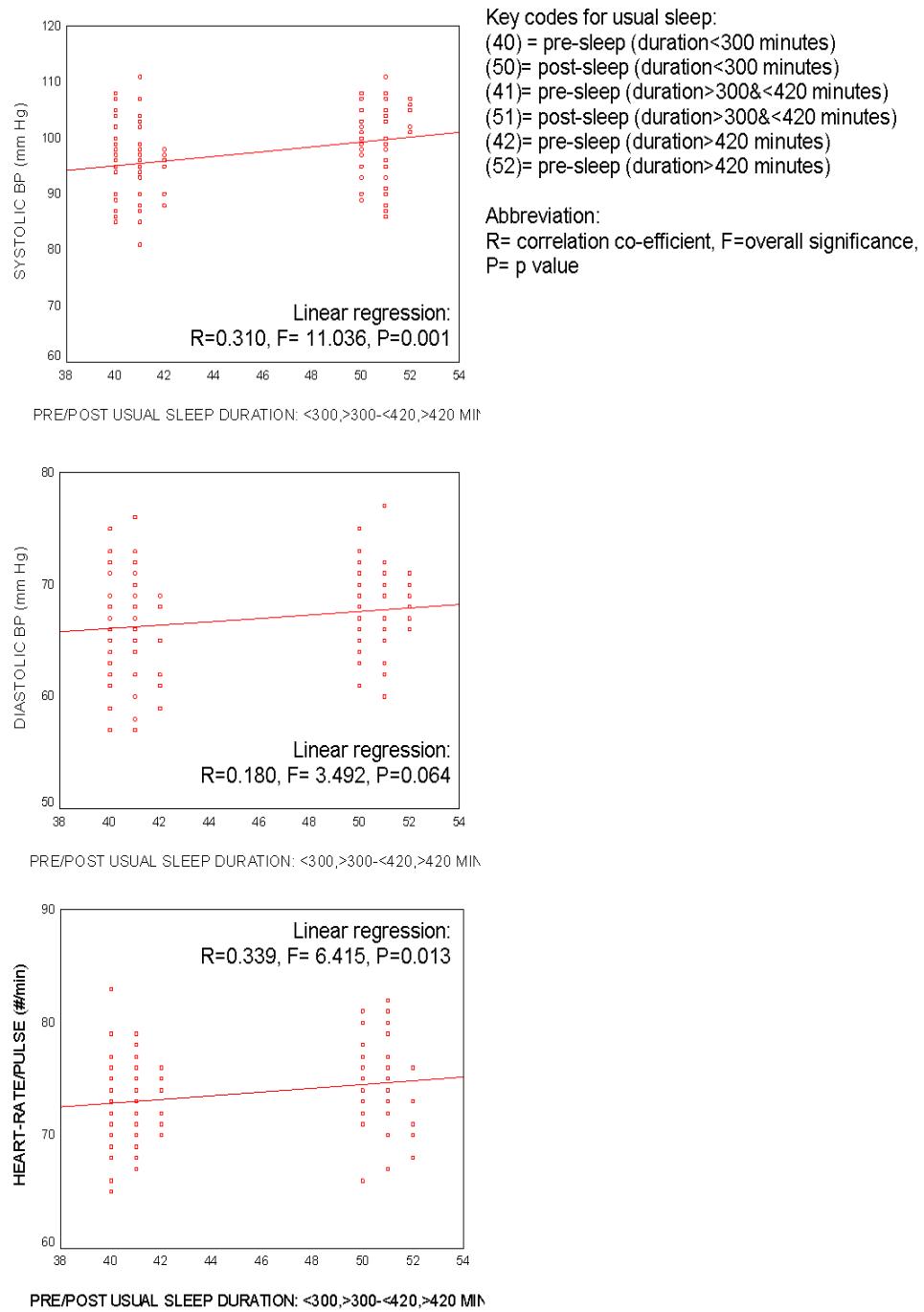
Sleep duration <300 minutes with natural sleep and with MgSO<sub>4</sub> spray aided- sleep occurred respectively in 50% and 0% of occasions; >300 to <420 minutes in 37% and 21% of occasions, and ≥420 minutes sleep in 13% and 79% of occasions.

Serum and red blood cell (RBC) magnesium were normal and were respectively 2.2 (normal = 1.8-2.5 Mg/dL) and 2.4 (normal = 1.5-3.1 mmol/L) tested after 6 weeks of regular sleep and 6 weeks of MgSO<sub>4</sub> aided-sleep.

Significantly higher SBP, DBP and H-R noted after natural sleep compared to that recorded just before sleep (paired T test significance p<0.05). Similar findings were noted for SBP and DBP for MgSO<sub>4</sub> aided-sleep but there was no significant difference for H-R pre and post sleep (Table 1). Linear regression analysis on natural sleep showed a significant increase in SBP and H-R with increasing sleep duration (Fig 1). DBP changes were not significant but tended to show an increase with sleep duration near significance (p=0.064). MgSO<sub>4</sub> spray aided-sleep, however, showed a significant decrease in SBP and DBP with increasing sleep duration without significant changes for H-R (Fig 2).

An evening BP dip was noted with both natural sleep and MgSO<sub>4</sub> aided-sleep. There was an increase in the next morning BP in both trials but H-R was higher on awakening from natural sleep only (Table 1). There was no significant difference in BP and H-R between the two trials (with independent T test). All analyses were performed with SPSS v12.

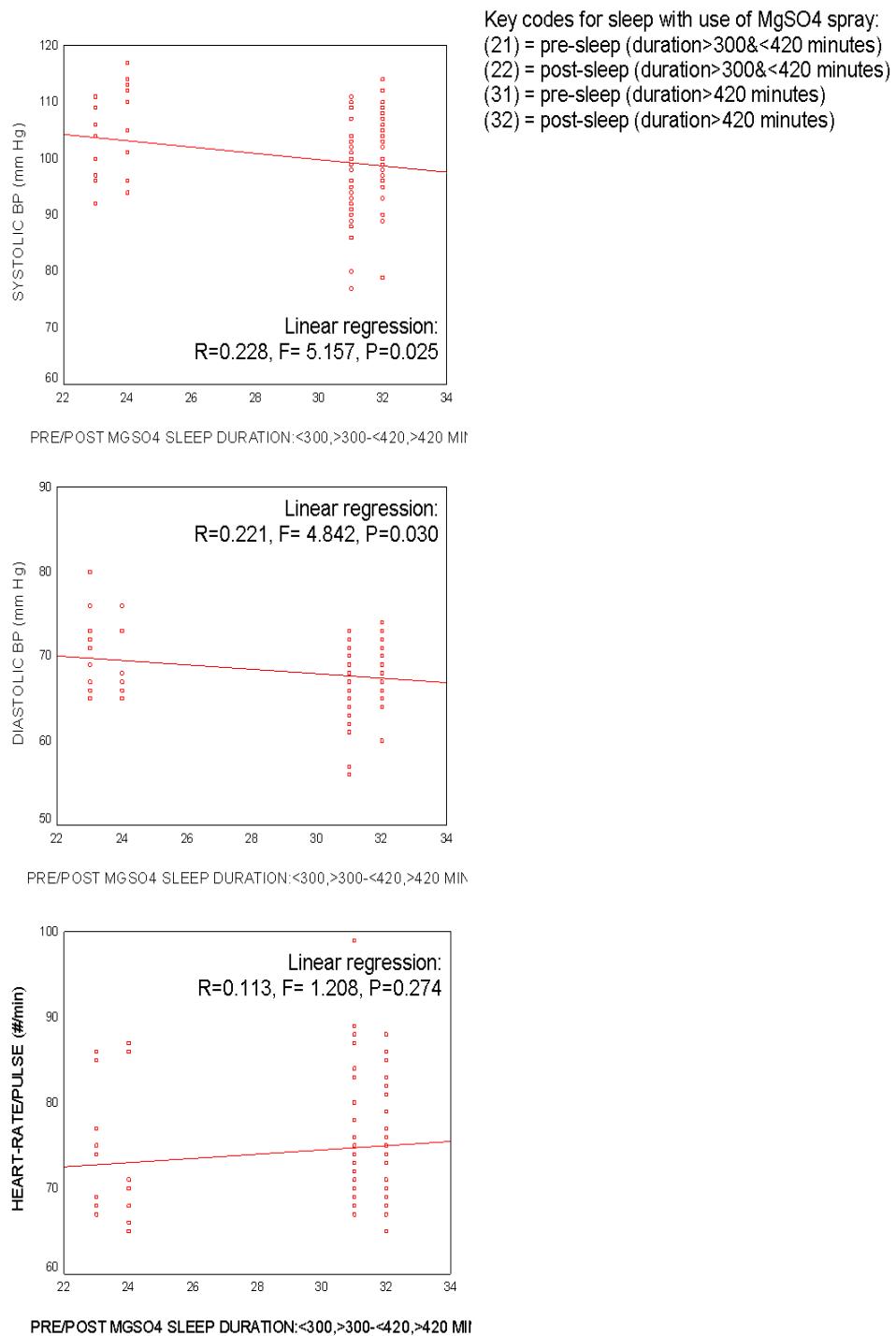
Figure 1. Regular/usual sleep: Effects of sleep duration on blood pressure and heart-rate

**Figure 1: Effects of duration of natural sleep on blood pressure and heart-rate.**

Key codes for usual sleep:

- (40) = pre-sleep (duration<300 minutes)
- (50) = post-sleep (duration<300 minutes)
- (41) = pre-sleep (duration>300&<420 minutes)
- (51) = post-sleep (duration>300&<420 minutes)
- (42) = pre-sleep (duration>420 minutes)
- (52) = pre-sleep (duration>420 minutes)

Figure 2. Sleep aided with MgSO<sub>4</sub> spray: Effects of sleep duration on blood pressure and heart-rate



**Figure 2: MgSO<sub>4</sub> spray aided-sleep: Effects of sleep duration on blood pressure and heart-rate.**

Key codes for sleep with use of MgSO<sub>4</sub> spray:  
 (21) = pre-sleep (duration>300&<420 minutes)  
 (22) = post-sleep (duration>300&<420 minutes)  
 (31) = pre-sleep (duration>420 minutes)  
 (32) = post-sleep (duration>420 minutes)

**Table 1: Effects on blood pressure and heart-rate from regular sleep and MgSO<sub>4</sub> spray-aided sleep.**

	MgSO <sub>4</sub> sprayed pre-sleep	Just awake from sleep with MgSO <sub>4</sub> spray	Pre-regular sleep	Just awake from regular sleep	Pre and post-MgSO <sub>4</sub> aided-sleep (paired T test)	Pre and post regular sleep (paired T test)
Number	N= 48	N= 48	N= 54	N= 54	N=48	N=54
Systolic BP (mm Hg) (p)	96±8	101±7	96±7	100±7	<b>0.000</b>	<b>0.000</b>
95% CI of difference	-7 to-2		-7 to -2			
Diastolic BP (mm Hg) (p)	67±4	69±3	67±5	68±4	<b>0.001</b>	<b>0.032</b>
95% CI of difference	-3 to 1		-3 to -1			
Heart-rate (#/min) (p)	75±8	75±6	73±4	75±4	0.968	<b>0.001</b>
95% CI of difference	-3 to 3		-3 to -1			

Abbreviations: BP = blood pressure. CI= confidence intervals, significance (p≤0.05).

**Table 2: Systematic reviews for non-pharmacologic therapies on sleep.**

Non-pharmacologic therapy	Trial characteristics and setting	Implications for practice
1. Changes to ventilator type and settings, earplugs and eye masks, relaxation therapy, sleep-inducing music, massage, foot baths, aromatherapy, valerian, acupressure, sound masking, and changing the visiting times of family members. <sup>[69]</sup>	30 trials, with a total of 1569 participants in ICU.	Earplugs or eye masks or both, may have some beneficial effects on sleep promotion and decrease the risk of delirium in intensive care unit adult patients. Low quality of evidence due to inconsistency in findings of contributing studies and the risk of bias.
2. "Light Box" which emits very high (typically 10,000 lux) fluorescent light for periods of around two hours daily with subjects sitting in front. <sup>[70]</sup>	Supervised participants screened to exclude those with dementia and/or depression. No trials met the inclusion criteria for the review.	Bright light therapy cannot be recommended to clinicians for the treatment of sleep problems in "normal" older adults.
3. Effect of listening to pre-recorded music daily, for 25 to 60 minutes, for 3 days to 5 weeks. <sup>[71]</sup>	6 studies with 314 participants. 4 trials measured the effect of participants listening to music in their own home, with data collected during a weekly visit to the participants' homes, or participants were also telephoned 1-2/week to ensure compliance with the protocol. One trial was in a sleep laboratory and 1 in a rehabilitation center for low back pain.	Music may be effective for improving sleep quality in adults with insomnia. The intervention is safe and easy to administer. More research needed to establish the effect of listening to music on other aspects of sleep and daytime consequences of insomnia.
4. (1) Exposure to bright light; (2) a napping opportunity during the night shift; or (3) others, like physical activity or sleep education for night shift workers. <sup>[72]</sup>	17 randomized controlled trials (with 556 participants) included in this review.	Too much uncertainty to determine whether any person-directed, non-drug interventions can really affect shift workers with sleepiness and sleep problems.
5. Melatonin therapy for treatment of non-respiratory sleep disorders in visually impaired children. <sup>[73]</sup>	Studies fulfilling the inclusion criteria as randomized controlled trials (RCTs) and quasi-RCTs, cross-over studies were not fulfilled. No outcome data are reported.	There is currently no high-quality data to support or refute the use of melatonin for sleep disorders in visually impaired children.
6. Treatment 1: For older adults 60+ years. 16 weeks of moderate-intensity community-based exercise training consisting of 4x 30-40 minutes endurance training [low impact aerobics; brisk walking] per week (n = 24). Treatment 2: No treatment, wait-list control (n = 24). <sup>[74]</sup>	Only one trial met the criteria for inclusion in this review. This involved 48 older people living in the community (mean age of 62). 43 participants completed the study (90%).	There is a lack of evidence from well-designed trials for the effectiveness of physical exercise for the treatment of sleep problems in "normal" older adults, although the intervention may be worthy of investigation.

7. Examines the efficacy of cognitive therapy in activities of daily living, sleep, challenging behavior, and psychiatric symptoms associated with dementia. <sup>[75]</sup>	Eleven trials (13 articles) met the inclusion criteria. Function, sleep, challenging behavior (agitation), or psychiatric symptoms associated with dementia in institutionalized patients.	No effect of light therapy on cognitive function, sleep, disruptive behavior (e.g. agitation), or psychiatric symptoms associated with dementia.
8. RCTs evaluating any form of acupuncture for insomnia. The comparison made between acupuncture with/without additional treatment against placebo or sham or no treatment or same additional treatment. <sup>[76]</sup>	33 trials involving 2293 participants aged 15- 98 years with insomnia, some with medical conditions contributing to insomnia (stroke, end-stage renal disease, perimenopause, pregnancy, psychiatric diseases), on needle acupuncture, electro-acupuncture, acupressure or magnetic acupressure.	Due to poor methodological quality, high levels of heterogeneity and publication bias, the current evidence is not sufficiently rigorous to support or refute acupuncture for treating insomnia. Larger high-quality clinical trials are required.
9. Evaluates whether melatonin taken by mouth can prevent or alleviate jet-lag associated with air travel across several time zones. <sup>[77]</sup>	Ten trials met the inclusion criteria. All compared melatonin with placebo; one additionally compared it with a hypnotic, Zolpidem. Nine of the trials were of adequate quality to contribute to the assessment; one had a design fault and could not be used in the assessment.	Melatonin is remarkably effective in preventing or reducing jet lag, and occasional short-term use by adults appears to be safe. Doses between 0.5 mg and 5 mg appear to be similarly effective, apart from the greater hypnotic effect of higher doses.

## DISCUSSION

### Pathophysiology

'Asleep' and 'awake' are actively promoted states of consciousness dependent on a network of sleep state-modulating neurons in the brain stem and hypothalamus. This network helps to coordinate the occurrence of a sleep state in billions of cortical neurons.<sup>[19]</sup>

During chronic sleep deprivation, the heart rate variability indices and RBC-Magnesium (RBC-Mg) decreased while norepinephrine release from sympathetic nerve terminals increased. The increase in SBP and H-R after awakening might be due to a greater sympathetic activation, similar to that of a stressful condition. Attenuation of DBP decline during sleep is partly due to incipient damage to the parasympathetic nervous system. A blunted heart rate decline leads to a decreased decline of cardiac output during sleep. This causes an autonomic imbalance leading to cardiovascular events.<sup>[20]</sup>

Magnesium deficiency increases muscle tone and increases sensitivity to stimulatory agonists by inhibiting N-methyl-D-aspartate (NMDA) receptors.<sup>[21]</sup> MgSO<sub>4</sub> is a calcium antagonist and a smooth muscle relaxant with ability to reduce BP.<sup>[22]</sup> Using our sleep protocol, MgSO<sub>4</sub> spray can be safely used even in individuals with normal serum and RBC Mg levels such as that noted in the corresponding author since any excess Mg absorbed transdermally or orally is excreted through urine and feces.<sup>[23,24]</sup>

Physiological rather than high or low, Mg levels are needed for normal sleep regulation.<sup>[25]</sup> We were also able to show that sleep duration enhancement occurred without changes in serum and RBC Mg levels. This indicates that dermal absorption likely potentiated function of extracellular Mg ions which are known to effect neural activity associating with sleep-wake state-dependent patterns.<sup>[26]</sup>

### Clinical Presentation

Sleep deficiency causes, associates or aggravates many diseases. Sleep durations of  $\leq 5$  hours per night were associated with significantly increased risk of hypertension compared with 7 hours sleep.<sup>[27-29]</sup> When there is an excess sleep-trough morning BP surge, the elevated BP equilibrium results in increased risk of cardiovascular outcomes.<sup>[30]</sup> Attenuated nocturnal dipping in BP is a sensitive prognostic marker for cardiovascular disease.<sup>[31]</sup> The 95% confidence interval for nocturnal dipping in our study usable as a reference was SBP of -7 to -2 mm Hg (Table 1).

Sleep deprived individuals may develop and present with cardiovascular disease<sup>[32,33]</sup> augmented by inflammation with C-reactive protein and interleukin-6,<sup>[34]</sup> arterial calcification,<sup>[35]</sup> increased arterial stiffening even after one night of sleep deprivation<sup>[36]</sup> and cerebrovascular disease.<sup>[37]</sup> Sleep duration of  $\leq 6$  hours/night and  $\geq 9$  hours/night are significant predictors of fatal and non-fatal ischemic stroke.<sup>[38,39]</sup> Just one night of total sleep deprivation promotes generalized hyperalgesia<sup>[40]</sup> from an enhanced secretion of inflammatory cytokines that augment pain.<sup>[41,42]</sup>

Many hospitalized individuals experience sleep deficiency from disturbances of circadian rhythm and upregulation of the hypothalamic-pituitary-adrenal axis.<sup>[43]</sup> Those who are critically ill suffer disturbances in homeostasis, hemodynamics and immune mechanisms.<sup>[44]</sup>

Sleep deprived patients may have insulin insensitivity,<sup>[45]</sup> type 2 diabetes mellitus,<sup>[46]</sup> obesity from increased caloric intake,<sup>[47]</sup> reduced testosterone in men,<sup>[48]</sup> cognitive decline and Alzheimer's disease,<sup>[49]</sup> depression especially in middle-aged and older men,<sup>[50]</sup> circadian disruption-associated increased breast cancer risk in

women,<sup>[51]</sup> and increased lung cancer risk in aging men.<sup>[52]</sup>

### Assessment and Diagnosis

Superior to BP measured in the clinic is morning BP measured at home, a strong predictor of future cardiovascular and cerebrovascular events.<sup>[53]</sup> Days with sleep duration <7 hours have shown higher morning SBP and H-R compared with days when sleep duration ranged between 7-8 hours.<sup>[54]</sup> This underscores the importance of measurement of morning BP which should be routine in those with pre-hypertension and hypertension.

With frequent awakening at night, gradual accumulation of sympathetic activation effect occurs with morning BP surge upon awakening.<sup>[55]</sup> The increase in sympathetic activity enhances hypertension.<sup>[56]</sup> The increase in nocturnal catecholamine levels develops the next evening after sleep deprivation from decreased nitric oxide synthase (NOS) immunoexpression and content in studies on rats.<sup>[57]</sup> Another similar experiment showed NOS and cyclo-oxygenase pathway alterations reduced endothelial-dependent vasodilatation independent of sympathetic activity.<sup>[58]</sup>

Additionally, vasoconstriction enhances platelet-dependent thrombosis to trigger cardiovascular events. A pro-thrombotic state occurs from systemic endothelial dysfunction with a concomitant enhanced release of cellular adhesion molecules and selectin.<sup>[59]</sup>

Increased BP during rapid eye movement sleep is from reduced baroreflex sensitivity similar to that occurring in sleep apnea patients.<sup>[60]</sup> MgSO<sub>4</sub>-spray aided sleep reduced BP, which may relate to its muscle relaxant effects.<sup>[12,13]</sup> As the areas over upper sternocleidomastoid originating at the mastoid process and entire trapezius muscles are routinely sprayed, reduction of noxious input probably occurred to the spinal accessory nerves from reduced intramuscular tension. These 2 muscles are supplied by the spinal accessory nerve to the vagus whose cranial portion is part of vagus nerve also responsible for baroreflex sensitivity. We have had prior experience with reduction of H-R in management of myofascial and neuropathic pain using ETOIMS on these 2 muscles.<sup>[15,18]</sup> We therefore infer that the non-significant changes in H-R pre and post MgSO<sub>4</sub> aided-sleep are not solely due to reduction of sympathetic activity but that there is increased activity of parasympathetic system.

Atrial fibrillation may result even in healthy sleep-deprived adults from associated reduction in left atrial early diastolic strain rate.<sup>[61]</sup> Coronary artery calcification is an early predictor of cardiovascular heart disease but as sleep duration lengthened, computed tomography identifiable calcification at 5 years follow up declined progressively.<sup>[62,63]</sup>

Chronic mental and physical stress with chronic sleep deprivation affect heart-rate variability indices with a decrease in RBC-Mg.<sup>[20]</sup> In contrast, our study showed that dermally absorbed MgSO<sub>4</sub> improved sleep duration without changing serum and RBC-Mg. It decreased sympathetic activity while returning vagal influence beneficial for cardiovascular health.

### Treatment

Pharmacological treatments are most commonly used for sleep disorders, particularly insomnia. In chronic insomnia, the sleep disturbance with associated day-time symptoms occurs at least 3 times/week for 3 months not related to another sleep disorder. The prime problems are difficulty initiating and maintaining sleep and undesired early awakening. Nighttime sleep difficulty leads to day-time fatigue and sleepiness; attention, concentration, motivation, initiative and behavioral problems; difficulties in social, family, occupational, or academic performance; mood disturbance/irritability and errors/accidents proneness.<sup>[64]</sup>

Most drugs used for insomnia have a slow onset of action and have many unwanted side effects and also not safe when used together with medications taken by the patient for co-morbid conditions/diseases. The different classes of sleep medications are: (1) barbiturates and benzodiazepines which bind to GABA receptor to increase the effect of gamma-aminobutyric acid (GABA). (2) Non-benzodiazepines that act on the hypothalamic ventrolateral preoptic nucleus (VLPO) and uses GABA to inhibit wakefulness. (3) Antihistamines block histamine in the ascending arousal system and (4) antidepressants inhibit serotonin. These medications interfere with noradrenaline-releasing neurons, block part of the ascending arousal system, and allow the VLPO system to activate. (5) Melatonin agonists that increase the activation of melatonin receptors, a circadian cue that primes the body for sleep via VLPO activation. (6) Orexin receptor antagonists are useful in blocking orexin neurons, inhibiting their wake-promoting signal.<sup>[65]</sup>

Unlike medications, non-drug interventions lack adverse effects, cross-reactions with other medications, tolerance, dependency, risk of abuse, daytime sedation, cognitive impairments, reduced motor co-ordination that interferes with work and quality of life. Furthermore, the use of hypnotics has been associated with suicide risk.<sup>[66]</sup>

Options for non-pharmacologic therapies for sleep use are multiple and only short-term use of melatonin is useful as a sleep-aid in the prevention of jet lag. (Table 2). A bath with Epsom salt before sleep has been found useful for sleep. One can choose the concentration one desires and immediately afterward take a quick shower to rinse off MgSO<sub>4</sub> residue.

Different from the common Epsom salt is that the spray we used was formulated with pharmaceutical grade

$MgSO_4$  used intravenously in hospitals, during surgery,<sup>[9-13]</sup> and in control of hypertension of pre-eclampsia/eclampsia.<sup>[22,67]</sup> This pure  $MgSO_4$  in dermal spray form dries rapidly after application, has a fast mode of action, time efficient, easy to apply and is very convenient to use just before sleep. Time of sleep onset that occurred within 10-15 minutes of application is likely related to completion of skin absorption. It can be safely re-applied to aid sleep during the night if needed and can be used daily. Magnesium sulfate has a protective effect on blood brain barrier integrity in multiple experimental models<sup>[78]</sup> and whether this action plays a role in sleep stability could be a topic for future related specialties research.

A 4 oz (118 ml) bottle of  $MgSO_4$  spray used once daily can last for about one month and the cost is comparable to daily oral intake of popular over the counter brands of sleep-aids that might necessitate taking a total 30 oz (887 ml) in one month. Most sleep aids may also have an after-effect on waking up. Additionally, we have documented the anti-hypertensive effect of the  $MgSO_4$  spray as an important and essential benefit for improvement of cardiovascular health with prolonged sleep.

Effective primary, secondary, and tertiary preventive measures for hypertension need to be sought for.<sup>[27-29]</sup>  $MgSO_4$  spray is excellent in safety, efficacy and cost effectiveness amongst non-drug interventions for extending, maintaining and improving sleep quality as well as simultaneously useful in hypertension management. It is important to have the brand to be used tested so that it is non-allergenic and non-sensitizing.

### Prognosis and study limitations

- (1) We did not study the effects of other magnesium salts on sleep.
- (2) The concentration of  $MgSO_4$  in spray form that provided our robust results is particular to the saturated solution that we used. We did not compare different concentrations of  $MgSO_4$ .
- (3) Capacity for dermal absorption and rapidity of absorption will also depend on amount and frequency of spray used, skin thickness, surface area sprayed and presence of other oils, lotions on skin.
- (4) The spray is essential for smooth and even delivery to back areas where patients with limited upper limb range of motion cannot reach if using formulations such as cream, gel or ointment.
- (5) The surface area sprayed should be expansive and must include large muscles on the dorsal aspect of the body as described in our protocol if the  $MgSO_4$  spray is to be used as a sleep-aid. BP and H-R elevations associated with curtailed or prolonged sleep duration also have potential to be corrected.

### CONCLUSIONS

$MgSO_4$  spray definitively increases sleep duration safely and efficaciously and has ability to reduce sympathetic

tone and increase parasympathetic function. It can be useful as an inexpensive adjuvant to prevent hypertension and also as a supplement for hypertension control. Any individual can self-investigate whether a treatment works or not on him/her.<sup>[68]</sup> In the case of using  $MgSO_4$  as a sleep-aid, a person can keep a daily log to record sleep duration, BP and H-R pre-sleep and on natural awakening the following morning to document the deleterious health effects of curtailed or prolonged sleep on cardiovascular health. Early detection of BP and H-R abnormalities can lead to earlier medical care, improvement of quality of life and reduction in the use of medical resources.

### ACKNOWLEDGMENT

All authors declare no conflict of interest in the writing of this manuscript.

**Question:** How can an individual self-detect sleep duration effects on cardiovascular health?

**Findings:** A female in her late sixties (corresponding author) measured blood pressure (BP) and heart-rate (H-R) data pre-sleep and on immediate-awakening the following morning. This was performed for 54 and 48 consecutive days respectively during regular sleep and on using magnesium sulfate ( $MgSO_4$ ) spray before sleep. Sleep duration increased on using  $MgSO_4$  spray. The increase in natural sleep duration was accompanied by significant increase in BP and H-R.  $MgSO_4$  aided-sleep reduced BP without changes in H-R.

**Meaning:** Statistically-controlled data assists self-documenting safe and efficacious use of transdermal application of  $MgSO_4$  as a sleep-aid. Any individual can assess his/her cardiovascular health related to sleep duration with self-monitoring daily BP and H-R pre and post sleep.

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