Commentary

On dialysis, sleep and melatonin

Sleep that knits up the ravelled sleeve of care
The death of each day's life, sore labour's bath
Balm of hurt minds, great nature's second course,
Chief nourisher in life's feast."

–William Shakespeare, *Macbeth*

There is no gainsaying that sleep is one of the most precious attributes of human physiology. Sleep-related complaints and sleep disorders are common in patients of end-stage renal disease. Nearly 80% of patients undergoing hemodialysis suffer from sleep abnormalities,[1] and the prevalence is much higher than that in general population. In a survey of 70 dialysis patients by Holley *et al.*,[2] 67% patients reported trouble falling asleep. Another 80% complained of nighttime waking, and 72% admitted to early morning waking. Walker *et al*., found daytime sleepiness to be the most commonly reported problem at 66.7% followed by restless legs syndrome in 57.4%.[3]

Melatonin has been described in medical literature as endogenous synchronizer of circadian rhythm and sleep. Endogenous melatonin profiles in chronic renal disease have become a field of increasing interest in recent years. The published studies do report an absence of the physiological rise of melatonin in serum in chronic kidney disease (CKD).[4,5] This has led to interest in exogenously administered melatonin as a pharmacologic intervention to improve quality of sleep in patients undergoing hemodialysis.

Further, lower endogenous melatonin levels have been associated with increased oxidative stress[6] and impaired immune response.[7] This leads to the obvious inference that restoration of normal melatonin levels through exogenous administration of this pineal hormone may, additionally, reduce oxidative stress and improve immune response in patients of end-stage renal disease (ESRD). Patients of CKD and ESRD exhibit a lack of 'nocturnal dip' in blood pressure and persistent hypertension. Exogenous melatonin has been shown to restore the nocturnal dip in blood pressure in patients of primary hypertension.[8]

There is, therefore, a need to vigorously evaluate whether exogenous administration of melatonin can improve the multiple sleep disorders in ESRD patients. Other hypothesized benefits of melatonin administration such as reduction in oxidative stress, improvement in immune response and restoration of nocturnal dip in blood pressure also merit investigation. The study published in this issue of the Journal is one such effort to assess the improvement in sleep quality following administration of melatonin in daytime hemodialysis patients. The authors have also looked at changes in lipid profile and erythropoietin dose requirement in these patients.

Previously published studies in literature have suffered from a small sample size and three different meta-analyses of the published studies have reached divergent conclusions, as recorded by authors of the present study. The present study has analyzed a total of 68 patients, and this sample size again appears to be small. The sleep quality was measured using the Pittsburgh sleep quality index scores and therefore, was only a subjective assessment of sleep quality. No actigraphy or polysomnography (PSG) was performed for objective assessment. Nevertheless, the investigators have reported an improvement in sleep duration, sleep disturbances, sleep efficiency and overall sleep quality at the end of 6 weeks of melatonin administration in a randomized, double-blind, placebo-controlled crossover fashion. They found no significant improvement in three other parameters, namely sleep latency, daytime dys-function and change in use of sleep medications.

The results are promising, but by no means conclusive.

They only serve to heighten the curiosity related to use of exogenous melatonin in hemodialysis patients, but do not allow firm conclusions to be drawn. The study once again highlights the need to vigorously study the effects of melatonin on sleep disorders in dialysis patients before practical guidelines can be arrived at. What is required is a larger sample size, a longer duration of administration of melatonin and objective assessment of parameters of sleep quality through PSG, in addition to the subjective questionnaire-based assessment.

A comment must be made on two other conclusions drawn by the authors. There was a small, albeit significant, increase in high density lipoprotein (DL) cholesterol levels in patients after melatonin administration over 6 weeks. There was also a significant decrease in erythropoietin requirement while maintaining relatively stable hemoglobin levels in the subjects under study. The authors have suggested that these effects may be due to the proposed anti-oxidative effects of melatonin. Future studies need to examine the effect of a longer duration of administration of melatonin on these parameters as well as the effect on blood pressure in patients on hemodialysis. Only time will tell whether melatonin will become a useful pharmacological intervention in ESRD patients or become a mere footnote in our quest to improve the quality of life of patients undergoing hemodialysis.

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