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Original Research Article

The role of melatonin in regulating sleep wake disorders in children attending the developmental pediatrics outpatient service of a tertiary care hospital in South India

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ABSTRACT

Background: We have observed that 75% of children with neurodevelopmental challenges visiting the Developmental Pediatrics department of this institution have sleep wake disorders. Disturbed sleep has a negative effect on learning and behavior. In this study we assessed the effectiveness of melatonin in improving sleep wake disorders in children with developmental compromise from this south Indian state.
Methods: Children with developmental challenges having sleep wake disorders confirmed by the *pediatric insomnia severity* index PISI, who were prescribed a daily dose of 3mg of melatonin participated in this prospective, observational, longitudinal study if the parents gave written informed consent. Parents were educated in the practice of sleep hygiene. The sleep disturbance scale for children (SDSC) was used to assess the overall pattern of sleep and six common disorders before and three weeks after starting melatonin.
Results: Based on the PISI scores, 13, 58 and 20 children had mild, moderate and severe insomnia respectively. Melatonin improved sleep latency, increased duration of sleep, decreased night awakenings, crying spells, dreams and daytime drowsiness. There was a significant improvement in the sleep pattern as indicated by better scores in the total SDSC score as well the scores for the six sleep disorders ($p<0.001$).
Conclusions: Melatonin has a significant role to play in regulating duration and quality of sleep and improving sleep pattern in developmentally challenged children with sleep-wake disorders.

Keywords: Melatonin, Sleep disorders, Neuro-developmental challenge, Sleep-wake rhythm disorders

INTRODUCTION

We have found that up to 75% of children with neuro-developmental challenges coming to the department of Developmental Pediatrics in this institution have sleep-wake disorders. Recent studies suggest that the prevalence of sleep disorders in children with developmental disabilities ranges from 25% to 86%.[1,2] This could potentially have a negative effect on learning and behavior.[3] Sleep-wake disorders affect the timing, quality and amount of sleep which may lead to daytime functional impairment for the child and family.[2]

The many negative consequences associated with untreated pediatric sleep disorders include insomnia, academic and cognitive difficulties, internalizing and externalizing behavioral problems, and risk for obesity.[4] The Pediatric Insomnia Severity Index (PISI), developed by Byar et al, is a reliable and valid tool to identify if the child has difficulties in initiating sleep, maintaining sleep and to record daytime drowsiness.[4] The sleep disturbance scale for children (SDSC) developed by Bruni et al assesses the overall sleep pattern and helps to identify six of the common sleep disorders of sleep in children.[5]

Medications are advocated in children with neurodevelopmental disorders accompanied by adequate instruction in good bedtime practices and sleep hygeine.[6] Good practices of sleep hygiene and sleep-promoting environment can resolve behaviour-related causes of disturbed sleep and help to train the intrinsic circadian rhythm to the external environment.[7]

Melatonin is a hormone naturally synthesized by the pineal gland, regulated by the suprachiasmatic nucleus in the hypothalamus in response to darkness. High levels of melatonin are secreted at night and low levels during the day from three months of age to maintain the circadian rhythm of the sleep-wake cycle. Melatonin has a pronounced chrono-biotic effect or circadian phase-shifting effect, and a less established hypnotic and sleep-promoting effect.[6]

Western studies have shown the efficacy of melatonin in treating sleep disorders in children with neurodevelopmental challenges. A metanalysis by Braam and associates (2009) reports the beneficial effects of melatonin treatment in children with sleep disorder with minimal side effects.[9] However this has not been well documented for Indian children with neuro-developmental compromise. There is also a gap in parental awareness of sleep hygiene and its benefits especially in our cultural context. Most parents in this community, from Kerala, south India, sleep together with the children in a shared bed, as was evident in all the families we studied, with the result that a wakeful child keeps the whole family awake. Administering melatonin to the wakeful child made a remarkable difference in the sleep quality of the entire family, The relief and gratitude of the parents inspired us to undertake this study to document the impact of melatonin in regulating sleep in children with disturbed sleep and neurodevelopmental compromise. The objective of this study was to assess the role of melatonin in regulating sleep wake disorders in developmentally challenged children attending the developmental paediatric outpatient service of this tertiary care hospital in south India alongside education on good sleep hygiene practices.

METHODS

This prospective, observational, longitudinal study to document the role of melatonin in regulating sleep wake disorders in children with neuro-developmental disorders, coming to the outpatient services of the developmental pediatrics department of Malankara Orthodox medical college, Kolenchery, Kerala, India. The study was conducted from May to September 2019. Children with neurodevelopmental disability, under the age of eight years, with complaints of sleep onset, sleep maintenance or daytime drowsiness as measured by PISI who were prescribed 3 mg of melatonin for sleep disorders were consecutively enrolled in the study, after obtaining written informed consent from the parents. Children who are obese and so receiving more than 3 mg of melatonin were excluded.

Ninety-one children with developmental compromise, who were prescribed 3 mg of melatonin for sleep wake disorders were serially recruited to participate in the study after receiving written informed consent from the parents. The severity and type of sleep disorder was identified using the pediatric insomnia severity index (PISI). The PISI is a six-item questionnaire that scores the symptom severity in children. The total sleep duration item is rated on a 6-point Likert scale with each rating designating an estimate of total hours slept on most nights in the past week. All other items are rated on a 6-point scale from "never" to "always" (seven nights/week). The severity of sleep disorder was classified based on the PISI scores as mild (6 to 12), moderate, (13-18) and severe (19 to 30). The type of sleep-wake disorder is classified as sleep onset problems (sum of PISI items 1+ 2 + 6 = >5), sleep maintenance problems (sum of the scores of PISI items 3+ 4 + 6 = > 5) and daytime drowsiness (complaint of daytime drowsiness at least once a week).[4]

The sleep disturbance scale for children (SDSC) developed by Bruni et al is a 26-item scale which is rated by the parents, to assess sleep difficulties in children. The statements are arranged so that higher scores reflect a greater clinical severity of sleep disturbance.[5] The questionnaire uses a Likert-type scale, with values 1-5, to assess six of the common sleep disorders. They include; difficulty in initiating and maintaining sleep (DIMS); sleep breathing disorders (SBD); disorders of arousal (DA); sleep wake transition disorders (SWTD); disorders of excessive somnolence (DOES) and sleep hyperhidrosis (SH).

The sample size was calculated by the formula for single proportion using nMaster Sample Size calculation software.[10] based on the prevalence of children (98%) with neuro-developmental disorders who responded to melatonin doses of 2.5 to 3 mg.[11] The required sample size for the expected proportion of 0.38 with a confidence interval of 95% and precision of 10% was found to be 91 children on melatonin. The SDSC was administered to the parents of the child at recruitment and at the first follow-up after three weeks of melatonin. After the child's existing sleep pattern was assessed in the pre-melatonin SDSC, the sleep intervention educational module was given to parents. This included an interactive talk, a handout on sleep hygiene and good bed-time practices and teaching the parents how to maintain a sleep diary, The child was then prescribed a daily dose of 3mg of melatonin. The family reported back after daily administration of melatonin, in three weeks and the post-melatonin SDSC was administered, where the parents were advised to fill the questionnaire keeping in mind the child's sleep parameters after administration of melatonin. The data was analyzed using STATA software. Mean (SD) was obtained for normally distributed data and median (IQR) for non-parametric data. The sleep scores in SDSC

before and after use of melatonin were compared using the paired t-test if normality was assured and the Wilcoxon signed-rank for non-parametric data. All tests were two tailed tests and were evaluated with the significance level at $p<0.05$ and the highly significant level at $p<0.001$. The study procedure is detailed in the flow chart in (Figure 1) following Strobe guidelines for observational studies.

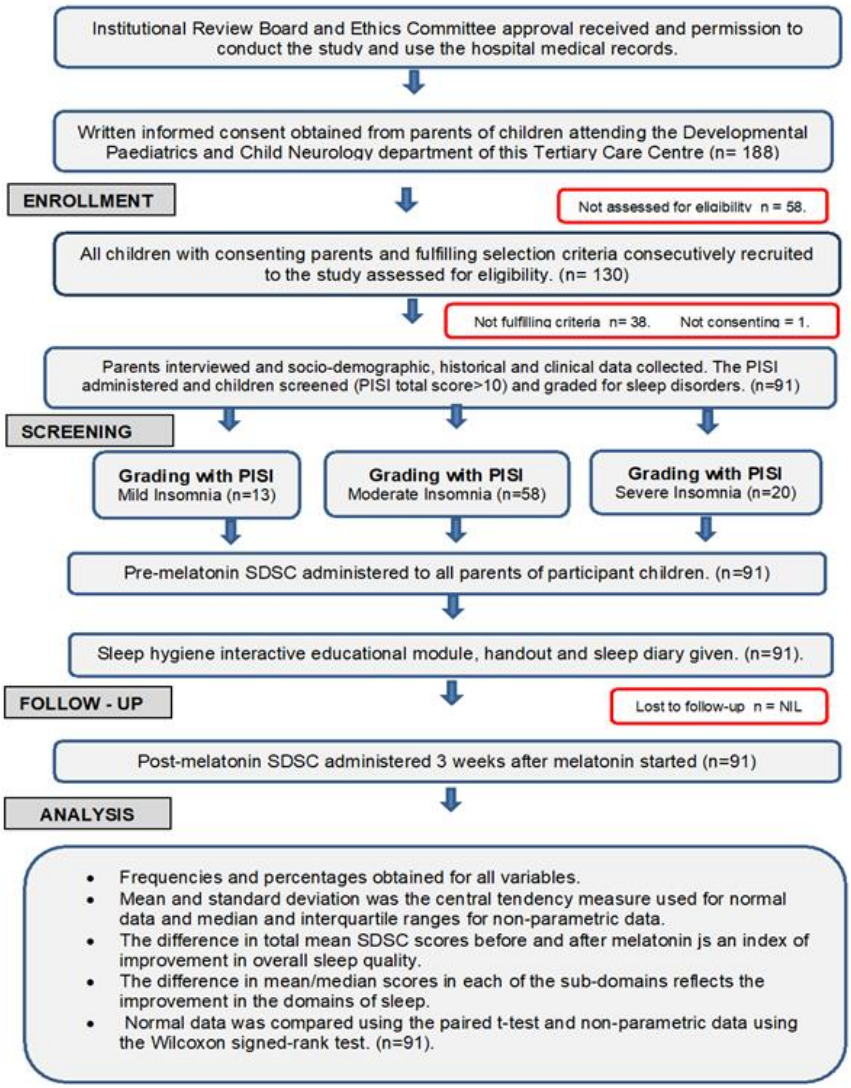

Figure 1: The study procedure is detailed in the flow chart following Strobe guidelines for observational studies.

RESULTS

Ninety-one neurodevelopmentally challenged children with sleep wake rhythm disorders on a daily dose of 3 mg of melatonin, were serially recruited. All the families reported that they benefitted from the educational module on good sleep hygiene and practices given to the family following the collection of data. On specific enquiry no adverse effects such as daytime somnolence or night awakenings were reported by any parent after melatonin use.

Baseline characteristics of the children enrolled in the study

The demographic data of the children included in the study. All children came from a south Indian community, nearly 90% living in urban areas. The mean age of the 91 children enrolled was 5.3 (SD 1.9) years. There were more boys 64 (70.33 %) than girls 27 (29.70 %) reflecting the greater proportion of male children compared to female brought to the department. The mean weight was 18.35(SD 4.4) kg and ranged from 10.2 kg to 31.7 kg. Most of the parents were educated and over 80% of mothers and 90% of fathers were graduates. Over 40% of fathers and 10% of mothers were professionals, over 50% fathers and 60% mothers did clerical work and while 7% of fathers were daily wage earners and did menial work, more than a quarter of the mothers were housewives or did menial jobs. Over 60% of children came from two-child families while more than 20% were single children. Most children had a birth order of being either the second or the third child in the family.

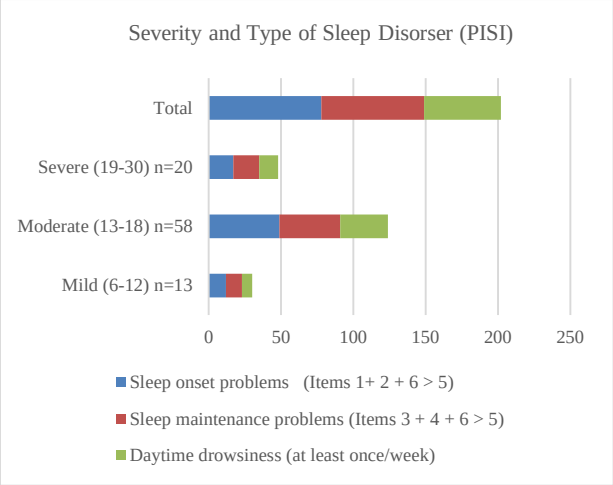

Figure 2: Severity and type of sleep wake problems assessed with PISI.

The severity and type of sleep disorder

The PISI was used to confirm that the child had a sleep disorder. The mean total PISI score for the 91 children in our study was 15.73 (SD 3.23) with a minimum score of 10 and a maximum score of 23. The PISI total score was used to classify the severity of insomnia to mild (PISI score of 6 - 12), moderate (PISI score of 13-18) and severe (PISI score of 19 - 30) sleep disorder as shown in (Figure 2).

Using PISI at the time of recruitment, on the 91 children with neurodevelopmental disorders who were receiving melatonin we found that 13 (14.29%) had mild insomnia, 58(63.74%) had moderate insomnia and 20 (21.98%) had severe insomnia. Sleep onset problems were found in 78 (85.71%) children, sleep maintenance problems in 71 (78.02%) children while 53 (58.24%) children had a history of daytime drowsiness prior to receiving melatonin.

Sleep hygiene

Regarding sleep hygiene, of the 91 children recruited to the study more than half had a regular bedtime (52.8 %) though most of the children had a regular waking time. It follows that the child may have been sleeping less on some days and more on other days. Only a few families (17.6%) encouraged the child to do quiet tasks before bedtime though a good number of parents made sure the child did not watch exciting videos or listen to loud music before bed.

Table 1: Baseline demographic data (n=91).

Variable	N (%)	Variable	N (%)
Age (years)		**Gender**	
1-2	8 (8.79)	Female	64 (70.33)
3-4	22 (24.18)	Male	27 (29.70)
5-6	34 (37.36)	**Domicile - Rural/Urban**	
7-8	27 (29.70)	Rural domicile	10 (10.99)
Education of mother		Urban domicile	81 (89.01)
1 - School education	4 (4.4)	**Education of father**	
2 - Passed HSc (Plus2) exam	12 (13.19)	1 - School education	2 (2.20)
3 - Graduate	75 (82.42)	2 - Passed HSc (Plus2) exam	7 (7.69)
Occupation of mother		3 - Graduate	82 (90.11)
1 - Not employed	16 (17.58)	**Occupation of father**	
2 - Menial work	11 (12.09)	1 - Not employed	0 (0)
3 - Clerical work	54 (59.34)	2 - Menial work	7 (7.69)
4 - Professional	10 (10.99)	3 - Clerical work	47 (51.65)
Number of siblings		4 - Professional	37 (40.66)
1-No siblings	21 (23.08)	**Birth order**	
2-One sibling	64 (70.33)	1 - First child (birth order 1)	1 (1.10)
3-Two siblings	6 (6.59)	2 - Second child (birth order2)	63 (69.23)
-	-	3 - Third child (birth order 3)	25 (27.47)
-	-	4 - Fourth child (birth order 4)	2 (2.20)

Over 75% of families had bedtimes routines and rituals to prepare the child for bed and around 44 % of the children went to bed with a favorite toy or object. Most families said they were able to provide a quiet cozy area for the child to sleep. In all the families the child shared a bed with one or both parents.

Neurodevelopmental diagnosis

The neuro-developmental diagnoses of the children included were attention deficit hyperactivity disorder (ADHD), autistic spectrum disorder (ASD), communication, speech and language disorders, learning disorders, motor disorders and other syndromic diagnoses.

Of the 91 children, 17 had identifiable syndromes such as Down, Asperger Coffin Siris, Fragile-X, Dyke Davidoff Mason, Klinefelter, Landau Kleffner, Russel Silver, Rubinstein Taybei, Sotos and Williams among others (Figure 3). The most commonly occurring diagnosis in children with sleep wake disorders was communication speech and language disorders (29.7%). Attention deficit hyperactivity disorder (24.2%) was next either manifesting alone or in combination with other conditions, followed by motor disorders (19.8%).

Table 2: The effect of melatonin on the sleep parameters.

Sleep parameters	Before melatonin, N (%)	After melatonin, N (%)
Sleeping duration (hours)		
6 or less	20 (21.98)	0
7	39 (42.86)	2 (2.20)
8	32 (35.16)	33 (36.26)
9 or more	0	56 (61.54)
Time to fall asleep (minutes)		
5	1 (1.10)	49 (53.85)
10	16 (17.58)	22 (24.18)
15	10 (10.99)	20 (21.98)
20	15 (16.48)	0
>30	49 (53.48)	0
Night-awakenings/week		
0 wakings	0	79 (86.81)
-2 wakings	24 (26.37)	11 (12.09)
3-4 wakings	17 (18.68)	1 (1.10)
>5 wakings	50 (54.95)	0
Dreams at night		
No	82 (90.11)	91 (100)
Yes	9 (9.89)	0
Difficulty waking up		
No	42 (46.15)	85 (93.41)
Yes	49 (53.85)	6 (6.59)
Daytime drowsiness		
No	38 (41.76)	90 (98.90)
Yes	53 (58.24)	1 (1.10)
Night-time crying spells		
No	82 (90.10 5)	91 (100)
Yes	9 (9.89)	0

Developmental functions and co-morbidities

The developmental assessment was done for each child using the Jeffree and McConkey Parent Involved Programme (PIP) developmental charts and the cognitive, motor, sensory and movement functions were classified as age appropriate or not. In this study, out of the 91 children enrolled, 90 (98.90%) did not have age-appropriate cognitive function, 54 (59.34%) did not have age-appropriate motor function or movement function and 15 (16.48%) did not have age-appropriate sensory function.

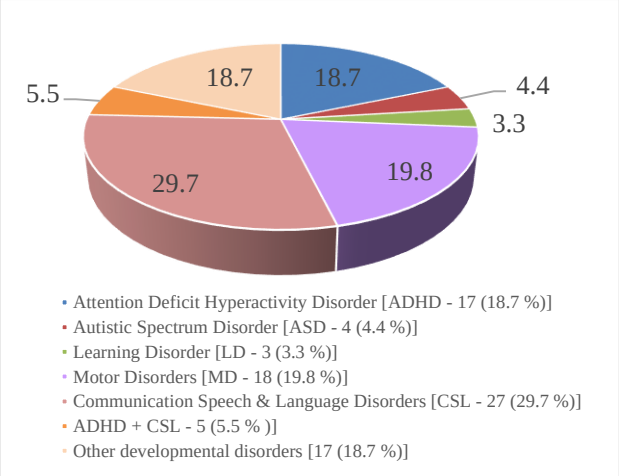

Figure 3: Primary neurodevelopmental diagnoses.

Thirty-seven out of the 91 children enrolled had co-morbidities such as seizures 32 (28.6%), anaemia 5 (5.5%), and 6 (6.6%) had both. Of the 38 children on anti-epileptic medication, 34 were managed on monotherapy while three received two drugs and one was on polytherapy. Most of the children on monotherapy were receiving carbamazepine, while others received sodium valproate. Clobazam and levetiracetam were the add-on drugs used.

The effects of melatonin on sleep parameters

The effects of melatonin on the parameters of sleep are given in (Table 2). While 59 (64.84 %) of the children slept less than seven hours before receiving melatonin, most of them 89 (97.80%) slept 8 hours or more after melatonin. The time to fall asleep was reduced from 20 minutes or more in 64 (70.33 %) children to 15 minutes or less in all the children 71 (78.02 %). The mean decrease in time to fall asleep was 19.4 minutes. Night awakenings were reduced in nearly all the children and 79 (86.81%) did not wake up at all in the night. All the children, who were waking up due to dreams before melatonin slept through the night.

The effect of melatonin on sleep disorders using SDSC

The change in mean SDSC scores before and after melatonin the overall sleep pattern (total SDSC score) and the six sleep disorders assessed by SDSC are given in Table 3 with their significance.

Change in total SDSC scores after melatonin

The total SDSC score reflects the overall pattern of sleep and is the sum of the 26 items of the questionnaire with a possible range from 26 to 130. Of the 91 children in the study, the mean total pre-melatonin SDSC score was 19.89±3.12 which was reduced to 3.62±0.16 after treatment with 3 mg of melatonin. The paired t-test found

that this change of score of 16.3 was highly significant (p<0.001).

Table 3: Change in mean/median SDSC scores after three weeks of melatonin (n=91).

SDSC Scores	Change in mean/median score after melatonin	Statistical test	P value
SDSC total score	16.3	Paired t test	<0.001
Difficulty in initiating and maintaining sleep (DIMS)	9.0	Paired t test	<0.001
Sleep breathing disorders (SBD)	0.4	Wilcoxon signed rank test	<0.001
Disorders of arousal (DA)	1.4	Wilcoxon signed rank test	<0.001
Sleep wake transition disorders (SWTD)	3.0	Wilcoxon signed rank test	<0.001
Disorders of excessive somnolence (DOES)	2.5	Wilcoxon signed rank test	<0.001
Sleep hyperhydrosis (SH)	0.2	Wilcoxon signed rank test	<0.001

Change in SDSC scores for sleep disorders after melatonin

The mean initial score in difficulty in initiating and maintaining sleep (DIMS) was (10.36±1.84). This was reduced to 1.38±0.84 after melatonin giving a change of score of 9, which was also highly significant (p<0.001). As the change in scores after melatonin for the remaining five sleep disorders; Sleep Breathing Disorders (SBD), Disorders of Arousal (DA), Sleep Wake Transition Disorders (SWTD), Disorders of Excessive Somnolence (DOES) and Sleep Hyperhydrosis (SH) were below 5, the median scores and inter-quartile ranges were taken and the scores compared using the non-parametric Wilcoxon signed rank test and there was a significant difference in all the five disorders as seen in (Table 2).

DISCUSSION

There was much anecdotal evidence shared by the parents about a more ordered and peaceful bedtime and overall satisfaction about the child's sleep after melatonin. Braam et al concluded in a meta-analysis that melatonin decreases sleep latency and number of wakes per night, and increases total sleep time in individuals with intellectual disabilities.[9] Another metaanalysis by Abdelgadir found sleep latency improved from 60 mins or more to approximately 30 mins.[3] Our study showed a significant increase in total sleep time with most of the children sleeping 8 hours or more after melatonin. The time taken to fall asleep (sleep latency) was reduced with all children falling asleep in 15 minutes or less after melatonin. Night awakenings were reduced in nearly all the children and the majority slept through the night. All the children, who were earlier waking up due to dreams slept through the night after melatonin. Weiss et al found the combined sleep hygiene and melatonin intervention resulted in a mean decrease of initial insomnia (sleep onset latency) of 16 minutes relative to placebo.[13] In our study the mean decrease in time to fall asleep was 19.4 minutes, which is comparable.

Smits et al studied 40 normal elementary school children, 6 to 12 years of age, to establish the effectiveness of melatonin treatment in childhood insomnia, in a double-blind, placebo-controlled study and found total sleep time increased 41(19-62) minutes.[14] In our study of the 91 children with neurodevelopmental disorders the median duration of sleep increased after melatonin was 78 (60-120) minutes. Only one of the reviewed studies of children with intellectual deficits reported melatonin-related side effects (i.e., daytime somnolence and naps).[15] In our study there was no report of night waking or daytime somnolence after starting melatonin.

Recent studies have implicated abnormalities in melatonin physiology and the circadian rhythm in children with autism spectrum disorders (ASD). Andersen reported 85% of autistic children treated with melatonin reported improvements in sleep.[16,17] Long-term melatonin treatment was judged to be effective against sleep onset problems in 88% of children with ADHD Cerebral palsy (CP) affects normal movement in different parts of the body with degrees of severity in posture, gait, muscle tone and coordination of movement. Between 23%–46% of children with cerebral palsy experience sleep problems.[18,19] Neuromuscular disorders encompass many diseases that impair the functioning of the muscles, either directly or indirectly like muscular dystrophy. Altered endogenous melatonin profiles have been documented in individuals with various other neuro-developmental disorders such as Down syndrome, Prader-Willi syndrome, and San Filippo syndrome with one notable exception tuberous sclerosis.[14] Four children (4.4%), with sleep disturbances, in our study had autism spectrum disorder (ASD), 22 (24.2%) had attention-deficit/hyperactivity disorder (ADHD), 8 (19.8%) had motor disorders, 27 (29.7%) had communication, speech and language disorders, while the remaining 20 (22.0%) had other neurodevelopmental disorders. Sleep hygiene practices are especially helpful to promote sleep in children with neurodevelopmental compromise. Providing a quiet, cozy and comfortable place to sleep, scheduling sleep and wake timings, a bedtime ritual that prepares the child for bed and quiet activities before bedtime are some

of the sleep-hygiene measures that can help in aiding the child to sleep. Though these and other sleep-hygiene practices may not treat the sleep problem itself, they need to be recognized and addressed to reinforce the regulation of sleep-in addition to melatonin.[7]

Many of the parents in our study commented that the interactive module, handouts and sleep diary were very useful in implementing a regular schedule for the child. The PISI has been found to be a valid and reliable tool for brief screening of insomnia in a busy practice setting. Using PISI at the time of recruitment, on the children with neurodevelopmental disorders who were receiving melatonin we found that most of then children had moderate, 58 (63.74%) to severe 20 (21.98%) insomnia and 13 (14.29%) had mild insomnia, Of the 91 children who participated in the study over 85% had sleep onset problems and less than 80% had sleep maintenance problems More than half the children (58%) gave a history of daytime drowsiness.

The SDSC assesses sleep behavior and disturbances during the previous six months. It was developed to provide a standardized measure of sleep disturbance in childhood through an easy-to-use sleep index score. The SDSC shows good internal consistency despite the relative heterogeneity of the items and is both a valid and reliable tool to assess sleep disorders in children. Besides the total sleep score, the SDSC provides scores for six common childhood sleep-wake disorders and will help the clinician in planning further investigation and management for the child.[5] Melatonin was found to improve the overall sleep pattern and improved mean/median scores for sleep in all the six domains.

Disorders of Initiating and Maintaining Sleep (DIMS) were defined by seven items related to sleep duration, bedtime resistance and sleep latency, problems in falling asleep and night awakenings. Sleep Breathing Disorders (SBD) were assessed by enquiring about breathing difficulties and snoring during sleep. Disorders of Arousal (DA) were defined by three items related to arousal disorders, sleep-walking, sleep terrors and nightmares. Sleep-wake Transition Disorders (SWTD) were included by asking about jerking, repetitive movements, leg movements grinding of teeth and vivid dreams. Disorders of Excessive Somnolence (DOES) were described by the items related to daytime somnolence, difficulty waking up, early morning tiredness and falling asleep during the day. Sleep Hyperhidrosis (SH) were assessed in relation to night sweating on falling asleep and during sleep.

The departmental protocol for children receiving melatonin includes a review after three weeks and melatonin is usually discontinued in three to six weeks. The three weekly review is usually very positive. Besides improvement of the child's sleep pattern and quality, the parents reported that all the members of the family slept better because of the reduction of care-burden and less night-time disturbance due to the child not sleeping. As it seems to be the cultural practice in this community, for the child to share the parent's bed, it follows that, if the child did not sleep the entire family did not sleep. Hence the parents of most of the children in the study were ecstatic about the child's improved sleep with melatonin as it was possible for the entire family to have a good night's sleep since the child slept better. They reported that they needed less effort in getting the child to get to bed and stay in bed and in addition daytime behavior and alertness also improved.

Melatonin is an effective medication for regulating sleep wake disorders in children with developmental compromise. It has a significant role to play in increasing total sleep duration, decreasing sleep latency reducing daytime drowsiness and improving the sleep pattern in developmentally challenged children.

As sleep disruption in one child disturbs the sleep of the entire family, restoration of good sleep with melatonin helps the entire family to get a good night's rest. Though this study gives us valuable information on sleep regulation by melatonin, it is an observational study and clinical trials are required to confirm that melatonin regulates sleep onset and maintenance disorders in children with neurodevelopmental compromise. The improvement seen in the sleep pattern in the electroencephalogram has not been alluded to in this report.

CONCLUSION

Melatonin is an effective medication for treating sleep wake disorders in children with developmental compromise. It has a significant role to play in regulating sleep onset and sleep maintenance in developmentally challenged children. Improvement of sleep invariably has a positive effect on learning and behaviour of the child besides preventing daytime drowsiness. As sleep disruption in one child disturbs the sleep of the entire family, restoration of good sleep with melatonin helps the entire family to get a good night's rest.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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