Developmental Neurorehabilitation, 2013, 1–8, Early Online

informa
healthcare

SUBJECT REVIEW

Effectiveness of melatonin for sleep impairment post paediatric acquired brain injury: Evidence from a systematic review

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(Received 12 October 2012; revised 15 October 2012; accepted 15 October 2012)

Abstract
Objective: To retrieve and review all the relevant literature describing the administration of melatonin to treat impaired sleep in children following acquired brain injury (ABI).
Methods: A systematic search and retrieval of the literature was conducted using advanced search techniques. The retrieval identified 589 papers, seven of which were relevant. Review/outcomes criteria were developed and study quality was determined.
Results: There is paucity of high-quality evidence to support use of melatonin for sleep impairment post paediatric ABI. Variation in dosage, screening and outcome measures, data reporting and a lack of impairment delineation and treatment stratification were recurrent themes.
Conclusion: Retrieved evidence for the effectiveness of melatonin for post paediatric ABI sleep impairment appears promising. There is a clear need for further study in this area to inform clinical and research practices. Recommendations are given.

Keywords: *Sleep impairment*, *paediatric*, *melatonin*, *acquired brain injury*

Introduction

Paediatric acquired brain injury (ABI) comprises predominantly of traumatic brain injury (TBI) and brain tumours. Head injury and malignant neoplasms of the eye, brain and central nervous system are significant causes in paediatric admissions, accounting for 36 513 and 7436 admissions, respectively, to UK hospitals in patients under the age of 15 years in 2010–2011 [1]. Sleep impairment, specifically problems with delayed sleep onset and maintenance of sleep, is reported commonly post paediatric ABI [2–4].

Human sleep architecture is structured into cycles of approximately 90 min, separating into rapid eye movement (REM) sleep and non-REM (NREM) sleep [5]. NREM subdivides into substages 1–4; stages 3 and 4 are the deepest and termed slow-wave sleep (SWS) [6, 7]. The different stages correlate with different patterns of cortical oscillations shown via electroencephalography and can therefore be demonstrated as distinct from one another [7]. Sleep plays a critical role in memory and learning, aiding the consolidation of learning and the improvement of memory, with each stage of sleep having its own individual input into memory consolidation processes [5–8].

Working memory performance is poorer in children when sleep is less efficient and sleep latency is greater [9]. Reduced, disrupted or fragmented

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ISSN 1751–8423 print/ISSN 1751–8431 online/13/000001–8 © 2013 Informa UK Ltd.
DOI: 10.3109/17518423.2012.741147

sleep increases the probability of cognitive and academic problems and impaired daytime performance [10–12]. Attention problems are also likely to increase, especially with heightened task complexity, as are behavioural problems [10, 13]. Simple reaction time and alertness also reduce in paediatric populations who are sleep restricted [14]. The impact of impaired sleep is especially problematic in the paediatric post-ABI population and can continue for many years [15, 16]. It places a significant burden on family functioning and can have adverse consequences for the child and their family [3]. This is observed particularly in the context of post-ABI fatigue [17].

Prescription of melatonin is common in the treatment of impaired sleep in the general population, aiming to replicate the desired effects of the melatonin produced endogenously by the pineal gland [18, 19]; that is, to modulate and aid the initiation and maintenance of sleep. A critical review of published evidence for treatment of impaired sleep in children following ABI has not been conducted previously. Given the established concerns for this population, determining effectiveness of melatonin is apposite.

Methods

A systematic search and retrieval of all existing literature was conducted using advanced search techniques and outcomes/review criteria were developed. An advanced search of AMED, CINAHL, EMBASE, MEDLINE, PsycINFO, BIOSIS Previews, Web of Science and CAB Abstracts was completed. All databases were searched from 1980 to present except AMED which was searched from 1985 to present. Cochrane Library including Cochrane Reviews, Database of Abstracts of Review of Effects was also searched.

Specified search terms were: brain adj2 injur* OR head adj2 injur* OR brain adj2 tumo?r* OR neurooncolog* OR neuro-oncolog* OR brain adj2 cancer* OR brain adj2 neoplasm* OR brain adj2 carcinoma* OR (head or cerebr$ or capitis or brain$ or forebrain$ or hemispher$ or intra-cran$ or inter-cran$) adj2 (injur$ or trauma$ or damag$ or wound$ or contusion$) AND Insomnia* OR Disorder* adj2 sleep* AND Melatonin OR Circadin OR *N*-acetyl-5-methoxytryptamine. MeSH terms were: 'Brain Injuries', 'Brain Neoplasms', 'Sleep Disorders', 'Hormones', 'Biochemistry studies – Proteins, peptides and amino acids', 'Sleep', 'Neoplasms', 'Brain Tumour', 'Melatonin 2 Receptor', 'Melatonin Receptor', 'Melatonin Derivative', 'Melatonin 1 Receptor', 'Brain Damage', 'Melatonin MT', 'Melatonin MT2', 'Traumatic brain Injury' and 'insomnia'.

Inclusion criteria

Inclusion was dependent on the following criteria: paediatric ABI population; under 19 years of age with a described impairment to sleep and administration of melatonin. Retrieved papers were reviewed independently and a decision was made using objective criteria established by the Oxford Centre for Evidence-based Medicine [20] to rate quality of evidence. Non-English language reports and studies of participants with ABI over 18 years of age with impaired sleep were excluded.

Analysis

The retrieved data did not permit meta-analysis or use of a vote count procedure because of inconsistencies across studies in their use of comparable outcomes or lack of detailed data reporting. Consequently, a descriptive analysis was performed.

Results

Of the 589 papers retrieved, seven [21–27] were relevant to the specified criteria, detailing the use of melatonin to treat sleep impairment post paediatric ABI. Retrieved data are presented in Table I, their year of publication spanning from 1994 to 2009. The total number of participants was 10. Age range was 5–17. A range of pathologies and conditions were identified: hypoxic-ischaemic injury [21], haemorrhagic lesion [22], bithalamic lesions [26], TBI [25], brain tumours [21, 23, 24, 27] and sensory impairments [21, 24]. Some experienced ABI in infancy [21, 24] and others sustained ABI later in childhood [22, 23, 25, 26]. One study did not state the age at which participants were diagnosed [27]. Level of evidence [20] was rated at Level 5 ('expert opinion without explicit critical appraisal, or based on physiology, bench research or ''first principles''') for five of the seven studies [21–24, 26]. All involved single case methodology. The remaining papers were rated at Level 2 b ('individual cohort study (including low quality RCT; e.g. $<80\%$ follow-up)') [25] and Level 4 ('Case-series (and poor quality cohort and case–control studies)') [27].

Discussion

The conducted systematic search incorporating advanced techniques and retrieval of the literature

Table I. All retrieved studies evaluating effectiveness of melatonin for the treatment of impaired sleep following paediatric ABI.

Studies		Study group and characteristics	Level of evidence [20]	Measures	Melatonin dosage	Key results	Comments
Jan et al. [21]	Case 1	$N=1$ (aged 14) Hypoxic-ischaemic insult after birth 'Fragmented' sleep pattern since infancy	Level 5 (single case study)	'Standardised sleep charting' completed by caregivers to record sleep pattern prior to and during testing	2.5 mg nocte	Improvement seen within three days Sleep not fully maintained but less distress on waking More alert during the day; afternoon naps decreased	• Screening for inclusion was 'a severe sleep disorder' – classified after failure to respond to 'conventional treatment', when family was in 'crisis' • Irritability and lethargy ceased • No side-effects after 10 months of treatment
	Case 2	$N=1$ (aged 5) Large optic nerve glioma (involving the chiasm, hypothalamus and partially involving both optic radiations) Developed at 9 months 'Fragmented' sleep disturbance	Level 5 (single case study)	'Standardised sleep charting' completed by caregivers to record sleep pattern prior to and during testing	2.5 mg nocte	No beneficial effect on sleep observed	• Mood and functioning improved when the dose was doubled • No adverse side-effects • After 6 months melatonin was ineffective even at 20 mg dose, phased out
	Case 3	$N=1$ (aged 5) Hypoxic-ischaemic brain damage present at birth 'Severe fragmented' sleep disturbance since infancy	Level 5 (single case study)	'Standardised sleep charting' completed by caregivers to record sleep pattern prior to and during testing	5 mg	Melatonin greatly improved sleep patterns Sleep was less restless and awoken less by noises	• Improved behaviour and seizure control • No adverse side-effects
Etzioni et al. [22]		$N=1$ (aged 14) Haemorrhagic lesion in the pineal region diagnosed age 14 Caused insomnia symptoms and no consolidated night sleep	Level 5 (single case study)	Parent and child report of sleep pattern. Blood serum melatonin levels measured prior to treatment. Three 7-day actigraphic sleep measures completed: prior to treatment, a week into treatment and after cessation of treatment	3 mg nocte	Melatonin found to improve sleep Direct correlation between melatonin levels and sleep disturbance	• When melatonin treatment stopped, sleep disturbance became worse than during the melatonin treatment, but milder than before treatment
Jan et al. [23]		$N=1$ (aged 13) Primitive neuroectodermal pineal tumour Chronic sleep disturbance	Level 5 (single case study)	Somnologs recorded by parents and hospital staff to monitor sleep duration. Plasma	5 mg nocte fast-release	Improved quality and quantity of sleep within couple of days Melatonin replacement	• Due to the lesion, nighttime melatonin production was suppressed • Other factors present:

(*continued*)

Table I. Continued.

Studies	Study group and characteristics	Level of evidence [20]	Measures	Melatonin dosage	Key results	Comments
	after tumour resection Fragmented sleep and severe delay in sleep onset		melatonin concentrations measured during hospitalisation. Parent report on quality of life		therapy benefits those who have deficient melatonin synthesis	had analgesic dependency and was depressed • Patient upped dose to 25 mg against medical advice and despite no beneficial effect to sleep pattern, patient was hospitalised and treatment discontinued. Sleep deteriorated immediately. On recommencing, 9 mg of fast-release and 6 mg of controlled-release melatonin was prescribed. Duration of sleep increased after melatonin treatment was restored • No adverse effects from four and a half years of melatonin treatment
Zotter et al. [24]	$N=1$ (aged 6) Optic glioma diagnosed at 11 months, had a severe sleep disorder Blind with a learning disability, and has moderate spastic tetraplegia	Level 5 (single case study)	Polysomnography and sleep diaries prior to melatonin administration. 24 h plasma melatonin measures taken prior to testing	6 mg nocte	Melatonin led to a synchronised sleep-wake cycle to a regular 24 h schedule, with a total nighttime sleep of 10 h	• Failure to respond to behavioural measures or hypnotic drugs • Awakenings continued between 02:00 and 05:00 • 2.5 mg methylphenidate administered at 1 pm as a stimulant medication to prevent day sleep • Participant had a normal melatonin profile prior to treatment
Kemp et al. [25]	$N=7$ (aged 16–65) TBI Chronic sleep disturbance	Level 2 b (randomised double-blind	Self-completed sleep diary during entire process. Neuropsychological	5 mg	Direct comparison between 5 mg melatonin and 25 mg amitriptyline	• Quality of sleep was self-reported • Some of the participants

		controlled cross-over trial)	testing and clinical interview completed three times, prior to testing, after first drug and after second drug. Provided measures on daytime alertness, sleep duration, sleep quality and sleep latency		No significant differences identified. However, effect sizes on four sleep variables reflected improvement. Effects of both drugs were in a beneficial direction	may be out of the selection criteria (age) • Cognitive performance and mood did not change during the study
Kothare et al. [26]	$N=1$ (aged 8) Bithalamic lesions, diagnosed age 4 Sleep fragmentation with alpha-intrusion in non-REM sleep, and poor SWS	Level 5 (single case study)	Baseline polysomnography, neuropsychological evaluation and parental report measure prior to treatment. Re-evaluation after 6 months of continuous treatment	Dosage not stated	Unresponsive to treatment with maximum dose of melatonin	• Unresponsive to treatment with traditional medications and interventions • No statement of what maximum dose of melatonin was or how this was assessed • Sodium oxybate achieved a near normalisation of the child's severely disrupted sleep profile and sleeping pattern. Marked improvement in behaviour, attention and executive functioning skills, including level of impulse control, frustration tolerance, processing and response speed and mental flexibility
Lipton et al. [27]	$N=3$ (aged 15, 15 and 22) Craniopharyngioma survivors Had undergone both surgical extirpation and radiotherapy All had REM-related obstructive sleep apnoea	Level 4 (case-series)	Wrist actigraphy for 2–3 weeks prior to testing. Plasma melatonin levels and 20-channel polysomnography during admission and testing	Dosage not stated	Rest/activity patterns were in general alignment with 24 h light–dark cycle Plasma melatonin levels and average nocturnal melatonin levels were all markedly decreased compared to historical controls	• Unclear whether hormonal supplementation administered was melatonin • One participant out of age selection criterion • All participants were morbidly obese • Irregular bed times, frequent nighttime activity and inappropriate daytime episodes of rest were observed despite a protocol of scheduled bed and wake times

revealed little and unclear evidence for the use of melatonin to treat impaired sleep following paediatric ABI. The outcome measures used in the studies were variable, totalling nine different measures; the most favoured being non-defined polysomnography or sleep charting [21, 23, 24, 26, 27]. Four of the retrieved references [22–24, 27] compared levels of endogenous melatonin produced post-ABI with impaired sleep patterns, but none measured melatonin levels in the body throughout the treatment period. This would allow levels of melatonin in the body to be directly linked to sleep patterns post-ABI, determining physiological and psychological impact of impaired sleep, and the effectiveness of prescribed melatonin in treating this.

Dosage of prescribed melatonin ranged from 2.5 mg to a maximum of 25 mg [21–25]. Two studies did not state the melatonin dose [26, 27]. One paper indicated that dosage needs to be assessed on an individual basis [21]. Treatment duration for melatonin also varied across retrieved studies [21–27]; ranging from 1 month to 4.5 years. Five studies [21, 22, 24, 26, 27] did not clearly define duration of administration. This variation may likely be attributed to the majority of relevant papers using the single case methodology which modified, continued or ceased melatonin treatment according to the individuals' response. From retrieved studies, the response to melatonin was reliable, some reported beneficial improvement [21–24], others reported no improvement [26, 27] and some found improvements that were neither long term nor significant [21, 25]. Consequently, there was little information by which to derive themes within the relevant papers, due to distinct differences in the key features and reported results. This made it difficult to build an accurate comparison between the papers, to produce clear information from which to inform future clinical recommendations or direction for research. Therefore, retrieved papers [21–27] have identified that oral melatonin may be useful in the treatment of sleep problems in those who have experienced ABI.

It is important to note the limitations common to all identified studies, such as the small number of participants. Of the relevant studies retrieved [21–27], many failed to discuss the type of melatonin administered – synthetically produced melatonin is available in either a fast-release or slow/controlled-release form. The fast-release form intends to aid the initiation of sleep and the controlled-release the maintenance of sleep [28]. No studies examined combination use. Only one study [23] stated both the form and the dosage of melatonin administered, and only one other paper acknowledged the existence of the two types [21].

Prescribed melatonin mode of action is also difficult to determine from the retrieved studies. Some present a direct relationship between low endogenous melatonin levels and sleep impairment [22], another refers to a patient with a severe sleep disorder with a normal melatonin profile [24] and another attributes the suppressed production of nighttime melatonin to the participant's brain lesion [23]. It has been the suggested that impaired sleep patterns are related to the suprachiasmatic nucleus in the hypothalamus [27], and this is also known to be a primary action point of melatonin [18]. However, although this area is known to have significant influence on sleep patterns, some studies identified individuals with sleep problems had intact hypothalamic areas, suggesting damage or dysfunction may not be the sole cause of individuals' sleep impairment [21]. Regardless of the mechanism, it is clear that response to melatonin varied among participants [21–27].

Recommendations

The retrieved literature demonstrates a lack of participant screening for a specified sleep disorder prior to treatment with melatonin. Many attempt to define sleep impairment using adjectives: 'fragmented', 'severe' or 'delayed onset'. Screening participants would enable the exclusion of rival hypotheses which could more appropriately account for impaired sleep such as the presence of an affective disorder, or absent sleep hygiene. Increased accuracy in sleep disorder diagnosis as specified in the International Classification of Sleep Disorders: second edition [29], may also help to delineate impairment and consequent stratification of treatment [30]. Later studies used neuropsychological measures and their continuing inclusion in future studies is vital to determining the potential benefits to neurocognitive and learning outcomes.

From retrieved evidence, melatonin has been used with paediatric patients experiencing impaired sleep after ABI with conflicting results (Grade D) [20]. Formal assessment and diagnosis of sleep incorporated into clinical assessments for the paediatric ABI group is advised (Grade D) [20]. Individualised *n*-of-1 monitored trials of melatonin for paediatric ABI with impaired sleep or inclusion in a therapeutic randomised controlled trial is advised (Grade D) [20]. The presence of a collection of inconsistent and inconclusive studies, predominantly with Level 5 evidence [20] indicates a very significant opportunity for further studies to determine the effectiveness of prescribed melatonin to the paediatric ABI population, to produce more cohesive results.

Some studies retrieved were commenced when caregivers and professionals had tried both pharmaceutical and non-pharmaceutical methods of sleep management strategies to no effect [21, 24, 26]. Only one pilot randomised double-blind controlled cross-over trial [25] comparing the effects of melatonin and amitriptyline on sleep-related variables involving children was identified. Although no significant differences were identified, effects sizes for melatonin relative to baseline on variables for alertness, duration, sleep quality and sleep latency demonstrated an improvement. Increased knowledge and replicated results in the use of melatonin for impaired sleep in paediatric ABI may mean it ceases to be a treatment of 'last resort' for certain types of paediatric sleep impairment post-ABI.

Conclusion

Evidence demonstrates that fatigue, irritability, diminished attention and impaired behavioural regulation are prevalent symptoms following paediatric ABI [21]. These have significant consequences for the child, neurorehabilitation outcomes and the child's family [3]. Improved routine assessment of sleep and its consequences post paediatric ABI may be of significant benefit to clinical practice and outcome. Agreed formal assessment [31] with potential selective use of actigraphy and polysomnography is indicated to further develop studies for this patient group [32]. Proposed studies should also seek to develop guidance directing combination prescription and efficacy of fast- and slow-release melatonin preparations. Given the established concerns for sleep impairment following paediatric ABI and the documented potential of melatonin, there is a concerning paucity of research in this area. This may reflect complexity and variability of ABI presentation and sleep disorders being hard to diagnose and treat. There are potential benefits of melatonin for the management of sleep problems following paediatric ABI and it is suggested that treatment using a closely monitored $n = 1$ trial approach occur and definitive RCTs should be conducted in order to establish the effectiveness of melatonin in the management of impaired sleep in children with an ABI [33, 34].

Acknowledgements

The authors thank Dr Michael Clarke, Consultant Paediatric Neurologist for his immensely useful comments.

Declaration of interest: The authors report no declarations of interest. The authors alone are responsible for the writing and content of this article.

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