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Comparing the effectiveness of sleep deprivation and melatonin for inducing sleep in paediatric EEG

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Abstract

Aim: Our aim was to compare the efficacy of the main methodologies in attaining sleep and EEG abnormalities in children with a view to producing recommendations on best practice.

METHOD: 51 UK centres participated. Methods for sleep induction (sleep deprivation, melatonin and combined sleep deprivation/melatonin) were compared. Data pertaining to demographics, achievement of stage II sleep and recording characteristics (duration of study, presence of epileptiform activity in awake/sleep states) were prospectively collected for consecutive patients between November – December 2013.

RESULTS: 565 patients were included. Age range was 1-17 years (mean 7.8), 27.7% had an underlying neurobehavioural condition. Stage II sleep was achieved in 69% of sleep deprived studies, 77% of melatonin studies and 90% of combined intervention studies ($p=0.0001$, χ^2). In children who slept there was no difference between the 3 interventions in eliciting epileptiform discharges. In children who did not sleep, epileptiform abnormalities were seen more often than following sleep deprivation alone ($p=0.02$, χ^2). Seizures were rare.

INTERPRETATION: Combined sleep deprivation/melatonin is more effective than either method alone in achieving sleep. The occurrence of epileptiform activity during sleep is broadly similar across the three groups. We recommend the combined intervention to induce sleep for paediatric EEG.

What this paper adds

- Sleep deprivation/melatonin is more effective in achieving sleep than either sleep deprivation or melatonin alone.
- Sleep latency is shorter with combined sleep deprivation/melatonin.
- When children do sleep, there is no difference in the occurrence of epileptiform abnormalities between different induction methods.
- Seizures are rare in sleep EEG recordings.

Running title: Paediatric sleep EEG

Introduction

Electroencephalography (EEG) remains a central investigation in children with epilepsy, providing diagnostic information and contributing to syndromic classification. However, the detection of epileptiform abnormalities remains around 50% for a standard, awake recording (1). In the event of a normal study, practice guidelines recommend a sleep deprived recording be obtained (2, 3). The exact mechanism behind any potentiation in diagnostic yield remains a little uncertain but it is possible that, at least in children, sleep deprivation, and not sleep per se, is the activating factor (4).

There are two main strategies for achieving sleep during an EEG in children; sleep deprivation and administration of melatonin. Some studies suggest there is little difference between the two in terms of efficacy, with melatonin as effective as sleep deprivation in achieving sleep and activating epileptiform discharges (5, 6). It is not clear if there is an additive or synergistic effect (7). Keeping a young child awake can be difficult and cause significant distress and disruption to both child and family and it has been suggested that melatonin may be a more suitable approach in such cases (8).

Many of the studies on the effect of sleep deprivation are several decades old and comprise heterogeneous patient populations (9). We sought to ascertain the effectiveness of the three most commonly employed methods to achieve sleep during a paediatric EEG recording in the UK; sleep deprivation, melatonin and combined sleep deprivation/melatonin. To do this we undertook a large, prospective multi-centre study incorporating both secondary and tertiary referral environments. Our aim was to compare the different methods in terms of achieving sleep and potentiating the diagnostic yield in terms of provoking epileptiform activity and seizures.

The present work is a National Service Evaluation designed to determine the efficacy of sleep deprivation in children to produce diagnostically useful information in a large population of paediatric patients. The participating bodies (Association of Neurological Scientists and British Society for Clinical Neurophysiology) represent professionals providing EEG services in the UK.

Methods

Eighty-three neurophysiology departments across the United Kingdom were invited to take part in this prospective service evaluation. Fifty-one centres participated (see appendix A) and each was free to use their own protocol for the different methods of achieving sleep. Details of these have been published previously (10). Data were collected through prospective completion of a questionnaire for consecutive patients between 1st November 2013 and 31st December 2013 (see appendix B). Questions included demographic details, duration of recording and the presence of co-existent neurobehavioural conditions such as autism, attention deficit disorder and learning disability. Further information on the achievement of sleep, duration of sleep and sleep latency was obtained. The study proforma was completed by the recording clinical physiologist (EEG technologist).

For the purpose of the present study sleep was documented as obtained if stage II sleep features were seen. The presence of epileptiform discharges (sharp waves/spikes with or without slow waves) in both the awake and sleep portions of the study was also detailed. Clarification of whether such discharges were seen on previous, standard awake EEGs was sought. Occurrence of seizures was documented. Group comparisons (sleep deprivation, melatonin and combined sleep deprivation/melatonin ("combined intervention")) were either by analysis of variance (ANOVA) with Tukey post-hoc testing (ANOVA+T), or χ^2 analysis as appropriate using GraphPad Prism (version 7). Post hoc tests were used as there were three groups and further exploration of the difference among means was required. Binary logistic regression was performed using SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, NY, USA). The goodness-of-fit of the model was assessed by means of the Hosmer and Lemeshow statistic (Chi-square = 13.820, p=0.084), indicating a good fit to the data. Residual analysis was performed and determined that the model met the linearity, normality, and homogeneity of variance assumptions of logistic regression. Ethical approval is not a requirement for the service evaluation of routine clinical practice (UK NHS National Research Ethics Service guidelines), nevertheless the project was registered as a service evaluation with Sheffield Children's Hospitals NHS Trust Clinical Effectiveness Unit.

Results

An initial total of 688 patients were submitted to the study. 119 recordings were natural sleep studies in very young children (i.e. not sleep deprived or melatonin induced) and 4 were sedation induced (chloral hydrate) and so were excluded from the present analysis. A total of 565 patients were included from the participating centres (table 1). The age range was 1-17 years with a slight preponderance of younger children in the melatonin group. This reached statistical significance in post hoc comparison between the sleep deprivation and combined intervention groups. 27.7% of included children had an existing diagnosis of a neurobehavioural condition with these children slightly over-represented in the combined intervention group with a post hoc significance difference observed between the combined intervention group and sleep deprivation group.

A high proportion of children achieved sleep across all groups (table 2). The combined intervention was more significantly effective than the single interventions alone. Similarly, the combined intervention was also associated with a shorter sleep latency and a shorter sleep time that the single interventions. There was no significant difference in the duration of the recordings between the different intervention groups.

Multivariate analyses demonstrated that children without neurobehavioural conditions were 1.65 times more likely to sleep than children with such diagnoses (table 3). Adjusting for the effects of a neurobehavioural condition, as well as age, we found that those receiving the combined intervention remained more likely to sleep than those receiving a single intervention alone. Children receiving melatonin alone were 2.7 times less likely to sleep than those receiving the combined intervention. For sleep deprivation alone children were 3.8 times less likely to achieve sleep.

The potential diagnostic yield of the different groups was also compared by examining the occurrence of epileptiform activity. In the larger group of children that did sleep, epileptiform activity was seen in sleep only (i.e. not in the awake portion of the recording) in approximately a quarter of recordings (table 4 “Slept: see epileptiform activity in sleep not in resting record, RR”). Similarly, epileptiform activity was seen more frequently in sleep than in the awake resting record in around one quarter of recordings (table 4: Slept: epileptiform activity exacerbated in sleep”). There was no significant difference observed between the three intervention groups for either of these analyses.

In children who did not sleep, a comparison was made to a standard recording when such a test was done i.e. when the child had not gone straight to a sleep deprived study (table 4 “No sleep: epileptiform activity not previously seen now recorded). In this analysis there was a slight improvement in the yield of epileptiform abnormalities which reached significance in the comparison between melatonin and sleep deprivation; abnormalities were more frequently observed in the melatonin group. Seizures were only rarely encountered: 6% in sleep deprivation, 4% in melatonin and 6% in the combined intervention group (χ^2, P=0.6).

Discussion

The accurate diagnosis of epilepsy in children is essential to enable clinicians to provide appropriate treatment and accurate prognosis. Estimates vary but up to 40% of children referred on to tertiary epilepsy centres may not have epilepsy (11). The routine outpatient EEG remains an integral part of the diagnostic work-up of patients with suspected epilepsy (12). In the event of a negative routine, awake study, most centres will then undertake a sleep recording. Although reports vary in the extent of the effect, it is accepted that sleep during an outpatient EEG increases the diagnostic yield (9, 13-15).

UK practice for obtaining sleep is variable with <20% of centres employing published guidelines and a mixture of methods employed (10). To our knowledge no direct comparison of sleep deprivation, melatonin and combined sleep deprivation/melatonin has been undertaken either prospectively or retrospectively. Determining the utility of the different means of undertaking sleep EEG recordings is an important issue as an interpretable awake recording can be difficult to achieve in children and standard sleep deprivation can cause significant disruption to both parents and child. Our aim was to establish which of three methods of achieving sleep – sleep deprivation, melatonin and a combined intervention – were efficacious in a large multi-centre study.

In our study, sleep induction was best achieved by the combination sleep deprivation and melatonin. An additive effect has not been reported in other reports comparing the two (7), although none have included a sample size of the size used in the present study. The percentage of patients achieving sleep ranged from 69% (sleep deprivation) to 90% (combined intervention), findings in keeping with previous reports. Wassmer et al., reported 78% of children sleeping following sleep deprivation (8); De Roos et al., 73%(4). For melatonin figures are similar, for example, Gustafson et al., 70%; Wassmer et al., 79% (6). It has been found that melatonin is more acceptable to the family than sleep deprivation which can exacerbate any behavioural issues (6). One might postulate that such effects are worse in children with neurobehavioral conditions. We did not collect data on the acceptability of the different tests and are not able to make such comparisons directly. However, our multivariate analysis adjusting for the effects of a neurobehavioural condition, demonstrated that the combined intervention was more likely to achieve its objective and induce sleep and so if behavioural difficulties were encountered on the day of the recording they did not impact upon its efficacy.

Sleep latency was also significantly reduced in the combined intervention group. This may be of value to both the recording physiologists and family in terms of ensuring appointments run to time. Interestingly, sleep duration was also of a shorter duration in the recordings undertaken using the combined intervention. Unfortunately, we are not able to definitively conclude why this was the case. One possibility is that this observation is linked to sleep latency i.e. the child falls asleep more quickly reducing the overall time of the recording. It may also be that the exact recording duration was at the discretion of the physiologists and that a judgement was made in favour of concluding the recording more quickly if the child fell asleep quickly.

Epileptiform abnormalities were found during periods of sleep in around one third of studies and there was no significant difference across the three interventions in our cohort. If the child did not sleep then epileptiform activity was significantly more common in those who received melatonin versus sleep deprivation. This contrasts with other reports in which parity has been documented (6). However, given the small numbers of children who did not sleep in our study, particularly in the combined intervention group, caution should be exercised in interpretation of our findings.

Overall, our data support previous assertions that sleep improves the sensitivity of the EEG in detecting epileptiform activity (1, 16). Our data would also support the possibility that sleep deprivation itself induces EEG abnormalities in the event of the child remaining awake. This is a debated area with evidence to support both sides of the argument (17) and has many potential confounding factors such as age, anti-epileptic medication, degree of sleep deprivation and underlying epileptic syndrome. For example, Gilbert et al., found no significant increase in the diagnostic yield from sleep deprivation but only requested parents keep their child awake two hours later than usual (18). Furthermore, it is possible that the increased diagnostic yield in the children who did not sleep may simply reflect a second recording, rather the effect of sleep deprivation.

There are several limitations to this report. As a service evaluation we did not seek to change the practice of different centres, rather, standard local practice was employed. As a result, there are variations in the amount of sleep deprivation undertaken, which may in turn be determined by the age of the child. For example, some centres in the UK advocate half the usual amount of sleep is recommended for young children, but for older children total sleep deprivation can be recommended. Overall, there would appear to be no clear consensus (9). Gilbert et al., attempted to compare two different approaches to sleep deprivation which they termed standard sleep deprivation, which varied the wake up time for the child based on age, and partial sleep deprivation, for which children were asked to stay awake 2 hours past the usual bedtime (if aged ≥2 years)(18). The odds of epileptiform discharges on the EEG were not increased by either paradigm, although changes to the frequency of epileptiform discharges were not made through a formal quantification process

In addition, there will be variation in the administration of melatonin, including both the dose and time given prior to recording. In some instances, a second dose of melatonin may have been given. This is a reflection of the different strategies employed in studies (5-7, 19). Furthermore, the duration of sleep time may have been affected by factors such as the time available for the test or a real-time clinical judgement on the utility of the examination. We have also included a large age range in our analysis. Future studies may clarify issues by employing a protocol defining, for example, sleep deprivation and melatonin doses and randomising children into different paradigms.

Conclusion

In our large, multi-centre prospective evaluation of sleep induction with sleep deprivation, melatonin or combined sleep deprivation and melatonin, the combined intervention was most effective with sleep captured in 90% of recordings. In children who slept, the detection of EEG abnormalities was similar across the three groups. Recording a repeat wake EEG in patients who received sleep deprivation and/or melatonin also improved the diagnostic yield. Seizure provocation was rare. While all 3 methods for recording sleep are valuable we would recommend the use of combined sleep deprivation and melatonin as the most effective in obtaining a sleep recording.

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Table 1. Demographic details.

	All patients n=565	Sleep deprivation	Melatonin	Combined intervention n= 143	P value	Statistical test
Mean age (years)	7.8	8.7[a]	6.1[a,b]	8.3[b]	<0.0001	ANOVA +T
Age range (years)	1-17	1-17	1-16	2-17		
Male, (%)	55.6	51.2	55.1	63.6	0.06	χ^2
Neurobehavioural condition, (%)	27.8	21.1[c]	28.4	38.5[c]	0.001	χ^2

Significant post hoc differences:

Age - [a]sleep deprivation vs. melatonin; [b]melatonin vs. combined intervention.

Neurobehavioural condition - [c]sleep deprivation vs. combined intervention.

Table 2. Achievement of sleep, sleep latency and duration and EEG recording length.

	Sleep deprivation	Melatonin	Combined intervention	P value	Statistical test
Achieved sleep, n (%)	172 (69)[a]	137 (77)[a]	128 (90)[a]	0.0001	χ^2
Mean (SD) sleep latency (mins)	19(13)[b]	19.2(16)[b]	13.8(11)[b]	0.0001	ANOVA+T
Mean (SD) duration of sleep (mins)	27(14)[c]	26(11)[c]	21(12)[c]	0.0008	ANOVA+T
Mean (SD) duration of recording (mins)	49(16)	51(18)	47(19)	0.1	AONVA +T

SD – standard deviation.

Significant post hoc differences:

Achieved sleep – [a]combined intervention vs. sleep deprivation or melatonin.

Sleep latency – [b]combined intervention vs. sleep deprivation or melatonin.

Duration of sleep – [c]combined interventionvs. sleep deprivation or melatonin.

Table 3. Odds ratio for attainment of sleep adjusted for age and neurobehavioural conditions

Variable	Category	n/N (%)	OR	95% C.I.	p
Neurobehavioural condition	Yes	157/565 (27.8%)	-	-	-
	No	408/565 (72.2%)	1.63	1.04-2.54	0.032
Age	-	565/565 (100%)	0.99	0.95-1.03	0.62
Intervention	Melatonin	176/565 (31.2%)	0.38	0.2-0.73	0.004
	Sleep deprivation	246/565 (43.5%)	0.26	0.14-0.49	<0.001
	Combined intervention	143/565 (25.3%)	-	-	-

Statistical test used: Binary logistic regression. The total accuracy of the model was 77.9%. The explanatory co-variables included in the model were strongly associated with the dependent variable (shown in Table 2).

Table 4. Recording epileptiform activity during studies with and without sleep.

	Sleep deprivation	Melatonin	Combined intervention	P value	Statistical test
Slept: see epileptiform activity in sleep not RR, n (%)	37/172 (22)	36/137 (26)	33/128 (26)	0.5	χ^2
Slept: epileptiform activity exacerbated in sleep, n (%)	38/172 (22)	33/137 (24)	38/128 (30)	0.3	χ^2
No sleep: epileptiform activity not previously seen now recorded, n (%)	6/56 (11)[a]	10/29 (34)[a]	3/9 (33)	0.02	χ^2

Post hoc: [a]difference between sleep deprivation and melatonin

Appendix A. List of centres that took part.

Addenbrooke's Hospital, Cambridge

Alder Hey Children's Hospital, Liverpool

Birmingham Children's Hospital, Birmingham

Bristol Royal Hospital for Children, Bristol

Calderdale Royal Hospital, Halifax

Craigavon Area Hospital, Belfast

Dorset County Hospital, Dorchester

Epson and St Helier Hospital, Surrey

Frenchay Hospital, Bristol

Gloucestershire Royal Hospital, Gloucester

John Radcliffe Hospital, Oxford

Kent and Canterbury Hospital, Kent

King's College Hospital, London

Lincoln County Hospital, Lincoln

Luton and Dunstable Hospital, Luton

Manor Hospital, Walsall

Mater Hospital, Belfast

New Cross Hospital, Wolverhampton

Ninewells Hospital and Medical School, Dundee

Norfolk and Norwich University Hospital, Norwich

North Manchester General Hospital, Manchester

Northampton General Hospital, Northampton

Nottingham University Hospital, Nottingham

Plymouth Hospital NHS Trust, Plymouth

Poole Hospital, Poole

Royal Derby Hospital, Derby

Royal Devon and Exeter Hospital, Exeter

Royal Hospital for Sick Children, Edinburgh

Royal Hospital for Sick Children, Glasgow

Royal London Hospital, London

Royal Manchester Children's hospital

Royal Preston Hospital, Preston

Royal United Hospitals, Bath

Royal Victoria Infirmary, Newcastle

Salford Royal Infirmary, Manchester

Sheffield Children's Hospital, Sheffield

St George's Hospital, London

St Lukes Hospital, Bradford

St Peter's Hospital, Chertsey

Sunderland Royal Hospital, Sunderland

The Ipswich Hospital, Ipswich

The James Cook University Hospital, Middlesbrough

The Queen Elizabeth Hospital, Kings Lynn

The Royal Surrey County Hospital, Guildford

The Whittington Hospital, London

Queen Alexandra Hospital, Portsmouth

Queen's Hospital, Romford

University College London Hospitals, London

University Hospital of North Staffordshire, Stoke-on-Trent

University Hospital of Wales, Cardiff

University Hospital Southampton, Southampton

Worcestershire Royal Hospital, Worcestershire

Appendix B. Data collection proforma

FORM B: Please complete for each patient

Postcode of Centre (Please complete)		**Local EEG number** (Please complete):		**Project code** (Do not complete – for office use only)	

1. What is the age of the patient?	
2. What is the gender of the patient?	M / F
3. What was the referral diagnosis?	Epilepsy Other (Please state)
4. Did the patient have previous standard EEG?	Yes / No
5. If Yes: was the previous EEG	Normal Abnormal Unrecordable / Uninterpretable
5. Did the patient have a previous failed sleep EEG? (Where child did not sleep)	No (no previous failed EEG) Yes – failed sleep EEG without melatonin Yes – failed sleep EEG with melatonin
6. Does the patient have an underlying neuro-behavioural condition? e.g. Autism, ADHD, Learning disability	Yes / No
7. What was the time of the appointment? (24 hour clock)	
8. What type of sleep study was undertaken?	Natural sleep Melatonin Sleep deprived (complete/partial) Sleep deprivation and melatonin Sedation
9. Did a seizure or any other adverse event occur?	No Yes – Seizure Yes – Other adverse event (please state)
9. Was sleep attained? **If No answer questions 10 and 11 only** **If Yes go to question 11 and complete questionnaire**	Yes / No
10. Did the record produce unequivocal epileptiform (i.e. sharp waves/spikes with or without slow waves) EEG activity NOT seen in the previous record?	Yes / No / No previous record
11. How long was the recording in total? (minutes)	
12. How far into the recording was sleep attained (please give latency to Stage 2 sleep in minutes)	
13. How long was sleep recorded for? (minutes)	
14. Did sleep produce unequivocal epileptiform (i.e. sharp waves/spikes with or without slow waves) EEG activity NOT seen in the resting record (either current or previous)?	Yes / No
15. Did sleep exacerbate epileptiform activity previously seen in the resting record?	Yes / No