THE ROLE OF MELATONIN IN THE EFFECTIVE ATTAINMENT OF ELECTROENCEPHALOGRAMS IN CHILDREN IN A SUB-SAHARAN AFRICAN SETTING

BY

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Statement: This research is based on independent work performed by the candidate. None of this work is being, or has been, submitted for another degree to any other university. This work has not been reported or published prior to registration for the above mentioned degree.

DECLARATION

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LITERATURE REVIEW

Introduction / background

The relevance of sleep EEG studies in children:

Electroencephalogram (EEG) is a useful tool for investigating specific problems of the central nervous system in children. In this age group, specifically, it can assist in the differentiation between non-epileptic events and epilepsy. For those found to have epileptiform activity on their EEGs, it can support a syndromic diagnosis with significant management implications for the patient.[1]

The state of sleep is often preferred both to avoid artifact and to increase the rate of detection of epileptiform discharges in certain types of childhood epilepsies.[1] Natural sleep is the preferred state and children are routinely sleep deprived prior to EEG studies in most centres, including this study's centre. Performing this procedure in children can be challenging, especially in those with intellectual and behavioural problems who struggle to keep still, as such, a proportion of children are unable to fall asleep without sedatives.

The use of sleep inducing agents to attain EEG studies in the state of sleep.

Many neurophysiological laboratories routinely use pharmacological agents to induce sleep, and this often results in distortion of the normal rhythms, such as increase in beta activity, thus masking the underlying activity, and or influencing the macrostructure of the sleep pattern.[2, 3] If an agent to induce sleep must be used then the product should be the one with the best efficacy, least side effects and drug interaction profile, and the least likelihood of interference with the EEG recording rhythms.

Chloral hydrate is a pharmacologic agent, commonly used to induce the state of sleep in order to perform EEGs, especially as it is considered to have minimal influence on the background and epileptiform activity. But there are reports suggesting unpredictable alterations in the EEG recordings, with either suppression or exacerbation of epileptiform activity, as well as excessive beta activity, or fast rhythms, which can obscure the background and mask epileptiform discharges.[2, 3] The efficacy of the agent as a sedative is well supported with studies reporting between 86-89% successful induction of sleep in patients requiring EEGs.[2, 4] This agent was one of the primary medications used in many units across South Africa, including the centre where the current study is based, to induce the state of sleep in children, especially for neurophysiological studies. This product is not registered internationally for this use, and it was discontinued quite abruptly in South Africa towards the end of 2013.

Chloral hydrate can have potential adverse side effects. It has an unpleasant taste and can induce nausea, vomiting, ataxia, agitation, prolonged sedation, delayed apnea events, gastric irritation, potential carcinogenicity and genotoxicity.[5, 6] It is contraindicated in patients with peptic ulcers, hepatic insufficiency, porphyria, respiratory insufficiency, anticoagulant ingestion and hypersensitivity. However during

the time that this agent was the primary agent used in many units managing children to induce the state of sleep, there were no national reports published that these side effects occurred in our population group. National withdrawal of the product occurred, on direction by the Medicine Control Council (MCC), when it came to their notice that the product was supplied by a Vetinerary medicine producing company, which was not licensed to supply to humans. The potential complications noted above remained of concern, and led our centre to investigate alternative sleep inducers, rather than reverting to import chloral hydrate from a supplier for human subjects, and continuing the previous practice of using it.

The Red Cross War Memorial Children's Hospital Neurophysiology Unit performs in the region of 100 EEG studies a month, about 30-40 of these are sleep studies. Even whilst using the chloral hydrate, 1-2 children a month failed to sleep, requiring a rebooked appointment or additional "top-up" sedation, a further 2-3 patients a week had inter-current infections and their studies were deferred since sedation is not given to children who are unwell. As a result, for a viable service, which receives referrals from across the Western Cape region, and from further afield, to operate, the capacity to perform safe and effective sleep EEG studies is essential.

Following the withdrawal of chloral hydrate at the end of September 2013, an **alternative agent** was explored. Other commonly used agents for sedation, such as propofol, benzodiazepines, or barbiturates, influence the EEG recordings and as such were not viewed as alternatives for the practice of attaining sleep EEGs.[6, 7]

Alternative agents under consideration to replace chloral hydrate, in this setting, were dexmedetomidine and melatonin.

Dexmedetomidine is an α2-adrenergic agonist that is approved by the US Food and Drug Administration (FDA) for intravenous (IV) administration by continuous infusion for up to 24 hours for the sedation of adults during mechanical ventilation in an intensive care unit (ICU) setting.[8] Dexmedetomidine is thought to work by enhancing an endogenous sleep pathway, specifically by decreasing noradrenergic output from the locus ceruleus. The agent mimics natural sleep and does not alter the EEG recording as dramatically as other sedatives. Paediatric population studies support efficacy for procedural sedation during noninvasive radiologic imaging and EEG.[8, 9] The limited effects on hemodynamic and respiratory function, may offer some advantages over other agents commonly used for EEG sedation. One of the major limitations however is that product data is predominantly based on intravenous and intramuscular routes (IM), which are not ideal for paediatric procedures. One recent study supported the IM route with good results but this appears unnecessarily invasive if oral alternatives are available.[10] Buccal dexmedetomidine has 82% bioavailability and is only viable if the drug is not swallowed.[11] The efficacy of intranasal administration in achieving sedation among adult volunteers is reported,[12] but this route has not been studied for children. Whilst this agent appears to have potential, in our setting the current requirements for the agent to be administered under the supervision of an anaesthetist is not realistic and the intranasal product untested and expensive. The study site deferred using this product based on these significant logistical issues.

Melatonin (5-Methoxy-N-acetyltryptamine) was the alternate agent considered. It is a pineal hormone, whose synthesis is controlled by external factors including environmental light. Melatonin regulates sleep–wake cycles through its action on the

suprachiasmatic nucleus in the hypothalamus.[13, 14] It has been recommended in the management of sleep–wake cycle disorders, jet lag, Attention Deficit Hyperactivity Disorder (ADHD), autism, visually disturbed children and other sleep disturbances.[15-20] Even add-on therapy for people with epilepsy has been suggested,[21, 22] as well as an anxiolytic and analgesic in the perioperative period.[23] The major side effect of melatonin is drowsiness and fatigue, with the main consistent message from studies that the substance is safe and well tolerated.[16-18, 24-26] Avoidance has been recommended in patients with epilepsy, and for people medicated with anticoagulants, based on case reports, which have not been substantiated. In relation to the possible exacerbation of epilepsy, review of the literature suggests that no firm conclusions can be drawn, but that there appears to be no marked overall effect on seizures, neither improvement nor worsening.[27] The group concluded that there is need for large, well-designed, randomised, double-blind, placebo-controlled trials to establish the role of melatonin in either predisposing to, or decreasing the likelihood of seizures. The later relates to few studies which have examined the potential anticoagulant properties of melatonin.[28, 29] Oral melatonin was found to attenuate the stress-induced elevation in the sensitive coagulation activation marker D-dimer without affecting catecholamine activity.[28] The researchers concluded that this provided preliminary support for a protective effect of melatonin in reducing the atherothrombotic risk in patients with acute mental stress. A population of healthy adults given a single dose of oral melatonin resulted in with lower plasma levels of procoagulant factors 60 minutes later.[29] The authors concluded that there might be a dose-response relationship between the plasma concentration of melatonin and coagulation activity. These studies support that there may be a beneficial

anticoagulant effect for patients at risk of artherothromotic conditions, but do not allude to the reverse concern of whether use of melatonin could place the patient at risk of bleeding tendencies. This issue, relating to avoiding dual prescribing for patients on anticoagulation therapy is a logical precaution, but not based on definitive findings of a clinical manifestation (excessive bleeding). The main issue with these indications is that the number of studies are few, the consistency and directness limited, and need for large randomized controlled studies noted repeatedly.[15, 16, 19, 21, 23, 25, 27, 30, 31] Most studies are performed using the "over the counter" formulation of melatonin, and as such limits the comparison across studies. A few registered formulations exist, including a slow release formulation.[30, 32, 33] The study by Gringras *et al* was a double blinded randomized placebo controlled phase III trial, which recruited 146 children.[25] The group noted a negative finding in that the children gained little additional sleep on melatonin, but they did report that the melatonin group fell asleep significantly faster. This response to melatonin is in-line with the ideal of rapid sleep initiation, in order to perform non-invasive studies, such as EEG, followed by awakening without the usual sedative "hangover" effect. Melatonin has been successfully used to acquire sleep EEGs in adults and children in centres overseas.[14, 34-38] The reports documented in the next section, and summarized in Table 1, illustrate the data which exists – although there are limitations with the range in formulations and regimens used and indices measured, the consistent conclusion is that melatonin works well for sleep induction for EEG studies and is well tolerated. Of note the natural induction of sleep with melatonin, is limited for interventions such as MRI, BSAER and VEP, where either the noise, or stimulation, of the study is likely to awaken the child from their natural sleep.

Review of the literature relating to the role for melatonin and world-wide unit practices (Table 1)

Published studies: Wassmer *et al* (2001) in 2 almost identical studies reviewed the role of melatonin as a sleep inducer for EEG studies.[34, 35] The group concluded that melatonin could reliably be used for obtaining sleep EEGs in children. They noted that the agent was a good alternative to pharmacological sedation and a complementary method to sleep deprivation. This was one of the earliest studies supporting a role for melatonin as a safe inducer of natural sleep, since then a number of units have made this standard policy (see world-wide unit practices below). Ashrafi *et al* (2010) compared melatonin to chloral hydrate for recording sleep EEG in a randomized controlled study involving 348 patients.[5] They concluded that melatonin was non-toxic in their patient group and recommended that a short course of low doses exhibited almost no side effects in healthy people. They stated that melatonin was available as a dietary supplement without prescription in most countries including the United States and Canada. The study by Eisermann *et al* (2010) found a very good efficacy in sleep induction for EEG recording in 70 children (80% efficacy), this included children with severe behavioural problems (72% efficacy).[33] Sleep duration was, however, short with a high proportion of spontaneous arousals but in all patients it was sufficient for EEG analysis. For this study the group used the fast-release formulation Circadian® LP. The study by Dirani *et al* compared use of chloral hydrate to attain sleep EEG to a new policy of starting with melatonin and only using hydroxine and then chloral hydrate for patients who failed to sleep.[38] This was a large study and the group found that there was a statistically significant reduction in the number of children needing add-on

sedation in the melatonin group. They found no difference in the time to sleep and duration of sleep between the two groups. They concluded that the use of melatonin was safe and highly effective in attaining sleep EEGs and would result in substantial reductions in service load. The study by Sander *et al* reviewed 50 children (27 with epilepsy and 23 non-epileptic) they were all sleep deprived and underwent sequential random allocation to sleep EEG studies with and without melatonin, such that all patients were screened using both modalities but in random order.[39] There was no effect on the background activity recorded on the EEGs with the addition of melatonin, the failure to attain sleep rate was marginally greater in the melatonin group (n=6 versus n=2 p = 0.289 ie not statistically significant), and no side effects occurred in the melatonin group. In particular, administration of melatonin was found to be very easy and was well tolerated by all patients. Gustafsson *et al* retrospectively reviewed if melatonin was as effective as partial sleep deprivation in both inducing sleep and that there was no difference in the interictal EEG data recorded.[40] They compared 129 EEG studies on children administered melatonin, compared to 113 EEGs following partial sleep deprivation. They found that melatonin was as effective as partial sleep deprivation in inducing sleep and that there was no difference in the capturing of interictal EEG discharges. The best results were in the younger children who were less than 4 years of age. Fallah *et al* in a parallel single-blinded randomized clinical trial compared the efficacy of melatonin to the intravenous formulation of midazolam given to children to attain sleep EEG.[41] The group found statistically better success for sleep in the melatonin group. Children in the midazolam group suffered more agitation, which was transient, and there was no difference in report adverse drug events between

interventions. Akaike *et al* (abstract) retrospectively reviewed their success rates for sleep induction in 862 EEGs studies on 523 patients.[42] They found that the patients administered melatonin achieved sleep more effectively than the control groups given CH and or triclofos sodium. They also found that the adverse events were far less in the melatonin group. The abstract presentation by Goyal *et al* supported that melatonin is being increasingly used in Clinical Neurophysiology departments worldwide to facilitate sleep EEG recordings.[36] The authors commented that the use of melatonin in children showed a potential to increase the efficiency of the sleep EEG service, which would have considerable cost and resource implications for often over-stretched services. This last point is of particular relevance to our setting to have an agent that is safe and does not have a "hang-over" effect so the children can be discharged timeously would be ideal.

The directness and consistency of these studies was poor, with differing methodologies, formulations, definitions of sleep latency and screening tools and as a result comparison between them is not reliable. Further the populations studied also varied for the age of the children, additional agents prescribed, associated learning or behavioural difficulties and so on.

Table 1: Literature review summary of studies using melatonin for sleep EEGs

Key CH = chloral hydrate; M= melatonin; RCT = randomized control trial; ADE – adverse drug event NREM – non-rapid eye movement; T = Triclofos sodium

Reference / location	Study type	Study question / group	Study size	Age range	Inclusion gp	Sleep deprived	formulation	Data collected	Results / Outcomes
Dirani *et al* 2016[38] Lebanon	Observational comparison study (Class 3)	Compared outcomes from group with CH versus group with melatonin +/- top-up meds	N=803 CH group n=385 M group n=418	0.5-17.7 years	All consecutive children admitted for sleep EEG	Yes (0.5 to 1.5 years, awake < one hour before study 1.5- to 3-years defer regular sleep time by 2, wake up usual time. < 3 years reduce total sleep time by 4 hours.)	2.5 mg liquid (1 mg/mL) > 5 years 5 mg capsule < 5 years	Recorded percentage of children requiring CH top-up from the melatonin group. Sleep onset latency (stage 2 sleep) EEG recording interictal activity Safety Efficacy	Sleep onset latency similar CH v M Sleep duration also the same Statistically significant reduction in need for top-up melatonin group ($p<0.001$) No difference in interictal EEG activity
Gustafsson *et al*[40] 2015 Sweden	Observational comparison study, retrospective (Class 3)	If M group had same sleep success, and interictal EEG pattern, as those partially sleep deprived.	N=242 M n=129 Partial sleep deprivation n=113	1-16 years	Compared the two study groups over 2 different time periods. Selected population either had M, or partial sleep deprivation. Included all children with suspected epilepsy	Yes for the non-melatonin group sleep from between 7 p.m. and 9 p.m. and wake at 4 a.m.	1 - 4 years 3 mg melatonin liquid 5 -16 years of age 6 mg, 15 min prior to electrode application.	Occurrence of epileptiform discharges Number of children who fell asleep Technical quality of the EEG	Melatonin was as effective as a sleep inducer as partial sleep deprivation. There was no difference in interictal discharges Older children may have performed better with sleep deprivation.
Fallah *et al*[41] 2014 Iran	Single–blinded parallel RCT (Class 1)	Compared sleep, EEG achievement and ADE in 2 groups given either M or	N=60 children	1-8years	All children referred for routine EEG randomized. Excluded if gastritis or any other severe systemic	Not stated	orally 0.3 mg/kg melatonin (Nature made Pharmaceutical Co, USA 3 mg tablet)	Efficacy of sedation Successful recording of EEG ADE	Found statistically better success for sleep in the melatonin group. More agitation (transient) in the midazolam group No difference in ADE.

		IV midazolam orally.			diseases, severe systemic reaction, head injury or received a sedative hypnotic agent within the past 48 hours		or 0.75 mg/kg ampoule of midazolam		
Sander *et al* 2012[39] Germany	Observational prospective comparison study (Class 2)	Compared routine EEGs in same patients with or without melatonin, random order of either study type	N=50 (27 with epilepsy; 23 non-epileptic) N=92/100 studies	1-18 years	Children with or without epilepsy referred for sleep EEG	Yes Awoken at 2 or 3am and kept awake and active.	Liquid melatonin (dissolved powder) (fast-liberation) < 7 years =5mg >7 years 10 mg	Patient demographics Sleep induction (stage 1) Quality and EEG characteristics Failures n=6 (melatonin group) n=2 (isolated sleep deprivation) p = 0.289	Melatonin led of no effect on the EEG background recording Found that melatonin did not improve the outcome of successful EEG acquirement versus isolated sleep deprivation. Acknowledged study size was small.
Ashrafi *et al* 2010[5] Iran	RCT Class 2 (not blinded)	Comparison of CH versus M for safety and efficacy in acquiring sleep EEGs	N=348	1/12 – 6 years	"uncooperative" children and those referred for sleep EEG	Yes (2 hours post usual bed-time and woken at 6am)	2-6mg (liquid – NuPharm lab ltd, UK) 2nd dose given if no sleep at 1 hour	Neurological diagnosis Sleep onset latency *(not defined)* Sleep duration *(not defined)* Drowsiness time *(not defined)* ADE (in first 24 hours post EEG)	Sleep onset latency similar CH v M Sleep duration and Drowsiness time shorter with M ADE: diarrhoea n=2 agitation n=2 EEG abn 53% M V 46% CH (p=0.005)
Eisermann *et al* 2010[33] France	Prospective observational study (Class 3)	Descriptive study of efficacy and tolerability of melatonin to acquire sleep EEGs (no control group)	N=70	Neonatal-17years	Children referred for sleep EEGs	Yes ('partially deprived of sleep the night before')	5mg capsule 1-6 yrs = 5mg >6yrs = 10 mg (hospital preparation, as capsules or dissolved in water) fast-release (Circadian® LP)	Patient demographics Sleep latency (from M to stage 2 NREM sleep) Sleep duration Telephonic interview 1 week after.	Effective sleep induction in 80% of the cohort Effective even in children with behavioural problems (72%) Sleep latency 25 (15-45) minutes Duration 13-17 (5-55)minutes No significant ADE

							2nd dose if no sleep		
Wassmer *et al* 2001[35] United Kingdom	Matched observational comparison study (Class 2)	Group 1:Melatonin Group 2: Age matched sleep deprived controls	N=68 (study) Versus n=68 control (sleep depirved)	Not supplied	Children referred for sleep EEGs	No (Control group sleep deprived)	< 5 years = 2.5 mg >5 years = 5mg *Formulation not provided*	Patient demographics Sleep latency (time from "lights out" until stage 1NREM sleep)	Both groups slept effectively. EEG background was not affected by melatonin Sleep latency was significantly shorter in the melatonin group
Wassmer *et al* 2001[34] United Kingdom	Matched observational comparison study (Class 2)	If Melatonin could induce sleep and not affect the EEG. Control group – age matched 30 children who were sleep deprived	N=163 M gp N=30 control gp (sleep depirved)	1-16 years	Children referred for sleep EEGs	No (Control group sleep deprived)	2mg or 10 mg (depending on age; Penn Pharmaceuticals, Tafarnaubach Industrial Estate, Tredegar, Gwent UK)	Patient demographics Sleep latency ADE EEG "acceptability"	Sleep occurred in 79% of M study group. Sleep latency 33 mins (mean) EEG not affected by M No significant ADE Minot ADE: headache (n=1); drowsiness (n=13); vomited (n=1); day 2 seizure (n=2) Behaviour of children on the study day more acceptable to parents in the M study group. Doesn't state if this group is different or includes the same patients in the other Wassmer *et al* study[35]
Akaike *et al*[42] 2016 Japan Abstract	Observational retrospective study (Class 3)	Comparison of sleep success for patinets given M, CH and or triclofos	N=862 EEGs in n=523 pts N=63 M T n=217 CH n=32 T&CH n=30	0-38 years	Children and adults referred for EEG	Not stated	Not stated Ramelteon	Sleep latency ADE	Found M was more effective of all interventions inducing sleep. M group had the least ADE of the intervention group

Goyal *et al* 2006[36] United Kingdom Abstract	Observational comparison study	Melatonin group compared to vallergan group	N=58 M group N=28 vallergan control gp	0.5-16 years	Children referred for sleep studies	No	Not stated	Measured successful attainment of stage 2 sleep (defined by the first 10second epoch containing sleep spindles)	At least 20 minutes of stage 2 sleep was recorded for all patients. Found M to be a good agent to induce sleep

Worldwide practice (Table 2): Colleagues on the International Child Neurology Association executive board and those on the Pediatric Commission for the International League Against Epilepsy where approached. These groups represent some of the key opinion leaders in the field of child neurology and are responsible for international guidelines relating to epilepsy management in children. They were asked two questions.

1. What agents do they use for sleep EEG studies in their countries / units?
2. If they have experience with melatonin – whether they have met any issues relating to its lack of registration?

In summary there was an overwhelming response that illustrated that melatonin is widely used and accepted in Europe and the States. Whilst the registered slow–release version is available in these regions, this has only been considered necessary to use in preference to the "over the counter product" in a few settings.

Table 2: World-wide responses (2013)

Region	**Country (personal communication / position)**	**Experience with melatonin**	**Comment**
Europe			
	Sweden (Prof Orvar Eeg-Oloffson - world leading expert in epileptology).	Yes	Use melatonin 3mg tablets "with good response"
	France (Monika Eisermann Clinical Neurophysiologist, Necker Enfants Malades Hospital, Paris Descartes University France – lead author of the 2010 study)	Yes	Finds melatonin to be very helpful and very safe. Now use half of the doses, means < 6 yrs 5mg, > 6yrs 10 mg, found it works as well as higher doses.

			Commented that initially it was very difficult to convince the pharmacology department to start this programme because an "authorisation for hospital use" was difficult to obtain, but they managed. This centre uses the fast-release formulation.
	Belgium Prof Lieven Legae, Head of Paed Neuro, Leuven University (President of the European Paediatric Neurology Society) And Linda de Meirleir (Head of Paediatric Neurology, metabolic expert, ICNA EB)	Yes (but not for sleep EEGs)	Commented that there are numerous papers showing efficacy and safety of melatonin for sleep problems. They often use melatonin for autistic and blind children, with sleeping problems. They have never used it as a sedative for sleep EEGs as they do these EEG's during the night. This would not be realistic in our setting
	United Kingdom (Helen Cross, Prof at Great Ormond Street Hospital for Sick Children – secretary of the ILAE. World leading expert in epilepsy)	Yes	They routinely use it in the GOSH unit. Their pharmacy coding committee also had concerns but accepted the "over-the-counter" product after motivation. They ensure access is from a single source, and that it can be prescribed.
	Bulgaria (Petia Dimova, Paediatric Neurologist – Pediatric Commission ILAE member)	Yes	Report excellent results with melatonin for EEG. Since 2010 it has been used instead of Chlorazin, and in up to 90% of

			patients it worked well. Occasional add-on Chlorpromazin for a few patients with severe learning difficulties and behavioral problems. Have data on > 150 children who underwent successful sleep EEG studies using melatonin. There are no regulations or standards in Bulgaria on how to perform EEG in children. They have at least 3 different formulations of melatonin but all are registered as a food supplement; so are not regarded as "drugs" and as such do not fall under any regulations.
	Germany (Hans Hartmann, paediatric neurologist Pediatric Commission ILAE member)	Yes	They have access to a commercially available melatonin product called Circadin. It contains 2 mg / prolonged release tablet. it is licensed by EMEA
Asia			
	India (Dr. K P Vinayan, Professor Division of Pediatric Neurology, Amrita Institute of Medical Sciences Cochin, Kerala; Peds Commission ILAE member)	No	Not using Melatonin – they have access to triclofos and have not been affected by the regulatory factors in South Africa.
North America			
	United States of America (Prof Kenneth Mack, Mayo Clinic; ICNA EB)	Yes	Use melatonin to attain sleep EEGs. It is considered a "food additive or vitamin" by the FDA, so

			therefore it is not regulated by this body.

Transition of the unit to use melatonin and the current study rational

Left without an alternate sedative agent it was felt, based on the available options, that melatonin would be the safest alternative to transfer over to. However beyond other centre's mostly anecdotal opinions (Table 2) and the limited data in the literature (Table 1),[5, 33-36, 38-42] our unit could not be confident that this change in sedation practice would be as effective as when chloral hydrate was the first line agent. Also that the patient load is still unique to our South African context for socioeconomic and disease structures and as such these patients may not respond in the same manner as in the published studies.

From September 2013 our unit changed its standard operating procedure to administer melatonin to children who required sleep EEG studies. Since this was a new practice, the efficacy was closely monitored, with the aim to review whether it should remain the standard operating practice in our unit based on safety, acceptability and efficacy for the attainment of sleep EEGs.

To the best of our knowledge there is no study to determine the use of oral melatonin for childhood EEG sleep studies in South Africa or sub-Saharan Africa. This was an observational exploratory study, which aimed to determine the safety, acceptability and effectiveness of oral melatonin as a natural inducer of sleep to acquire useful EEGs in South African children. If shown to be effective this data would assist other centres in South Africa faced with the same challenge following the withdrawal of chloral hydrate.

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Part B. Chapter 2.

The role of melatonin in the effective attainment of Electroencephalograms in Children in a sub-Saharan African setting

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Abstract

Rationale: The paucity of access to electroencephalograms (EEGs) in sub-Saharan Africa results in a high patient load attending the few centres with neurophysiology units. Sleep state for EEGs performed on children improves yield and reduces artefact. Melatonin induces "natural sleep" without the risk of airway compromise. This study evaluated the effectiveness of oral melatonin in attainment of useful electroencephalograms in South African children.

Methods: Consecutive children booked for routine EEG who were either unable to cooperate or were referred for sleep EEG received oral melatonin (3mg < 15kg; 6mg > 15kg) (September 2013-March 2014). Comparison was made to a retrospective control group who received the previous sleep protocol agent, chloral hydrate. Outcome measures were the proportion of children who achieved sleep, useful EEG study data, sleep latency and duration, presence and level of artifacts and presence of recorded EEG study abnormalities.

Results: 173 children were recruited, 88 (51%) male, median age 4 years 9 months (interquartile range of 2 years 2 months – 7 years 6 months). 87% of the children achieved stage 2 sleep and were deemed to have successfully entered sleep state. The median sleep latency was 44.5 minutes and the duration of sleep was 25 minutes (range 18.5 – 29 minutes). Children showed no signs of post-sedation irritability or persistent drowsiness. They were awoken and were immediately able to go home. In the melatonin group there were no adverse events, and no child needed their study deferred due to inter-current illnesses. All children administered melatonin cooperated

and permitted a successful EEG recording with useful records even if sleep was not achieved. Sedation with melatonin was less successful (74% compared to 88%) in children with developmental and behavioural problems (χ^2 = 6.18, P= 0.046), they also had higher rate of artifacts (χ^2 = 5.83, P=0.05).

33.5% of the study group children (n=58) had abnormal EEG studies. These outcomes were comparable to a historical cohort of age equivalent children who were sedated with chloral hydrate (45.5%) (χ^2 = 1.22, P= 1.27). 79% that received melatonin compared with 86% of those that were sedated with chloral hydrate had artifacts (χ^2 = 0.63, P= 0.42)

Conclusion: Melatonin is effective and safe in inducing sleep for EEG recording in our setting.

Key words: epilepsy, sleep, melatonin, children

Background

Sleep state is important in performing electroencephalogram in children because it reduces the amount of artifacts and can unravel certain epileptiform discharges.[1, 2] It is also especially useful in young children and those with behavioural and developmental challenges because they are unable to lie still for the procedure. Unfortunately most sedative medications such as propofol, benzodiazepines and barbiturates affect EEG recordings either by distorting background readings or suppressing epileptifiorm activities, hence the state of natural sleep is preferred and can be achieved after sleep deprivation.[3, 4] However, in a proportion of children this can not be achieved and sleep inducing medication has to be used.

Chloral hydrate is the primary agent used in many units managing children to induce the state of sleep, especially for neurophysiological studies as it has minimal influence on the EEG.[5-7] It could however cause persistent sedation after examination leading to prolonged observation or even hospitalization; moreover it is not licensed globally and is no longer manufactured within South Africa.

Melatonin (5-Methoxy-N-acetyltryptamine) is a pineal hormone and has been widely used to treat sleep disturbances. It has been successfully used to induce sleep EEGs in adults and children in centres overseas.[8-10] To the best of our knowledge there is no study to determine the use of oral melatonin sedation for childhood EEG sleep studies in South Africa. This study aims to determine the safety and effectiveness of oral melatonin as natural inducer of sleep to acquire useful EEGs in South African children. If shown to be

effective this data will assist other centres in South Africa faced with the same challenge following the withdrawal of chloral hydrate.

Aim

To assess the efficacy, safety and acceptability of melatonin to induce sleep in patients for routine sleep state EEG studies in the Neurophysiology unit of Red Cross War Memorial Children's Hospital.

Objectives:

Assess the role of melatonin as an effective inducer of sleep for successful attainment of EEG by evaluating the impact on the patient outcomes using the following measures:

1. Sleep onset latency (defined as the duration from full wakefulness to the earliest of non-REM stage 2 sleep as recorded on the EEG)[11]
2. Sleep duration (the time the child enters non-REM sleep until they are roused at the end of the study or they spontaneously awake)
3. Second dose of sedation, (if no sleep 1 hour post first dose)
4. Behaviour (agitated, hyperactive, anxious, aggressive) and suspected adverse drug events,
5. Yield in terms of EEG abnormalities – number of abnormal studies, number of studies yielding outcomes which will alter patient management
6. To make recommendations for the regular use of melatonin for sleep studies to achieve optimal outcomes for these studies.
7. To develop a sleep EEG protocol which is effective and viable in our setting and can be used across the country.

8. To compare the EEG recordings in comparison to a historical group of age matched recordings sedated with chloral and to establish if the outcomes achieved are in line with the previous unit practice.[12]

Methodology

Study Location

The study was conducted at the neurophysiology unit of the Paediatric Neurology department of the Red Cross War Memorial Children's Hospital, Rondebosch, Cape Town.

The Neurology department of Red Cross War Memorial Children's Hospital is a tertiary / quaternary referral centre for children with Neurological diseases in the Western Cape. EEGs are performed in this unit for both patients managed in the department, referred from other internal departments, outside hospitals and the private sector.

Study Population: These were children who were booked for sleep EEG by the referring Physician or were unable to keep still for awake EEG.

Timing of study: September 2013 –March 2014

Sleep EEG protocol routinely used in the study site: (Figure 1)

Sleep deprivation protocol: All children were encouraged to be sleep deprived prior to attending for a sleep EEG. Unit guidelines for children over 3 years of age, recommend that the child is kept awake until midnight, is awoken at 4 am and is not allowed to sleep between then and the arrival time at the hospital for the EEG.

Sedation protocol: Once children presented to the department if they had not been sleep deprived, appeared unable to keep still and or were unable to fall asleep despite being sleep deprived, then the carers were provided with a leaflet to read which advised

them of the recommendation to use an agent to induce sleep state (Appendix 1). They kept this document as it also addressed possible side effects, during and after, the procedure, with a plan of what to do if any of these occured. Before administering the agent all carers were spoken to, to ensure that they had no questions and gave permission for the agent to be given to their child. Further the child was examined to ensure that they had no evidence of intercurrent illness or evidence of possible airway compromise which induced sleep could exacerbate. At the original time of booking the referring doctor was also asked if there were any contraindications to the situation where their patient may need sedation.

Standard unit intervention consists of giving melatonin by mouth (3mg for children < 15kg, 6mg for those > 15kg) 1 hour before the scheduled EEG by the unit nurse. The same brand of Melatonin capsules (Swanson®, manufactured by Swanson Health Products in the USA) via Equity Pharma was used throughout the study period. Basic health checks were maintained throughout the time in the department including the post study recovery phase (blood pressure, pulse and respiratory rate). If the child failed to fall asleep within one hour of administration of the melatonin then a second dose of 3mg was given, assuming that this was convenient for the carer to remain longer in the department, if not the patient was re-booked for a further date and the need for effective sleep deprivation was reinforced.

Recording the EEG and data collection

The EEG was recorded immediately the child fell asleep by the neurophysiologist (LJ). EEG surface electrodes were placed on the patients' head according to the 10/20 system (standard practice in our unit) and EEG recordings were obtained over 25 -30

minutes period. The calibration was at high-frequency filter of 70 Hz and sensitivity of 10 uV/mm. The neurophysiologist documented the sleep latency period (defined as the duration from taking the medication to stage 2 non-REM sleep as recorded on the EEG), whether the child remained adequately asleep for the required period of the study, and the observed adverse events into the case record form (CRF) (Appendix 2).

After the procedure any observed adverse effects were noted while in the hospital (by the unit nurse). Parents were encouraged to document any observed adverse event within 24 hours and report to LJ.

The EEGs were evaluated by LJ (Senior Clinical Technologist) and RI (PI) with an aim of determining the quality of the records in terms of peak frequency and amplitude on a digital monitor at the frontal and parieto-occipital regions of the EEG, both were responsible for the assessment and categorization of EEG findings. Quantitative assessment of these recordings were based on the system used by Sander *et al* [9] grading artefact on a scale 1-5 (1=no artifacts; 2= some, minor artifacts; 3=moderate amount of artifacts; 4= substantial artifacts, but EEG recording could be assessed; 5=unsatisfactory / invalid such that EEG could not be assessed). Overall data was reviewed and discussed with JW to ensure consistency and consensus. LJ is a senior clinical neurophysiology technologist who is qualified to report paediatric EEGs. RI is a fellow in paediatric neurology training. As part of his curriculum he was trained in EEG interpretation by both LJ, the other senior neurophysiology technologist and JW. Throughout the study he was supervised by LJ and JW. The reports generated were part of the standard outcomes for the unit and as such this data was not specifically new. Standard unit practice is to generate reports which include the age and state of the

children, and the proposed diagnostic concern. The EEG report itself includes comment on specific background rhythms, namely the presence of delta, theta, alpha, beta rhythms (including symmetry and region), sleep spindle formation, V waves, and normal variants. The presence and extent of artifact is always noted (further if it is physiological or non-physiological) and whether it precludes effective reporting i.e. it dominates the recording or is minimal to a few pages. Specific abnormalities are documented (epileptiform activity, encephalopathic background). Response to hyperventilation and intermittent photic stimulation responses, this last aspect was not routinely be performed in the study group as their EEG focused on attaining sleep. An overall summary of the key findings is documented. The report is then completed with a conclusion.

For the study purposes additional data was recorded relating to the proportion of a recording affected by artifact (graded as listed above 1-5), the quality of the sleep recording (the stage reached) and the implications of the findings on the EEG. Normally a report is generated which confirms if sleep was attained (with or without sedation), the stage of sleep attained, a comment of whether there was artifact is stated (but not the extent, unless extreme) and the specific EEG findings which may or may not relate to a syndromic diagnosis and a specific treatment intervention. The correlation and interpretation of the clinical event and the EEG findings, is not usually undertaken, but for the purposes of this study patient records were reviewed to ensure that this data was included. The conclusion may provide outcomes which could alter the management of the patient, for example if the EEG pattern was consistent with a recognized syndrome such as epileptic spasms, or childhood absence epilepsy.

In 2012 a study was completed in the same department which included data on the effectiveness of the units previous sedation policy. Whilst chloral hydrate was no longer available to form a control arm for this study, the findings and outcomes from this 2012 study permitted some comparison of efficacy and side effects of the two sedation options, namely chloral hydrate compared to melatonin.[12] Key areas which both studies had comparable data on were the successful completion of the EEG study, whether the EEG was normal, abnormal or could not be reported due to excessive artifact, whether the EEG was diagnostic of epilepsy, and when the EEG findings altered the actual patient management. The final decision on how the findings from the current study affected subsequent diagnosis and management were made after review by RI and JW.

<u>Specific aspects recorded include</u>

- Whether sleep was attained or not,
- The sleep latency (time to enter non-REM stage 2 sleep) from when the melatonin was given according to Rechchaffen and Kales parameters,[11]
- The lack or presence of EEG artifact (an effective enough recording taken to be able to generate a useful report),
- Whether or not abnormalities were recorded and whether this outcome affected the patient management (normal study supported a suspected paroxysmal disorder, confirmed a diagnosis of benign centro-temporal epilepsy, and so on).

Recruited children had their demographics recorded such as age, sex, underlying aetiology, co-medications, intercurrent infections and co-morbid factors (developmental delay, behavioural issues) on case record forms (CRF) [Appendix 2]. Post-study a record was kept relating the child's "return to normal" i.e. how long it took the child to

fully awaken, return to previous level of activity and function, also any post discharge complaints (all caregivers were encouraged to contact the unit if this occured and they attended another unit after hours) and any apparent adverse effects following 24 hours after the procedure (excessive sedation, break-through seizures).

Comparison group: Since supply of choral hydrate was no longer available a direct comparison group was not possible between children given chloral against those given melatonin. However the study performed the previous year in the department measured several parallel and useful outcomes.[12] This study addressed the usefulness of electroencephalograms in a South African population. A proportion of this group screened in 2012 in our unit underwent sleep studies, sedated with chloral (n=22). These patients were drawn from the same regional pool, with the same disease demographics, and the same sleep deprivation and procedural techniques to the current group. This group was screened for several common denominators used in the current study, and comparison was made between these, namely the proportion of patients with successful attainment of sleep studies, the proportion of studies with excessive artifact (precluding interpretation) and the usefulness of the data attained detailing whether the studies were able to assist or alter patient management. Whilst the comparison study group size was acknowledged to be small, gaining an indication as to whether the chloral might have a blunting effect on detection of epileptiform activity was a concern and explored as part of the study. As such the proportion of abnormal EEGs was compared across groups.

Data storage and analysis: All data obtained was coded with confidential individual number codes (known only to the investigators) and entered into an excel spread sheet

with statistical analysis using software from SPSS version 19. to analyse outcomes. Means and standard deviations were determined for normally distributed variables, while median were determined in non-normally distributed variables, and differences in proportions were tested for statistical significance using the chi-square test or Fischer's exact as appropriate. The non-parametric data (comparison between the key outcomes of the historical chloral hydrate group versus the melatonin group) was studied using Mann-Whitney U tests. Significance level was set at $p< 0.05$, with 95% confidence level.The computer where the data was located is in a secure part of the neurophysiology department.This data was recorded in a secure database only accessible to the study personel with patient identifier data coded and names withheld.

Ethical issues: This study was approved by the Faculty of Health Sciences, Research and Ethics Committee of the University of Cape Town (Protocol ID 070/2014) and is registered with clinical trial.gov (NCT02195661). This study to the best of our knowledge, and as supported by the literature, did not expose the children to any unnecessary danger. Melatonin is a natural product and is considered to be generally safe. Participants were not paid for participating in the study as their investigation were completed as part of standard practice.

RESULTS MELATONIN

Demographics

173 children presented for sleep EEG procedures during the study period (88 males and 85 females), the median age of the subjects was 4years 9months ((interquartile range of 2years 2months - 7years 6months (age range 0-14 years))

Ninety percent of the referrals were internally generated from within the hospital. The emergency department and the Medical outpatient department (MOPD) were the source of most of them (Table 1). Most requests for EEGs were from Medical officers and General Pediatricians from the MOPD and the emergency department. Referral for EEG was based on concern of a diagnosis of epilepsy or to establish if the background activity had improved in a patient with established epilepsy.

One reason for performing sleep EEGs was because the subjects were deemed unlikely to cooperate n=73 (42.2%), these included children who were either too young to cooperate n=51 (29.5%), had severe intellectual disability n=17 (9.8%) or had behavioral problems n=5 (2.9%). The other set of children were those whose previous awake records were inconclusive; some had normal recordings in the presence of strong clinical suspicion of epilepsy n=31 (17.9%) or abnormal but with either significant artifact or the finding was inconsistent with clinical presentation n=13 (7.5%) and or the referring physician specifically requested asleep EEG on account of suspicion of epileptic seizures with sleep specific EEG findings n=5 (2.9%).

Sleep outcome (Table 2)

150 (86.7%) children achieved stage 2 sleep and were deemed to have successfully slept, of these 5 required an additional dose of melatonin for them to achieve sleep state (a “top-up”). All the subjects including those who did not sleep achieved successful EEG recording.

The median sleep latency was 44.5 minutes, with interquartile range of 30 -67 minutes. The median duration of sleep was 25 minutes (range 18.5 – 29 minutes).

All the children had no post sedation irritability or persistent drowsiness. They were awoken and were immediately able to go home.

Eleven children had minor upper airway infections but were able to complete their EEG studies; in fact no child had their EEG deferred due to inter-current infections. There were no recorded adverse events.

The information of the behavioural/ developmental status of 103 children was documented. Thirty-five children had developmental delay and or behavioural problems. Twenty-six percent of the children (n=9) with developmental delay and behavioral problems did not sleep compared to 12% (n=8) of those without developmental/behavioural problems delay ($\chi^2 = 6.18$, p=0.046). The age, sex and EEG findings did not significantly differ between those who slept and did not sleep (Table 3).

Report of EEG findings

Background findings

Since these were sleep records, it was difficult to comment on slowness of background. However, 31 records were asymmetric while the remaining records had symmetric records. Sleep spindles were noted in all the records of children who successfully slept.

Artifact

The recorded artifacts were muscle, movement and electrode artifacts, and excessive beta waves. The EEG records of 36 (20.8%) children were free of artifacts. As shown in Figure 2, of the 137 records with artifact 84 (61.3%) and 36 (26.3%) were grades 2 and 3 artifacts respectively and such such did not preclude reporting the EEGs.

More children who slept 32/141 (23%) had no artifacts compared to those that did not sleep 0/22 (0.00%) (χ^2= 6.21, P= 0.008).

33/36 (92%) children with behavioral or developmental problems were statistiacally more likely to have artifacts in their records, when compared to those without behavioral problems (n=53/70 (76%)). (χ^2=5.83 p=0.05)

The median sleep latency time of children with artifact in their records was 45 minutes (30 -69 minutes) and 43 minutes (29 -59 minutes) for those without artifacts. (z = -1.19, p =0.23).

The median duration of sleep of children with artifacts in their record was 24 minutes (range 19 -29 minutes) while it was 26 minutes (range 17 – 30 minutes) for those without artifact. (z =1.11, p = 0.27).

EEG changes

The EEG records showed that 115 (66.5%) records were normal while 58 (33.5%) records were abnormal. Of the abnormal studies 25 (43.1%) recorded focal discharges, 31 (53.4%) recorded generalized discharges and 2 (3.4%) had suppression recorded. While 33% of (50/98) the children who slept had abnormal EEG recordings, among those that did not sleep 30.4% (7/23) had abnormal recordings (χ^2= 0.08, P =0.78).

Children with abnormal EEGs were not significantly younger than those with normal recordings (χ^2 = 3.19, P= 0.20). Among children with behavioural and or developmental problems 20/36 (56%) had abnormal EEG recordings. When compared to those without developmental and or behavioural problems 19/56 (27.5%) had abnormal EEG record

(χ^2 = 7.96, P= 0.006). Other variables including gender were not statistically associated with EEG artifacts as shown in Table 4.

Comparism with the EEG of the Historical group of Patients previously sedated with chloral hydrate[12]

In a retrospective comparison group of 22 children who were sedated, 21 (95%) achieved stage 2 sleep, while artifacts were noted in 19 (86.3%) of them. Of those with artifacts 8 (42%) were grade 2 and 11(58%) grade 3. There were no grade 4 or 5 artifacts noted. There was no statistically significant difference in the amount of artifact compared to the melatonin group (79.19%) (χ^2 = 0.63, P= 0.42)

Ten (45.5%) of the EEG records were abnormal, of these 4 showed generalized discharges, 4 focal discharges, one had hypsarrythmia and another generalized slow waves. The percentage of EEG abnormality in the melatonin group 58/173 (33.5%) was not significantly different when compared to this historical group of children sedated with chloral hydrate 10/22 (45.5%) (χ^2 = 1.22, P= 1.27).

DISCUSSION

This study supported that melatonin is effective for sleep EEG recording in our setting. 86% of the children were able to achieve stage 2 sleep with melatonin; this is within the limits of 75 – 90% reported in the literature.[8, 10, 13-18] It is however interesting to note that for all the children a useful EEG record was achieved even among those that did not sleep. Despite not sleeping the children were relaxed and calm mainly because some of them achieved stage 1 sleep but did not sleep deep enough for sleep spindles to be noted and hence were recorded not to have slept.[9]

The previously reported reduced efficacy of pharmacological agents to achieve sleep in children with behavioural and learning difficulty as compared to normal children was confirmed in the present study.[19] In keeping with previous reports melatonin was less successful in achieving sedation in children with behavioural and developmental problems. 70% of these children successfully achieved sleep compared to 88% of those without bahavioural or developmental challenge. The reason for this is not quite clear, melatonin is used to achieve sleep in these children.[20] However the logistical difficulty of achieving sleep deprivation in this class of children may have contributed.[17] Though, it should be noted that these otherwise difficult children remained calm for the duration of the EEG even when they did not sleep.

The median sleep latency was 45 minutes, indeed for all of those who achieved sleep, they fell asleep within 69 minutes. The reported median sleep latency/ onset of sleep varied between 5 minutes to 45 minutes.[9, 10, 21] The reason for this wide difference includes the variance in melatonin dosing, differences in application of sleep deprivation and subject selection. However, Ashrafi*et al*[8] in their comparison of melatonin and chloral hydrate noted that sleep onset time was significantly shorter in the melatonin group. The mean duration of sleep in our study was 25 minutes; the children woke up easily at the end of the procedure with no post sedation drowsiness, vomiting or “hang over” observed. At the end of the procedure they were ready to go home. This finding has been previously reported. [13, 21] This made for efficient use of the Neurophysiology department as more patients could undergo studies compared to when chloral hydrate was used and children had to remain longer while recovering post sedation.

Our findings demonstrate that melatonin use for children in an EEG laboratory is safe and effective. The induced sleep took effect rapidly and lasted long enough to permit electrode application or recording of sleep or both. There was no report of any immediate or later complications; this was similar to experiences in other centres.[16, 18] Wassmer *et al* [10, 13] also did not report any side effects, while Eisermann *et al*[21] and Milstein [22] reported only increased sleepiness in a minority of their subjects.

Sleep state is encourage as it decreases muscle and movement artifacts and improves the organization of normal sleep features. However artifacts were reported in 79% of the records, this was comparable to the 86% artifact reported from the historical comparative group sedated with chloral hydrate previously reported from this centre. These artifacts were mainly grades 2 and 3 artifacts that did not affect the readings of the EEGs. Sanders *et al* [9] reported that there was the presence of more artifacts, 52% among their melatonin group compared with non-melatonin group 32%, though this difference was not statistically significant. The reason for the higher recorded artifact in this study compared to the report of Sanders *et al* is not clear.[9] However, we suspect that compliance with sleep deprivation was not strictly adhered to by our subjects. Melatonin also tends to lead to light sleep with periods of arousal which may account for the high artifact rate.[23, 24]

Sixty-six percent of the subjects had normal EEG records; this is higher than reported in previous studies.[9, 13] Comparison is however difficult because of the heterogeneity of the sample selection but is comparable to the 62% normal recording reported previously from this centre.[12] Referrals for EEG in this centre came from different sources. Kander

et al observed that inappropriate referral for EEG studies accounted for the majority of the non-useful EEG findings.[12]

Melatonin has become increasingly popular as a sleep-inducer for both children and adults and has been found to be effective even among children with neurological abnormalities.[20, 25, 26] Among neurophysiology units worldwide, there have been reports of its effectiveness in inducing sleep for EEG and the fact that it does not affect the sleep structure or the epileptiform discharges.[8-10, 16-18, 21, 27]

Study limitations related to the inability to confirm the quality of compliance with sleep deprivation. In addition the lack of a parallel control group would have strengthened the study, this was not possible as the comparison agent was no longer available at the time of the study. So, whilst a control group was identified, using data from the historical study, which had recorded comparable variables, this control group size was relatively small.

In summary: This is the first report of the use of melatonin for sleep EEG in children in sub–Saharan Africa. Melatonin had no effect on the EEG record and as such did not interfere with the EEG reading. Further there was no difference in the proportion of studies which recorded interictal epileptiform discharges between the two study group and the control group. There were statistically greater artifacts in the children in melatonin group with developmental and or behavioural problems, this group was also statistically less likely to achieve stage 2 sleep and were the group statistically most likely to have abnormalities recorded on their EEG studies. Use of melatonin to achieve EEGs in our setting has proved a viable and effective policy change. We feel that the transition to using this agent is in-line with facilitating the significant service load, as well

as the quality of care for patients due to the rapid recovery and absence of reported adverse events.

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Legends

Figure 1: Neurophysiology Unit Sleep Policy

Figure 2: Distribution of artifacts in children sedated with melatonin according to grading by Sander *et al*.[9]

Table 1: A summary of patients' referral sources (n=173)

Table 2: Association of sleep outcome and some variables among children that were given melatonin to achieve sleep EEGs

Table 3: Association between the presence of artifacts and some variables among children that received melatonin to achieve sleep EEG

Table 4: Association between the presence of abnormal EEG finding and some variables among children that received melatonin to achieve sleep EEG

Figure 1: Neurophysiology Unit Sleep Policy

Child booked for EEG

Referring clinician, or staff taking the booking, identify that sleep study required

Parent advised how to sleep deprive child (over 3 years of age) (stay up until midnight, awake at 4am)

On arrival in the Neurophysiology unit, parent counselled of the study required, time it will take, and the need for their child to sleep.

Policy of using melatonin explained (parents at this stage can request that no agent is given but they accept that the child may not cooperate or sleep).

Child reviewed to document safe to undergo the procedure i.e. no systemic illness, airway issues etc.

Melatonin given 3mg (<15kg) or 6mg (>6mg)

Child monitored for up to 1 hour (nurse supervised assessment of heart rate and respiratory rate)

Once asleep EEG performed

If fails to sleep 1 hour after melatonin given – top-up 3mg dose of melatonin given

If fails still to sleep – study differed, clinician advised and further booking made with reattempt at sleep deprivation at a later stage if study still needed

If study successful – child awoken at end of study, nurse performs basic observations and allows child home when eaten, passed urine and carer happy.

Table 1: A summary of patients' referral sources (n=173)

Sources	Frequency	Percent
MOPD	35	*29*
emergency	29	*24*
NOPD	16	*13*
Neurology	10	*8.*
development	9	*7*
Day hospitals	9	*7*
Private practitioners	4	*3*
Wards	3	*2.5*
Cerebral palsy clinic	3	*2.5*
Child psychiatry	2	*2*
Genetics	1	*1*
ENT clinic	1	*1*

Table 2: Association of sleep outcome and some variables among children that were given melatonin to achieve sleep EEGs

	No sleep N=23	**Sleep N=150**	χ^2	**P-value**
Age group (years)				
< 1	3	9	1.99	0.36
>1 -5	13	80		
>5	7	61		
Gender				
Male	11	74	0.02	0.89
Female	12	76		
Developmental/behavioural problems				
Abnormal	9	26		
Normal	8	60	6.18	**0.046**
EEG finding				
Abnormal	7	50		
Normal	16	100	0.08	0.78
Artifact				
Present	23	114	6.75	**0.009**
Absent	0	35		

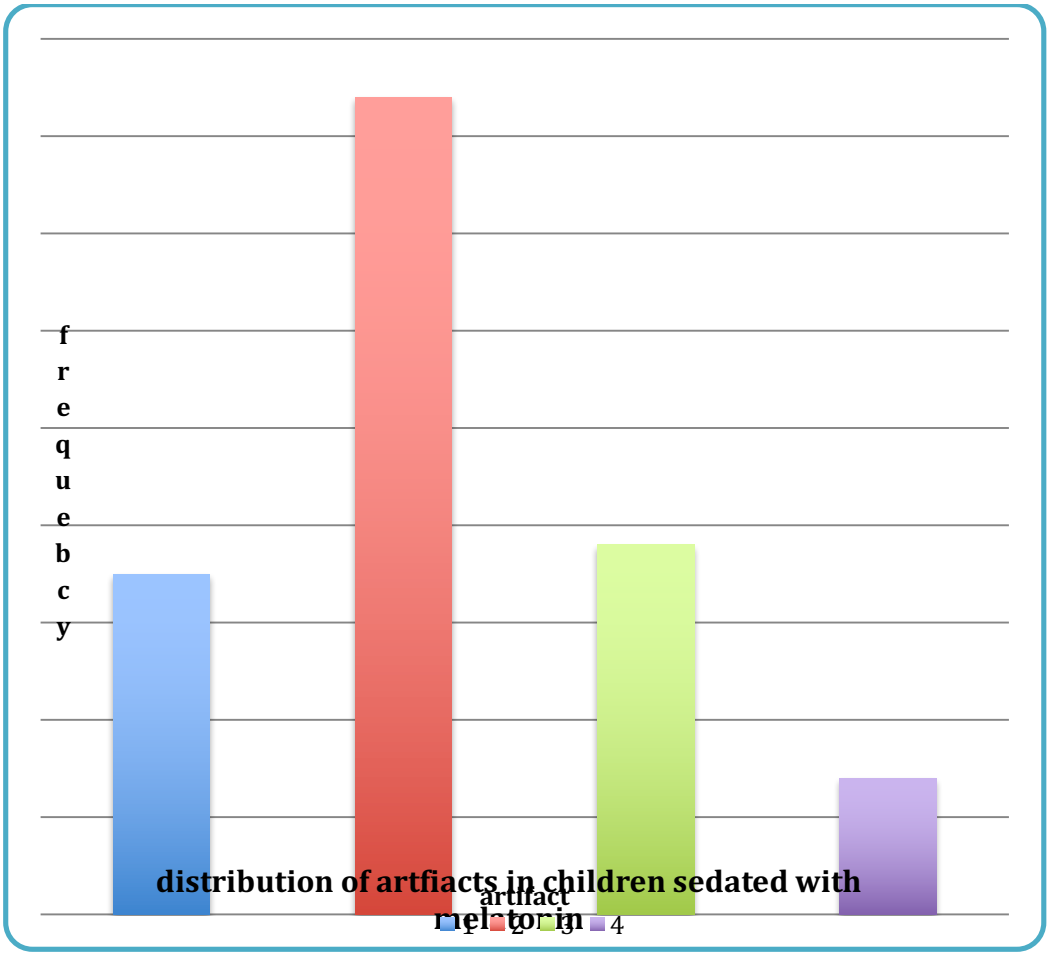
Table 3: Association between the presence of artifacts and some variables among children that received melatonin to achieve sleep EEG

	No artifact N=36	**artifacts n=137**	χ^2	**P-value**
Age group (years)				
< 1	4	8	4.09	0.13
>1 -5	22	70		
>5	9	59		
Gender				
Female	19	66	0.42	0.52
Male	17	71		
EEG results				
Abnormal	14	42		
Normal	21	95	1.12	0.29
Developmental/behavioural disorders				
Abnormal	2	33		
Normal	16	52	5.83	**0.05**

Table 4: Association between the presence of abnormal EEG finding and some variables among children that received melatonin to achieve sleep EEG

	Abnormal EEG N=58	**Normal EEG N=115**	χ^2	**P-value**
Age group (years)				
< 1	2	10	3.19	0.20
>1-5	28	65		
>5	27	41		
Gender				
Female	34	51	3.76	**0.05**
Male	23	65		
Developmental/behavioural disorders				
Abnormal	19	16		
Normal	19	49	9.05	**0.01**

Figure 2: Distribution of artifacts in children sedated with melatonin according to grading by Sander *et al*.[9]



Appendix 1

Patient / carer information form

What happens during an EEG study insleep in the department of neurophysiology, Red Cross War Memorial Children's Hospital.

1 - Why are we giving you this form?

Some children need to sleep for their EEG test because they are too anxious and or too young to keep still on their own. Sometimes the EEG test produces more information when your child is asleep as the brain waves can show us more useful activity which may help us to tell whether your child may have, or be at risk of having, epilepsy. Unfortunately most of the available medicines which can make your child go to sleep interfere with the brain waves readings that we record on the EEG. Chloral Hydrate (50mg/kg) and droperidol (0.2mg/kg) are, or have been, the medicines currently used to make children go to sleep. These agents all have side effects and can affect the brain waves. Recently supply of chloral hydrate was stopped in South Africa. Melatonin is used in other countries to induce sleep for EEG tests in children. We have started to use the same agent in our centre and want to monitor how effective it is for our patients. Melatonin is a natural product that is currently used for conditions such as jet lag. It is an "over – the counter" product, available in most health stores, it is not a prescribed drug.

2 - Who is monitoring the effectiveness of sleep induction for EEG studies in the department?

Dr. Roland Ibekwe, Lata Jeave and Professor J Wilmshurst , who are doctors and Neurophysiologists at the Red Cross Memorial Children's Hospital Rondebosch

3 - Background Information – monitoring and evaluation of the use of melatonin.

Your participation is requested because your child needs a sleep EEG test. We will ask you certain questions some of which will be personal and also carry out some simple examinations including blood pressure, heart beat rate and breathing rate on your child in this regard. The results from this study will allow us to improve on how we currently perform sleep EEG studies on children coming to our unit. We hope that it will also help other centres in South African who no longer have access to chloral hydrate.

4 - What Happens In this study

Your child will be given our standard dose of melatonin. This drug should help your child sleep within 45 to 90 minutes. When your childsleeps the technologistwill apply electrodes on your child's head and perform the EEG. This testlasts about25 -45 minutes, after which your child will be woken up, the same standard health checks will occur (heart rate, breathing and blood pressure). No needles are used, and the leads are fixed to your child's head through a gel which is completely removed at the end of the study. There is no harm from the EEG test itself.

5 - Possible Problems

This study to the best of our knowledge would not expose you or your child unnecessarily to any danger. Melatonin is a natural product and is considered to be generally safe.Drowsiness extending into the day after the study has been described in a few reports. We will not give your child melatonin if he or she is taking anti-clotting medicines as there is concern that it could put your child at risk of bleeding.

6 - Possible Benefits for You and Your Child

The information that this study provides will allow us to provide better care for children who require sleep EEGs in the future.

7 - Payment

Neither you nor your child will receive any money for participating in this study.

8 - Your Rights to Participate, Not Participate, or to Withdraw from the Study

Taking part in this study is voluntary. If you choose to not have your child participate in this study, you and your child will suffer no penalty. You will not lose any benefits to which you or your child is otherwise entitled. Your child's present or future medical care at the Red Cross War Memorial Children's Hospital will be the same whether or not your child takes part in the audit.

9 - Confidentiality

Your name and your child's name will never be made public by the investigators. The medical records of your child's care will be treated the same as all medical records at the Red Cross War Memorial Children's Hospital

The information about your child taken during this study, will be identified by a code number to make it very difficult for anyone to identify your child. All information will be stored in a secure place. Information from

this study and from your child's medical records may be used for research purposes and may be published in the medical literature; however, neither you nor your child's name will be made public by the investigators.

10 - Payment for A Research Related Injury:

In the event that an unanticipated complication results from a study-related procedure, you should contact Dr Roland Ibekwe at Department of Neurology, Red Cross Memorial Children's Hospital Rondebosch(0832430528) or Lata Jeaven at the department of Neurology, Red Cross Memorial Children's Hospital Rondebosch (Tel 021 6585289)

Appendix 2: Melatonin supplier data (http://www.swansonvitamins.com/swanson-premium-melatonin-3-mg-120-caps) : The information below is documented by the suppliers with the substance melatonin 3mg capsules, 120 tablets.

- Plays a crucial role in how well we sleep at night
- Helps control the sleep/wake cycle
- May help restore normal sleep patterns when you need them

Control your sleep/wake cycle naturally with the help of Swanson Melatonin! This useful hormone works to restore normal sleep patterns while delivering excellent antioxidant support to the body. Each capsule supplies 3 mg of melatonin.

Supplement Facts

Serving Size 1 Capsule

	Amount Per Serving	% Daily Value
Melatonin	3 mg	*

*Daily Value not established.

Other ingredients: Rice flour, gelatin.

Suggested Use: As a dietary supplement, take one capsule with water one-half hour before bedtime.

WARNING: As melatonin may produce drowsiness, do not drive an automobile or operate heavy equipment after taking. Do not take this product if you are pregnant or nursing, have an autoimmune condition or a depressive disorder, or are under 16 years of age.

The company states:

2. **Purity & Potency**

Since 2001 Swanson Health Products has voluntarily participated in independent third party Good Manufacturing Practices (GMP) audits, long before the FDA released their final regulations for the dietary supplement industry. Ingredients are tested at various stages throughout the production process to verify purity and potency, and finished products are tested for potency and stability by independent third-party laboratories to ensure that each supplement contains exactly what is stated on the label.

Appendix 3

CASE REPORT FORM EFFICACY OF MELATONIN IN INDUCING SLEEP

Identification code		
Date of birth		
Sex	Male	Female
Weight (Kg)		
Referral source		
Reason for referral		
Medication the child is receiving including but not limited to anticonvulsants	1. 2. 3.	
Inter-current illness	Yes	No

Specify illness	

Sleep deprivation	Yes	No
Premedication vital sign	Blood pressure	Pulse rate
	Respiratory rate	Temperature

Time of sleep onset (minutes)	

Duration of sedation (minutes)	

Need for top up medication	Yes	No

Post medication vital signs	Blood pressure	Pulse rate
	Respiratory rate	Temperature

Any other observed event			
Sedation successful		Yes	No

EEG FINDING

Background record			

Artifact		Yes	No
Type of artifact			

Abnormality		Yes	No
Type of abnormality			

Finding affects diagnosis		Yes	No
Affects management		Yes	No

Appendix 4:

Author roles

Roland Ibekwe collated the protocol, conducted the study data, analysed the data and completed the write up of the study

Lata Jeaven completed the EEG studies on the children, assisted with the data collection (sleep latency, EEG reporting)

Jo Wilmshurst supervised Dr Ibekwe through the development of the protocol, the overall study, the review of the findings, the write up and analysis of the data.

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Seizure is keen to publish focused reviews, especially on the latest developments in particular fields or on topics which are currently debated by clinicians and researchers. Authors are welcome to approach the Editor-in-Chief with their idea for a focused review prior to submission. Focused reviews should be preceded by an abstract. Focused reviews should be 1,500-2,500 words, and include no more than 3 figures or tables and 50 references.

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The body of the text of these articles should be limited in length to 4,000 words, and there should be a maximum of 6 figures or tables. Additional figures, tables and other material (such as associated videos) can be submitted as online only Supporting Information (see section 'preparation of manuscripts' for further details). Full length research articles should be preceded by an abstract. The body of the text of the article should be clearly structured into 1) Introduction, 2) Methods 3) Results, 4) Discussion, 5) Conclusion and 6) References.

d. Short communications.

Comprise a number of different kinds of previously unpublished materials including

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