The effect of chronotherapy on delirium in critical care- a systematic review

Delirium is prevalent within intensive care and high dependency units (critical care), affecting 1 in 5 high dependency patients and 4 in 5 mechanically ventilated patients with clear causation between critical illness and incidence of delirium (Page and Ely, 2011). However, despite its incidence, preventative measures are limited and treatment interventions focus on symptom control once delirium has manifested (Barroso and den Brinker, 2013).

Delirium is a syndrome characterised by acutely altered mental state, cognitive impairment and fluctuations throughout the course of the day (American Psychiatric Association, 2013). Delirium has serious short and long term consequences for patient outcome independent of severity of illness, including fewer days alive without mechanical ventilation, increased 6-month mortality, prolonged hospital stay, and higher incidence of cognitive impairment on discharge (Ely, 2004). Acute confusional states can develop and patients can go on to experience post traumatic stress disorder (PTSD). Long-term studies have shown that prolonged episodes of delirium increase risk of long-term cognitive impairment at 3 months (p=0.03) and 12 months (p=0.02) post-discharge (Girard et al., 2010), with impairment of quality of life (Gunther et al., 2012).

Although the pathogenesis is not fully understood, delirium is known to be caused by neuronal dysfunction secondary to systemic disorders and multiple coexisting risk factors (Madrid-Navarro et al., 2015). Predisposing risk factors include older age, high APACHE-2 score, mechanical ventilation and metabolic acidosis (Zaal et al., 2015). Studies have also linked the development of delirium to precipitating risk factors such as abnormal levels of melatonin and loss of circadian rhythms (Meagher et al., 2007; Bellapart and Boots, 2012; Fitzgerald et al., 2013; Madrid-Navarro et al., 2015; Oldham et al., 2016).

The artificial critical care environment and iatrogenic sleep disturbance are linked to circadian disruption with likely development of delirium (Wenham and Pittard, 2009; Delaney et al., 2015). Attention has turned to the potential benefits of chronotherapy, defined as “modifying circadian rhythms with therapeutic intent” (Oldham et al., 2016, p. 209). This incorporates interventions which modulate the environment (light, noise control) as well as drugs which influence circadian rhythm.

Chronotherapeutic options such as bright light therapy (BLT) and dynamic light applications (DLA) are well proven within psychiatry to treat seasonal depression (Koyama et al., 1999; Madrid-Navarro et al., 2015). Bright light therapy is the use of lighting up to 10,000 lux for at least two hours/ day, whereas dynamic light application is the periodic dimming of lighting from, for example, 1700 lux to 300 lux. Exogenous melatonin and melatonergic agents have also been shown to improve sleep in the critical care setting, as well as reduce incidence of delirium in acutely ill elderly patients (Shilo et al., 2000; Bourne et al., 2008; Sultan, 2010; Al-Aama et al., 2011; Oldham et al., 2016). Delirium guidelines (NICE, 2010) recommend multicomponent nonpharmacological interventions (MNI), such as the use of ear plugs, to modify external environment cues, promote the sleep-wake cycle and entrain the circadian rhythm (Madrid-Navarro et al., 2015). The use of drugs that may enhance circadian rhythm are not within the NICE (2010) guidelines.

Research question: Can chronotherapy reduce the prevalence of delirium in adult patients in critical care?

Aim: To understand whether implementation of chronotherapy within the critical care setting can reduce the prevalence of delirium.

Objectives:

- To identify specific research that has evaluated the effect of chronotherapy interventions
- To ascertain the potential benefits of chronotherapy interventions in critical care.

Methodology

Search strategy

A systematic search of recent research (2006- 2016) was undertaken using the databases Academic Search Complete, CINAHL Plus with Full Text, E-Journals, MEDLINE Complete, PsycARTICLES and PsycINFO. This was supplemented by a hand search of relevant articles and journals. The key search terms, which incorporated MeSH terms, were chronotherap* OR chronoenhancement OR light therapy OR environmental light* OR environmental

factor* OR dynamic light* OR melaton* AND deliri* OR psychos?s OR acute confusional state AND critical care OR ITU OR ICU OR intensive therapy OR intensive care OR critically ill.

Selection criteria and screening process

During the selection process, inclusion/ exclusion criteria were applied:

Inclusion criteria

- Primary research investigating chronotherapy interventions and their effects on delirium in adults in critical care.
- Quantitative study design
- English language
- Adult patients (18+ years)
- Critical care settings
- Articles published since 2006

Exclusion criteria

- Research with a different focus
- Secondary research/ literature reviews
- Paediatric studies

Identified studies were screened for relevance using a three stage process ensuring a systematic approach. Firstly the title was reviewed. Secondly, the abstract was reviewed to ensure the inclusion/ exclusion criteria were adhered to. The final stage of screening involved reviewing the studies in full to ensure all fulfilled the search criteria. Both authors undertook the screening process independently and then agreed on the eligibility of the studies for inclusion.

Data extraction and quality appraisal

Both authors extracted the data, such as methodology, sample sizes and statistics (mean scores, standard deviation, p values) from each included study, using a standardised extraction form. Outcomes for delirium such as CAM- ICU scores were extracted as well as other data recorded during the study which could lead to delirium (such as hours of sleep).

The eligible studies were appraised using either the critical appraisal skills programme (CASP) randomised controlled trial (RCT) checklist or the CASP cohort study checklist depending on research methodology/ design. This allowed the authors to appraise the quality of the studies in relation to, for example, appropriateness of study design and methods of data collection, sample size, outcome measures and statistical significance of results.

Results

Search outcome

The initial search returned 99 results from the databases used. A hand search of relevant critical care journals identified three further studies. After applying the exclusion criteria and removing duplicates, 49 articles were left. 31 studies were then excluded following title and abstract scrutiny as they did not meet the inclusion criteria. The full text of the remaining 18 articles were read and a further 12 excluded due to having the wrong focus for example, delirium and circadian disruption caused by weaning from mechanical ventilation. This resulted in six studies being identified from the main search and a PRISMA flow chart was developed (figure 1).

Five studies were randomised controlled trials (RCT) and one study used a cohort-based design with historical control for 'pre-intervention' data (table 1). Two of the studies were conducted in Europe and four were conducted in East Asia. All studies measuring delirium used validated delirium assessment tools: CAM-ICU, DRS-R98 and J-NCS. Interventions included dynamic light therapy, bright light therapy, Ramelteon and multicomponent non pharmacologic interventions such as noise reduction, use of music, use of eye shades and patient orientation

Following data extraction, common themes were inductively identified through a narrative review approach (Aveyard, 2014). Themes were identified by the two authors independently, then compared and refined. Four key themes were found:

1) delirium prevalence and duration;
2) circadian rhythm: arrhythmia and entrainment;

3) sleep efficiency and disturbance;
4) other therapeutic effects.

Delirium Prevalence and duration

All studies measured the effect of different chronotherapeutic interventions on the incidence of delirium within critical care. Hatta et al. (2014) found delirium occurred in 1/33 (3%) of patients taking the melatonergic agonist Ramelteon vs. 11/34 (32%) in the control group. Likewise, Hatta et al. (2014) found statistically significant reductions in the risk of developing delirium for the group receiving Ramelteon (p=0.002), along with slower time to development of 6.94 day vs. 5.74 days for the placebo group. Guo et al. (2015) found a reduced occurrence in delirium in the group receiving multicomponent nonpharmacological interventions (MNI) (10/81 (12%) vs 25/79 (31%)) as did Patel et al. (2014) (55/167 (33%) pre-intervention compared to 24/171 (14%) post-MNI). These were all statistically significant reductions in the overall incidence of delirium with P-values respectively p<0.003, p<0.006 and p<0.001. MNI strategies included, for example, reduction of noise, use of eye shades and earplugs. MNI bundles also reduced the duration of delirium with Patel et al. (2014) finding an average of 3.4 days of delirium pre-intervention to 1.2 days post (p=0.021) while Guo et al. (2015) reported an average of 28.1 hours in the MNI group vs. 60.2 hours in the control (p<0.001).

Ono et al. (2011) and Taguchi et al. (2007) demonstrated marked reductions in delirium occurrence in the groups receiving bright light therapy (BLT) (collectively 2/16 BLT vs. 10/17 control). However, these results were not statistically significant due to limited sample sizes of 22 and 11 respectively, reducing the reliability of the results. In contrast, Simons et al. (2016) found a slight increase in the cumulative incidence of delirium in the patients receiving dynamic light application (DLA) 137/361 (38%) vs. 123/373 (33%) patients in the control group (OR 1.24, 95% CI 0.92-1.68, p=0.16). However, Simons et al. (2016) measured cumulative duration of delirium and coma free days and found a reduction of one day in the DLA group, however this was not statistically significant (p=0.29). Taguchi et al. (2007) also reported a reduction in the duration of symptoms of delirium following implementation of BLT, identifying that visual and auditory hallucinations stopped a day after BLT, whereas these symptoms persisted for several days in the control group.

Circadian Rhythm: Arrhythmia and Entrainment

To assess the efficacy of chronotherapy in maintenance of circadian rhythm, the circadian biomarkers of melatonin and cortisol were tested in two of the studies (Guo et al, 2015; Simons et al (2016). Guo et al. (2015) found that while there were no significant differences in the neurohormone levels pre-operatively between the two study groups, postoperative nocturnal urine levels consistently showed statistically significant increases in melatonin and decreases in cortisol in the MNI group compared to the control group suggesting improved circadian rhythms with use of MNI.

Conversely, Simons et al. (2016) assessed a subgroup of 20 patients (11 DLA vs. 9 control) and found no differences between the groups in the total excretion of the biomarkers when measured hourly during night-time or morning periods. Simons et al. (2016) also found that levels of melatonin did not vary significantly across the course of the day, suggesting abnormal secretion of melatonin and therefore circadian arrhythmia.

Circadian rhythm was also measured through monitoring of physical and autonomic activity. Taguchi et al. (2007) showed reductions in physical activity on night four of the BLT intervention group, this was not significant in comparison to the control. Alternatively, Ono et al. (2011) conducted a time series of physical activity and found that the circadian cycle was 24.1 ± 3.2 hours for the BLT study group vs. 21.9 ± 1.5 hours for the control group, indicating BLT may assist with the entrainment of the circadian rhythm. Between the two groups however, no well-defined 24 hour periodicity of autonomic nervous system activity was found.

Positive results from the MNI and BLT studies suggest that a combination of chronotherapeutic interventions may have more effect on the entrainment of circadian rhythm and reduce the prevalence of delirium, although the weight of the evidence is limited.

Sleep Efficiency and Disturbance

Sleep metrics, such as hours asleep and physical activity, were investigated in three of the studies. These studies used actigraphy (non invasive monitoring of activity and rest) and nurse assessment which can be inaccurate (Beecroft et al., 2008) rather than the gold-

standard polysomnography, which records biophysiological changes (such as muscle, brain and eye activity), that occurs during sleep and offers more accurate sleep data . Patel et al. (2014) measured sleep quantity and quality using subjective measurements (patient reported sleep questionnaires and nursing assessments): with high compliance of the MNI bundle (>90%) the study showed significant reductions in night-time noise (p=0.002), light (p=0.003) and iatrogenic sleep disturbance (p=0.003). This led to a significant increase in mean hours of night-time sleep from 6.6 hours (55%) before the intervention vs. 8.6 hours (72%) after (p<0.001), and more windows of 3 hours uninterrupted sleep (32% before vs. 39% after, p=0.029). Additionally, Patel et al. (2014) found that patients reporting high sleep efficiency index scores (length of time asleep vs length of time in bed) had a reduced risk of delirium with odds of developing delirium around 10% less (OR 0.90, 95% CI 0.84-0.97). However, this finding has limitations due to only 59/338 patients reporting sleep efficiency scores

Using actigraphy, a significant reduction in physical activity was found on post-operative night 4 and 5 in patients receiving BLT (Ono et al, 2011). This suggests this group had greater night-time rest and deeper sleep. Sympathetic nervous activity was persistently reduced during the night compared to the control group especially at 2 am on night 5 (p<0.05).

Hatta et al. (2014) however did not find any benefit of Ramelteon on sleep efficiency based on sleep parameter measurements and no significant difference was found in the rate of Hydroxyzine use (for insomnia) between the group receiving Ramelteon and the control group.

Other Therapeutic Effects

Other benefits of the chronotherapeutic interventions were found. During BLT, Ono et al. (2011) measured the occurrence of post-operative cardiac arrhythmias which were consistently lower in the intervention group with significant differences found on night 4 and day 5 (p<0.05). Taguchi et al. (2007) found that ambulation started around 2 days earlier in the intervention group with a mean of 5.5 ± 1.0 days in comparison to 7.6 ± 2.5 days in the control group, although this difference was not found to be statistically significant.

As part of the MNI research, Guo et al. (2015) monitored the patients' Richmond Agitation Sedation Score (RASS) twice daily and asked all patients to complete a 40 item quality of recovery score (QoR40). At each time interval measured for three days post-operatively the mean RASS scores were consistently lower in the intervention group (p<0.05). The QoR40 score was also consistently higher (p<0.05) indicating a greater quality of recovery, taking into consideration emotional, physical and psychological factors.

Discussion

There is a large body of literature discussing the effects of circadian disruption and potential benefits of chronotherapy, but only a limited amount of primary research studying the effects of these interventions on delirium as a primary outcome within critical care. Following appraisal, mixed results for the efficacy of the chronotherapeutic interventions were found.

Multicomponent Nonpharmacologic Interventions

Both Patel et al. (2014) and Guo et al. (2015) explored the effectiveness of MNI (reduction in light and noise, use of eye shades, frequent patient orientation and provision of music) and found marked reductions in the incidence and duration of delirium. As delirium in critical care is associated with multiple adverse outcomes, this is a clinically significant finding (Girard et al., 2008; Bulic et al., 2015). Although non- critical care studies have shown that it is possible to reduce delirium prevalence through MNI (Inouye et al., 1999; Vidan et al., 2009), the reviewed studies are the first to show the effect of MNI within critical care.

The importance of increased staff education, awareness and understanding of delirium is a significant factor in the effectiveness of delirium intervention (O'Mahony et al., 2011). Patel et al. (2014) provided staff with ongoing training and information about sleep and delirium and reported a 90% compliance rate with the planned interventions which included substantially reducing night time noise and light levels as well as iatrogenic sleep disturbance. This significantly improved qualitative and quantitative sleep measures.

Exogenous Melatonin and Melatonergic Agents

The use of Ramelteon showed significant reductions in incidence, risk and frequency of delirium in acutely ill elderly patients even after controlling for risk factors (Hatta et al,

2014). This indicates potential use of Ramelteon as a prophylactic treatment option for elderly patients at high risk of developing delirium. However, the generalisability of the results in view of the critical care population is substantially limited.

Research studying the effects of exogenous melatonin is limited but has encouraging results. Three RCTs, which were conducted outside of a critical care setting, measured the effects of exogenous melatonin in acutely ill elderly patients and two studies found the incidence of delirium two to four times lower than in the control group (Sultan, 2010; Al-Aama et al., 2011). The third study found no differences in the incidence of delirium, however significantly fewer patients receiving melatonin had a duration of delirium more than two days when compared to the control (26% vs. 47%, p=0.02) (de Jonghe et al., 2014)

Melatonin has gained interest in critical care for its potential benefit as a physiological sleep aid due to its role in synchronisation of the circadian rhythm and sleep-wake pattern. Elliot et al. (2013) used polysomnography to assess sleep in critical care, finding an average total sleep time of 5 hours however, 41% of this was during day time hours indicating a diurnal shift of the sleep-wake cycle. The majority of sleep was also found to be in stages 1 (19%) and 2 (73%) with scant deeper, restorative phases of sleep. This indicates sleep quality is severely affected, leading to sleep deprivation which is associated with delirium, difficulty weaning, prolonged stay and increased mortality (Boyko et al., 2012). Of three studies which have looked at the effect of melatonin therapy to improve nocturnal sleep for critically ill patients, two found that melatonin improved sleep length and quality (Shilo et al., 2000; Bourne et al., 2008). The third study did not find any difference in observed nocturnal sleep (Ibrahim et al., 2006).

Dynamic Light Application/ Bright Light Therapy

The studies within this review that evaluated the use of light therapy had mixed results regarding the effect on the prevalence of delirium. Simons et al. (2016) carried out the most extensive study of DLA to date however, no differences were found in the incidence of delirium with only a 1-day reduction of delirium and coma-free days. The study design however had significant limitations and not all clinically important outcomes were measured such as sleep efficiency. Wilson (1972) found that twice as many episodes of delirium occurred in critical care areas without windows compared to those with windows suggesting

that poor visible daylight contributes to the development of delirium; lack of visible daylight was also found by Van Rompaey et al. (2009) as being a significant risk factor for the development of delirium (OR 2.39, 95% CI 1.28-4.45, *p*=0.003).

Both Ono et al. (2011) and Taguchi et al. (2007) used BLT of 5000 lux for 2 hours in the morning, which had the benefit of being closer to the subjective dawn, which has been shown to have a stronger circadian effect (Wirz-Justice et al., 2009). Both studies demonstrated favourable measures of sleep efficiency and marked deductions in the rates of delirium.

While it is difficult to come to any conclusions for the efficacy of BLT or DLA in reducing the prevalence of delirium, a mixed methods study by Engwall et al. (2015) compared patients' experiences of critical care rooms with different lighting environments. One had a cycled lighting system specially adapted to support patients' circadian rhythm while the other used an ordinary lighting system. Results from the study showed significant differences in favour of the daytime brightness in intervention room (p=0.004) with patients describing the light as pleasant and healthy, with increased alertness and positive impacts on mood and feelings of security. This suggests important psychological benefits that light therapy may have in critical care, and may reduce the incidence of traumatic stressors associated with PTSD, including delirium (Vanderbilt University Medical Center, 2013).

Recommendations

The complex and multifactorial nature of delirium within critical care suggests that no single intervention is likely to be successful (Bourne and Mills, 2006). The use of MNI within critical care found consistently marked reductions in the prevalence of delirium. To enable the use of MNI within critical care, education of the multidisciplinary team a key factor. Guo et al. (2015) and Patel et al. (2014) identify that all critical care staff should have advanced training and education in order to implement MNI effectively with heightened awareness of delirium risk factors, correct assessment and treatment. Changes in clinical practice should also include reductions in iatrogenic sleep disturbance, modification of environmental noise and light and daily sedation targets (Patel et al., 2014; Guo et al., 2015; Madrid-Navarro et al., 2015).

Although it is too early to recommend the use of melatonin or melatonergic agents as a prophylactic treatment of delirium, melatonin has been licensed in the UK for the short-term treatment of insomnia in adults who are aged 55 and over (Bellapart and Boots, 2012; NICE, 2016). With significant chronotherapeutic benefits of improved sleep quality and latency, morning alertness and increased quality of life, this may also provide a clinically relevant alternative to conventional sedative-hypnotic agents currently being used in critical care (Lemoine and Zisapel, 2012; Huang et al., 2014). This is especially relevant for older patients in which use of conventional agents may adversely affect cognition, memory, sleep structure and increase their risk of delirium (Glass et al., 2005).

While evidence is not strong enough to suggest BLT or DLA would be relevant in current practice to reduce the prevalence of delirium, all studies did agree that a natural bright lighting style is preferable in the critical care setting, and potential benefits were found regarding psychological well-being (Engwall et al., 2015). Application of real time monitoring of environmental variables (noise, light and temperature) may help to provide healthcare staff with accurate feedback necessary in order to promote circadian rhythms (Madrid-Navarro et al., 2015).

The identified chronotherapeutic interventions, in particular MNI interventions such as frequent patient orientation, enhancement of a 'day night' cycle in regards to noise and lighting, have promising results, however there is a clear need for large, multicentre RCTs which are well coordinated and measure all relevant physiologic outcomes of chronotherapy within the critical care setting. This should include delirium prevalence, sedation use and sleep metrics (Logan and Sarkar, 2012; Oldham et al., 2016). Given the clinical benefits of restorative deep phases of sleep, further research should also look to use validated sleep assessments such as polysomnography in order to be able to gain an accurate measure of not only the quantity but also the quality of the sleep which has been linked to reductions in delirium (Weinhouse et al., 2009; Parthasarathy and Friese, 2012; Patel et al., 2014).

Limitations

The studies were undertaken globally and it is not clear how this may affect the epidemiology of delirium in the critical care setting as there is a paucity of data regarding the global prevalence of delirium (Salluh et al., 2010). However, it is important to acknowledge that differences in clinical practice may play a significant role in delirium prevalence and critical care outcomes (Beale et al., 2009; Patel et al., 2009). All identified studies had limitations regarding research design, control of confounding variables and lacked validated measures of important outcomes such as sleep. Between the different studies, a variety of different interventions were evaluated and different assessment tools were used; this inconsistency is a limitation to the review.

Conclusion

This review assessed whether chronotherapy can be used to reduce the prevalence of delirium in the critical care setting. Based on critical appraisal of the current research available, mixed results were found regarding the efficacy of the interventions. MNI showed greatest chronotherapeutic value for reduced delirium incidence, risk and duration. The melatonergic agent Ramelteon also showed promising results, significantly reducing incidence of delirium with less risk and frequency of occurrence. BLT and DLA studies obtained indeterminate results as no statistically significant differences regarding delirium prevalence were found.

Based on these findings recommendations for practice include increasing the multidisciplinary team's awareness of delirium through training and education, encouraging proactive review of medications, iatrogenic sleep disturbance and the critical care environment. Whilst more research is needed into the potential chronotherapeutic benefits of melatonin and light therapy and their effect on delirium, melatonin as a drug may provide a relevant alternative to sedative-hypnotics in older adults and increasing the light/dark contrast may provide therapeutic benefits and reduce delirium susceptibility.

What is known about this topic:

- Delirium within the critical care setting has a negative impact on patient outcome
- Chronotherapy may help to maintain circadian rhythm and reduce the likelihood of delirium.

What this paper adds:

- Multicomponent nonpharmacological interventions can significantly reduce the prevalence and duration of delirium within critical care
- Chronotherapeutic interventions may maintain circadian rhythm and increase quality of sleep
- There may be a role for the use of bright light therapy and melatonergic agents within critical care
- Staff education and training to introduce and establish interventions to promote a clear day/ night cycle within critical care areas is essential

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