

COMMENTARY

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Scope of chronotherapy in perioperative medicine—a topical review

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Introduction

Chronobiology is a subspecialty of biology that deals with biological phenomena that exhibit a cyclical behaviour. Chronophysiology is the timely organization of biochemical and behavioural processes that synchronize to ensure the body's homeostatic mechanism. Similarly, chronopathology identifies alterations in homeostatic parameters which deviate from an average value and thus helps in identifying a pre-pathological condition. This leads to the coining of a terminology called chronotherapy which involves administering a treatment modality, i.e. medication which could be oral or injectable at a specified time so as to have its optimal effect in maintaining homeostasis and minimal adverse effects (Selfridge et al. 2016).

Methods

We searched PubMed, Scopus, MEDLINE, Web of Science, Google Scholar and Embase with the following keywords: chronobiology, chronotherapy, anaesthesia, perioperative. The published articles which described the role of chronotherapy in the perioperative period were reviewed.

Perioperative period and chronobiology

The perioperative period is vulnerable as many unwanted events occur in this period especially in high-risk patients. Principles of chronotherapy can be applied by understanding the diurnal nature of physiological changes in surgical patients (Chassard et al. 2007). Figure 1 shows the systemic framework for chronobiology-based personalized medicine. The objective of chronobiology-based personalized medicine is to optimize timing, amount and composition of a drug so as to promote the efficacy and minimize the toxicity.

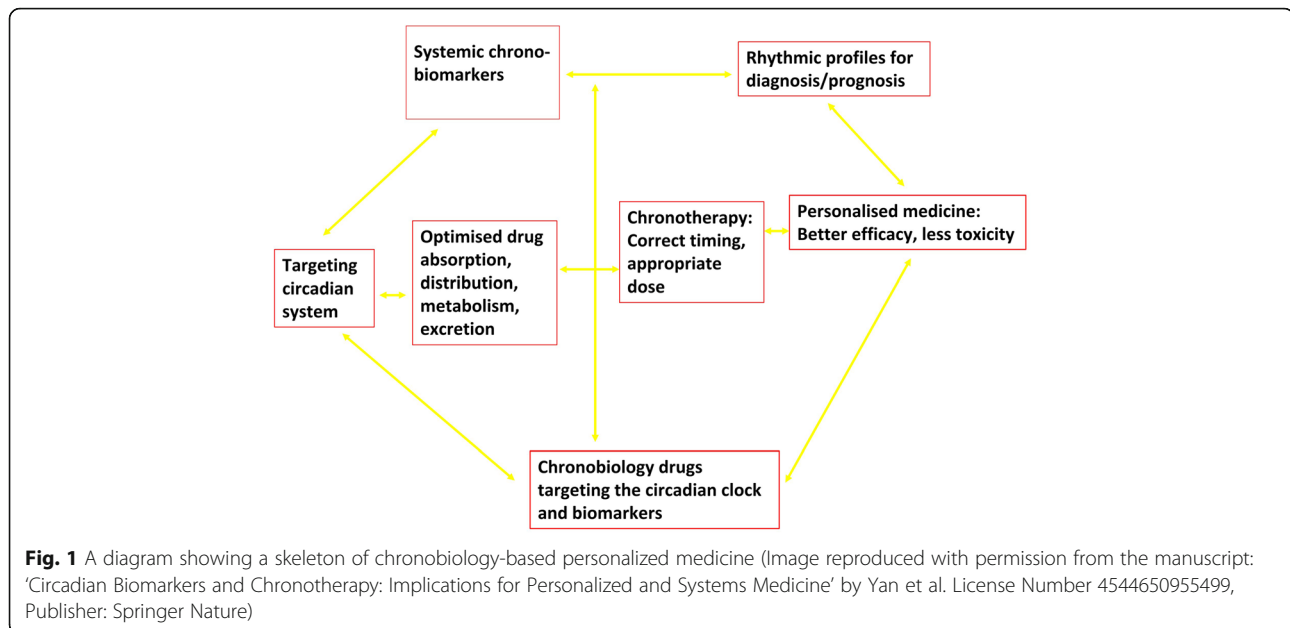
Chronobiology of the cardiovascular system

Heart rate variability, pacing and defibrillation threshold, cardiac refractoriness and conduction abnormalities show diurnal changes. Therefore, acute coronary syndromes and rhythm disturbances occur in the early morning hours, between 6 AM and 12 noon (Brainard et al. 2015). Therefore, patients using beta blockers or other rate-control drugs, nitrates and anti-arrhythmics, should continue them perioperatively at the same time. The timing of consuming aspirin is highly debatable. Some recommend it in the morning hours while another group supports evening dosing. As incidence of acute syndromes in the early hours of the morning appears high, an evening dose appears suitable compared to a morning dose. Energy requirement for defibrillation has also been found to be more in the morning hours compared to mid and late afternoon. The concentration of coagulation factors, more pronounced platelet aggregation and a decrease in fibrinolytic activity have been noticed in the morning hours. This makes thrombotic events leading to acute coronary events and acute cerebrovascular events common during the early hours of the morning (McKenna et al. 2018). The success of thrombolysis after thrombotic events is better for afternoon and evening events than that in the early hours of the morning. Montaigne et al. felt that afternoon surgery might provide better perioperative myocardial protection and can lead to improved patient outcomes compared with morning surgery due to circadian changes precipitating cardiovascular events in the morning hours (Montaigne et al. 2018). Chronobiology of catecholamines is usually affected in the perioperative period as the baseline circadian rhythm is disturbed due to multiple factors.

It has long been known that cholesterol biosynthesis occurs at night, roughly between 12 midnight and 6 AM. Therefore, hypolipidaemic drugs like statins were prescribed at bed time so as to have an optimal effect in

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lowering cholesterol levels. Contrary to this, Izquierdo-Palomares et al. who published a systematic review in the Cochrane database found that chronotherapy was not important when taking statins (Izquierdo-Palomares et al. 2016). The authors found no difference in cholesterol levels when statins were administered in the evening or in the morning hours. Using statins based on chronotherapy has shown no harm or inferior lipid-lowering effect.

Hepatorenal function, respiratory system and chronotherapy (Chassard and Bruguerolle 2004)

Renal function measured using inulin clearance is better during daytime than at night. Hepatic blood flow also keeps changing throughout the day. Therefore, drugs undergoing hepatic metabolism like propofol, inhalational anaesthetics and benzodiazepines can have unpredictable effects depending on the time of administration and circadian phase. Airway hyper-reactivity and susceptibility to bronchospasm in asthmatics have been found to be more in the evening hours and night time compared to morning and noon.

Chronotherapy for seizures

Patients who undergo neurosurgery are prescribed anti-epileptic drugs (AED) either for seizure prophylaxis or for a pre-existing seizure disorder. In spite of prescribed medications, some patients' manifest seizures which lead to a lot of interventions like brain scanning, use of benzodiazepines, re-exploration and prolonged ICU stay. In a recent study published by Karoly et al. involving 1118 patients, authors have described that at

least 90% seizures have a rhythmic diurnal pattern (Karoly et al. 2018). AED use by itself can cause sedation which can affect the patients' circadian cycle. A lot of circadian disturbances depend on the location of epileptic focus (temporal lobe epilepsy).

AED prescription using principles of chronotherapy is largely an unexplored area, especially in surgical patients. This cannot be uniform because a lot depends on the location of seizure, duration of medications and hepatorenal function which eventually metabolizes and excretes these medications.

Chronobiology in perioperative pain

Circadian changes in nociception and cyclic changes in pain perception have been studied but have not been successfully correlated. Theoretically, pain scores could be higher in day time when patients ambulate or are made to mobilize as a part of physiotherapy. This was observed in certain studies where opioid consumption was found to be more with patient-controlled analgesia between 8:00 and 12:00 noon compared to evening and night. Circadian variation in secretion of opioid peptides like enkephalin and endorphins could also be responsible for the difference in perception of pain (Martin et al. 2018). Analgesics have better efficacy and lesser side effects if administered at a specific time. If non-steroidal anti-inflammatory drugs (NSAIDs) are administered in the morning, there is better absorption, more protein binding and decreased nephrotoxicity and opioid sparing. Similarly, opioids work effectively when administered in the evening than in the morning hours which was studied in healthy volunteers

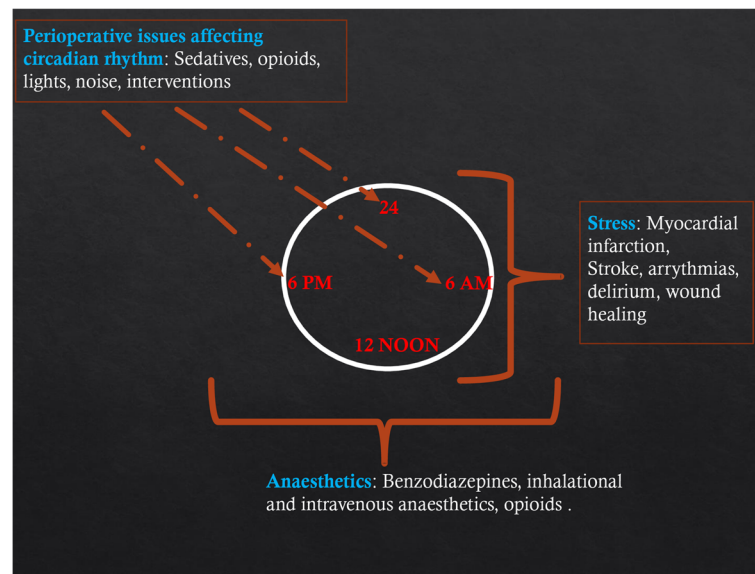


Fig. 2 Diagram showing the relationship of anaesthesia and perioperative factors in affecting the circadian rhythm and its sequelae

(Boom et al. 2010). These chronopharmacological properties can be used in managing acute postoperative pain effectively.

Dynamics in the immediate postoperative period

In health, the pineal gland secretes melatonin at night which facilitates sleep and has analgesic effects which thereby facilitate rest to the body. Along with serotonin, melatonin controls blood pressure, appetite, mood and memory. Due to the use of inhalational agents, opioids and benzodiazepines in the perioperative period along with surgical stress and the intensive care unit (ICU)/hospital environment, the secretion of melatonin and serotonin is affected. Figure 2 shows the consequences of a disrupted circadian rhythm in the postoperative period. Patients with a disrupted circadian rhythm after major surgeries, sepsis and shock have high chances of developing postoperative delirium. Other factors like sedatives, pain, lighting, noise and patient-care interactions are also responsible for delirious events. Hansen et al. reviewed existing literature regarding therapeutic and prophylactic use of melatonin in treating or preventing cognitive dysfunction in such patients and found that there is no robust evidence for using melatonin in such patients (Hansen 2014). Perioperative melatonin administration needs to be studied further to maintain homeostasis, to avoid insomnia and delirium in susceptible patients. Timing of surgery affecting the release of melatonin and serotonin has not been studied and understood which could be explored in the future.

In conclusion, the circadian rhythm plays a vital role in homeostasis. Once this is understood more precisely, medications can be timed accordingly. Further studies are the need of the hour which could not only answer a lot of queries but should also make way for redefining guidelines for perioperative medicine.

Abbreviations

AED: Anti-epileptic drugs; ICU: Intensive care unit; NSAIDs: Non-steroidal anti-inflammatory drugs

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References

- Boom M, Grefkens J, van Dorp E et al (2010) Opioid chronopharmacology: influence of timing of infusion on fentanyl's analgesic efficacy in healthy human volunteers. *J Pain Res.* 3:183–190
- Brainard J, Gobel M, Bartels K, Scott B, Koeppen M, Eckle T (2015) Circadian rhythms in anesthesia and critical care medicine: potential importance of circadian disruptions. *SeminCardiothoracVascAnesth.* 19:49–60
- Chassard D, Bruguerolle B (2004) Chronobiology and anesthesia. *Anesthesiology.* 100:413–427
- Chassard D, Duflo F, de Queiroz SM, Allaouchiche B, Boselli E (2007) Chronobiology and anaesthesia. *Curr Opin Anaesthesiol.* 20:186–190
- Hansen MV (2014) Chronobiology, cognitive function and depressive symptoms in surgical patients. *Dan Med J.* 61:B4914
- Izquierdo-Palomares JM, Fernandez-Tabera JM, Plana MN, Añino Alba A, Gómez Álvarez P, Fernandez-Esteban I, Saiz LC, Martin-Carrillo P, Pinar López Ó (2016) Chronotherapy versus conventional statins therapy for the treatment of hyperlipidaemia. *Cochrane Database Syst Rev* 11:CD009462
- Karoly PJ, Goldenholz DM, Freestone DR, Moss RE, Grayden DB, Theodore WH et al (2018) Circadian and circaseptan rhythms in human epilepsy: a retrospective cohort study. *Lancet Neurol.* 17:977–985
- Martin D, McKenna H, Galley H (2018) Rhythm and cues: role of chronobiology in perioperative medicine. *Br J Anaesth.* 121:344–349
- McKenna H, van der Horst GTJ, Reiss I, Martin D (2018) Clinical chronobiology: a timely consideration in critical care medicine. *Crit Care.* 22:124
- Montaigne D, Marechal X, Modine T, Coisne A, Mouton S, Fayad G et al (2018) Daytime variation of perioperative myocardial injury in cardiac surgery and its prevention by Rev-Erba antagonism: a single-centre propensity-matched cohort study and a randomized study. *Lancet.* 391:59–69
- Selfridge JM, Gotoh T, Schiffhauer S, Liu J, Stauffer PE, Li A, Capelluto DG, Finkielstein CV (2016) Chronotherapy: intuitive, sound, founded...but not broadly applied. *Drugs.* 76:1507–1521

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