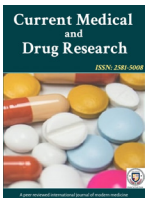
Global SciTech Ocean

Current Medical and Drug Research
(Contents available at www.globalscitechocean.com)



Influence of Circadian Rhythm on Postoperative Endodontic Pain and Inflammatory Cytokine Expression

Paul Chrepa[1], Mohammad Saleem[2]

[1]*DDS*
[2]*BDS, MDS, Oral & Maxillofacial Surgery*

Article history

Received: November 28, 2022
Accepted: December 15, 2022

Keywords

Circadian rhythm, postoperative endodontic pain, inflammatory cytokines, melatonin, BMAL1, chronobiology, oxidative stress, immune response, periapical healing, artificial intelligence, endodontics.

https://doi.org/10.53517/a98h8398

ABSTRACT

Postoperative pain remains one of the most common complications following endodontic treatment and is primarily influenced by inflammatory responses within the periapical tissues. Recent evidence suggests that circadian rhythm, the body's intrinsic biological timing system, plays a significant role in regulating pain perception, immune activity, hormonal secretion, and inflammatory mediator production. Variations in the expression of pro-inflammatory and anti-inflammatory cytokines throughout the day may contribute to differences in the intensity and duration of postoperative endodontic pain among patients. Circadian regulators, including melatonin and clock-related genes, have demonstrated protective effects by modulating oxidative stress, enhancing immune balance, and promoting tissue repair. Understanding these biological mechanisms provides new opportunities for optimizing treatment timing, improving postoperative pain control, and supporting faster healing. Furthermore, advances in digital dentistry and artificial intelligence offer promising approaches for integrating patient-specific biological rhythms with clinical decision-making to develop personalized pain management strategies. This review examines the influence of circadian rhythm on postoperative endodontic pain and inflammatory cytokine expression, highlighting the underlying molecular pathways, clinical implications, and emerging technologies that may enhance therapeutic outcomes. A chronobiology-based approach has the potential to improve patient comfort, reduce inflammatory complications, and contribute to more predictable and individualized endodontic care.

INTRODUCTION

Postoperative pain following endodontic treatment is a common clinical concern that can adversely affect patient comfort, treatment satisfaction, and overall quality of life. Although pain is generally transient, its severity varies considerably among individuals due to differences in inflammatory responses, immune regulation, and neuroendocrine activity. Increasing evidence suggests that circadian rhythm, the endogenous biological timing system regulating physiological and biochemical processes, influences pain perception, inflammatory cytokine production, and tissue healing through coordinated hormonal and molecular mechanisms (Chrousos, 2000; Yiallouris et al., 2019).

Circadian regulation affects the secretion of cortisol, melatonin, and other mediators involved in immune homeostasis and oxidative stress. Melatonin, in particular, possesses antioxidant, anti-inflammatory, and analgesic properties that may reduce postoperative discomfort and promote tissue repair following endodontic procedures (Kurdi & Patel, 2013; Maitra et al., 2013). Furthermore, clock-related genes such as BMAL1 have emerged as important regulators of inflammatory pathways and periapical healing, suggesting

that disruption of circadian homeostasis may influence the progression and resolution of apical periodontitis (Küçük et al., 2022). The interaction between oxidative stress and inflammatory cytokines further highlights the biological complexity of postoperative healing and pain modulation (Halladin, 2015).

Advances in chronobiology have also created opportunities to optimize the timing of endodontic interventions and postoperative pain management. Additionally, artificial intelligence has shown considerable potential in integrating biological, clinical, and patient-specific data to predict treatment outcomes and support personalized endodontic care (Singh, 2022). The diverse immunomodulatory actions of melatonin reported in systemic inflammatory conditions further reinforce its potential relevance in dental inflammation and tissue repair (Yang et al., 2018). This review explores the influence of circadian rhythm on postoperative endodontic pain and inflammatory cytokine expression, emphasizing the underlying biological mechanisms, clinical significance, and emerging approaches for improving treatment outcomes.

Circadian Rhythm, Endodontic Pain, and Inflammatory Mechanisms

Circadian rhythm is an endogenous biological timing system that regulates physiological processes over a 24-hour cycle through central and peripheral molecular clocks. These rhythms coordinate hormonal secretion, immune surveillance, oxidative balance, and cellular metabolism, thereby influencing tissue repair and inflammatory responses. The hypothalamic suprachiasmatic nucleus synchronizes peripheral clocks using environmental cues such as light, ensuring homeostasis (Chrousos, 2000).

Pain perception also exhibits circadian variation because fluctuations in cortisol, melatonin, and inflammatory mediators alter nociceptive sensitivity throughout the day. Melatonin possesses antioxidant, anti-inflammatory, and analgesic properties that suppress oxidative stress and modulate immune cell activity, potentially reducing postoperative discomfort following endodontic treatment (Kurdi & Patel, 2013; Maitra et al., 2013; Yang et al., 2018). Conversely, dysregulated stress responses and altered cortisol secretion may intensify inflammation and pain perception, particularly in susceptible individuals (Chrousos, 2000; Yiallouris et al., 2019).

Postoperative endodontic pain is closely associated with inflammatory cytokines, including interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and the anti-inflammatory cytokine interleukin-10 (IL-10). Elevated oxidative stress further amplifies cytokine production, prolonging tissue inflammation and delaying healing (Halladin, 2015). Recent evidence also highlights the importance of the circadian clock gene BMAL1, which, together with melatonin, may regulate immune homeostasis, reduce periapical inflammation, and improve healing outcomes in apical periodontitis (Küçük et al., 2022). Furthermore, artificial intelligence has emerged as a promising tool for integrating circadian biomarkers with clinical variables to predict postoperative pain and personalize endodontic treatment planning (Singh, 2022).

Influence of Circadian Rhythm on Endodontic Treatment Outcomes

Circadian rhythm significantly influences the biological processes that determine healing and pain following endodontic treatment. Daily oscillations in hormonal secretion, immune regulation, and inflammatory mediator release can affect tissue responses after root canal therapy, contributing to differences in postoperative pain intensity and recovery among patients. Understanding these temporal variations may improve treatment planning and postoperative management.

The timing of endodontic procedures may influence treatment outcomes because pain sensitivity and inflammatory responses fluctuate throughout the day. Cortisol, a key stress hormone regulated by the hypothalamic–pituitary–adrenal axis, exhibits circadian variation and plays an essential role in modulating immune activity and inflammatory responses. Alterations in cortisol levels may influence the magnitude of postoperative inflammation and pain experienced after treatment (Chrousos, 2000; Yiallouris et al., 2019). Consequently, circadian biology has emerged as a potential consideration when scheduling clinical procedures.

Melatonin has attracted considerable interest because of its antioxidant, anti-inflammatory, and analgesic properties. Beyond regulating the sleep–wake cycle, melatonin suppresses oxidative stress, limits inflammatory cytokine production, and enhances tissue repair, thereby contributing to improved healing following endodontic intervention (Kurdi & Patel, 2013; Maitra et al., 2013). Experimental evidence further

Circadian factor	*Biological function*	*Influence on endodontic pain and inflammation*	*Reference*
Melatonin	Antioxidant and immunomodulator	Reduces pain, oxidative stress, and inflammatory cytokines	Kurdi & Patel (2013); Maitra et al. (2013); Yang et al. (2018)
Cortisol	Stress hormone	Regulates immune response and pain sensitivity	Chrousos (2000); Yiallouris et al. (2019)
BMAL1 Gene	Circadian clock regulation	Promotes immune balance and periapical healing	Küçük et al. (2022)
IL-1β, IL-6, TNF-α	Pro-inflammatory cytokines	Increase postoperative pain and tissue inflammation	Halladin (2015)
Artificial Intelligence	Predictive analytics	Supports personalized pain prediction and treatment optimization	Singh (2022)

suggests that melatonin interacts with the circadian clock gene BMAL1, promoting protection against apical inflammation and supporting periapical tissue regeneration, indicating a promising biological pathway for improving endodontic prognosis (Küçük et al., 2022). In addition, melatonin-mediated regulation of immune responses has been associated with reduced inflammatory damage and enhanced cellular homeostasis (Yang et al., 2018).

Postoperative cytokine expression is also influenced by oxidative stress generated during tissue injury and repair. Elevated oxidative stress may amplify inflammatory cascades and prolong pain, whereas improved antioxidant defenses can facilitate healing and reduce tissue damage (Halladin, 2015). Advances in digital dentistry further enable the integration of circadian biomarkers with clinical information through artificial intelligence, allowing prediction of postoperative pain risk and supporting personalized treatment scheduling and follow-up strategies (Singh, 2022). Collectively, these findings indicate that incorporating chronobiological principles into endodontic practice may optimize healing, minimize postoperative discomfort, and improve overall treatment outcomes.

Clinical Applications and Future Perspectives

Growing evidence suggests that incorporating circadian biology into endodontic practice may improve postoperative pain control and tissue healing. Scheduling root canal procedures according to periods of lower inflammatory responsiveness and greater endogenous analgesic activity could reduce postoperative discomfort and enhance patient recovery. Circadian regulation of cortisol, melatonin, and immune mediators influences pain perception and inflammatory cytokine production, highlighting the importance of biological timing in clinical decision-making (Chrousos, 2000; Kurdi & Patel, 2013).

Melatonin has attracted considerable interest as a potential adjunctive therapy because of its antioxidant, anti-inflammatory, and analgesic properties. Experimental findings indicate that melatonin suppresses oxidative stress, modulates cytokine release, and promotes tissue repair, making it a promising option for minimizing postoperative inflammation and improving periapical healing (Maitra et al., 2013; Yang et al., 2018). Furthermore, the BMAL1 circadian clock gene has been proposed as a protective regulator against apical periodontitis by maintaining immune homeostasis and reducing inflammatory tissue damage (Küçük et al., 2022).

Monitoring inflammatory biomarkers, including IL-1β, IL-6, TNF-α, and oxidative stress indicators, may facilitate individualized risk assessment and enable clinicians to identify patients susceptible to severe postoperative pain or delayed healing (Halladin, 2015). Variations in stress responsiveness associated with age and circadian disruption should also be considered when planning treatment and postoperative care (Yiallouris et al., 2019).

Artificial intelligence offers additional opportunities to integrate patient demographics, treatment variables, circadian characteristics, and biomarker profiles into predictive models for personalized pain management and treatment scheduling. Machine learning systems may support clinicians by forecasting postoperative pain intensity and optimizing therapeutic interventions, thereby advancing precision endodontics (Singh, 2022).

DISCUSSION

Circadian rhythm represents an important biological regulator of immune activity, inflammatory signaling, and pain perception, suggesting a potential relationship between biological timing and postoperative endodontic outcomes. Following root canal treatment, tissue injury and microbial-related inflammation trigger cytokine release, oxidative stress, and nociceptive responses that contribute to postoperative discomfort. Circadian variations in these processes may influence the severity and duration of pain experienced by patients. Stress-related hormonal fluctuations, particularly involving cortisol regulation, can modify immune responses and inflammatory balance, thereby affecting tissue recovery after endodontic procedures (Chrousos, 2000).

Melatonin appears to be a key mediator connecting circadian regulation with inflammation and healing. Its antioxidant, analgesic, and immunomodulatory properties may reduce inflammatory damage and support periapical tissue repair. The potential protective influence of melatonin and the circadian clock gene BMAL1 in controlling apical

Table 2: Clinical Applications and Future Perspectives of Circadian Rhythm in Endodontics

Clinical application	*Biological basis*	*Expected clinical benefit*	*Supporting references*
Chronotherapy-based treatment scheduling	Circadian regulation of pain and immune response	Reduced postoperative pain and improved patient comfort	Chrousos (2000); Kurdi & Patel (2013)
Melatonin adjunct therapy	Antioxidant, anti-inflammatory, and analgesic actions	Enhanced healing and reduced cytokine-mediated inflammation	Maitra et al. (2013); Yang et al. (2018)
BMAL1-targeted therapeutic strategies	Regulation of circadian clock and immune homeostasis	Improved periapical tissue repair and prognosis	Küçük et al. (2022)
Cytokine and oxidative stress biomarker monitoring	Assessment of inflammatory activity	Early identification of high-risk patients and personalized care	Halladin (2015); Yiallouris et al. (2019)
AI-assisted predictive models	Integration of circadian, clinical, and biomarker data	Precision treatment planning and individualized postoperative pain management	Singh (2022)

periodontitis highlights the importance of chronobiological mechanisms in endodontic healing outcomes (Küçük et al., 2022). Additionally, melatonin's role in perioperative medicine suggests that modulation of circadian pathways may improve postoperative recovery and reduce inflammatory complications (Kurdi & Patel, 2013; Maitra et al., 2013).

Inflammatory biomarkers and oxidative stress pathways also play significant roles in postoperative pain development. Elevated oxidative and inflammatory mediators may amplify tissue injury and delay healing, emphasizing the need to understand biological variations in inflammatory responses (Halladin, 2015). Age-related alterations in stress responsiveness may further influence circadian regulation and immune recovery, affecting individual differences in postoperative outcomes (Yiallouris et al., 2019).

Emerging artificial intelligence approaches provide new opportunities for integrating circadian biomarkers, clinical parameters, and patient-specific factors to predict postoperative pain and optimize endodontic treatment strategies (Singh, 2022).

CONCLUSION

Circadian rhythm has a significant influence on postoperative endodontic pain and inflammatory cytokine expression through regulation of hormonal activity, immune responses, oxidative stress, and tissue repair mechanisms. Melatonin and BMAL1-related pathways represent promising targets for improving periapical healing and pain management (Küçük et al., 2022). Future research integrating chronobiology, biomarker analysis, and artificial intelligence may facilitate personalized endodontic protocols, enabling more predictable healing and enhanced patient-centered care.

REFERENCES

1. Küçük, M., Aksoy, U., & Şehirli, A. Ö. (2022). Possible protective effects of the Bmal1 gene and melatonin on the prognosis of apical periodontitis. *Medical Hypotheses*, *162*, 110806.
2. Singh, S. (2022). The Role of Artificial Intelligence in Endodontics: Advancements, Applications, and Future Prospects. *Well Testing Journal*, *31*(1), 125-144.
3. Kurdi, M. S., & Patel, T. (2013). The role of melatonin in anaesthesia and critical care. *Indian journal of anaesthesia*, *57*(2), 137.
4. Chrousos, G. P. (2000). The stress response and immune function: clinical implications. *Ann NY Acad Sci*, *917*(8), 38-67.
5. Ravikumar, V. (2014). Fair and optimal resource allocation in wireless sensor networks.
6. Maitra, S., Baidya, D. K., & Khanna, P. (2013). Melatonin in perioperative medicine: Current perspective. *Saudi journal of anaesthesia*, *7*(3), 315.
7. Halladin, N. L. (2015). Oxidative and inflammatory biomarkers of ischemia and reperfusion injuries. *Dan Med J*, *62*(4), B5054.
8. Yiallouris, A., Tsioutis, C., Agapidaki, E., Zafeiri, M., Agouridis, A. P., Ntourakis, D., & Johnson, E. O. (2019). Adrenal aging and its implications on stress responsiveness in humans. *Frontiers in endocrinology*, *10*, 54.
9. Yang, H. L., Zhou, W. J., Gu, C. J., Meng, Y. H., Shao, J., Li, D. J., & Li, M. Q. (2018). Pleiotropic roles of melatonin in endometriosis, recurrent spontaneous abortion, and polycystic ovary syndrome. *American Journal of Reproductive Immunology*, *80*(1), e12839.