Review Article

JOMP
Journal of Oral Medicine and Pain

pISSN 2288-9272 eISSN 2383-8493
J Oral Med Pain 2015;40(3):89-95
http://dx.doi.org/10.14476/jomp.2015.40.3.89

The Circadian Rhythm Variation of Pain in the Orofacial Region

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Received August 23, 2015
Accepted September 2, 2015

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All living organisms have a biological clock that orchestrates every biological process and function, and this internal clock operates following a circadian rhythm. This biological clock is known to influence various clinical indicators such as blood pressure and body temperature. Also, the fluctuation of signs and symptoms of diseases including pain disorders are affected by circadian rhythm. It has been reported that the pain intensity of various somatic and neuropathic pain disorders show unique pain patterns that depend on the passage of time. The generation of pain patterns could be explained by extrinsic (e.g., physical activity, tactile stimulation, ambient temperature) and also intrinsic factors (neural and neuroendocrine modulation) that are related to the circadian rhythm. It is important to recognize and identify the individual pain pattern in pain therapy to approve treatment outcome. Moreover, chronotherapeutics which considers pain patterns and pharmacokinetics in context of the circadian rhythm could produce greater analgesia in response to medication. However, only a limited number of studies handle the issue of pain patterns according to circadian rhythm and chronotherapeutics in the orofacial region. The present review intends to reflect on the most recent and relevant data concerning the bidirectional relation between pain disorders of the orofacial region and circadian patterns.

Key Words: Chronotherapy; Circadian rhythm; Neuropathic pain; Orofacial pain; Somatic pain

INTRODUCTION

The attempt to observe and measure the internal rhythm of life forms has been made for a long time. The nocturnal occurrence of asthma has been described in a medical textbook of the 5th century and Sanctorius made a self-record of the 24-hour change of his body weight related to the release of sweat in the early 17th century.[1)] Nowadays, the development of technology has enabled continuous monitoring of biological parameters and large-scale data processing. Such approaches has let us know that all living organisms have a biological clock that orchestrates every biological process and function at every level—gene to organ—and eventually forms something analogous to a biological rhythm.

The scope of biological rhythms is broad ranging from a few seconds to years. Among them, the most studied cycle is the circadian rhythm (20 to 28 hours cycle). It is generated and controlled by its own master clock network comprised by the paired suprachiasmatic nuclei in the hypothalamus and the pineal gland.[2,3)] The clock genes—per^1, per^2, per^3, bml, clock and CRY—and their gene products along with the cyclic secretion of melatonin from the pineal gland constitute a biological time control apparatus. This master clock network regulates the biological rhythm of peripheral subsystems ranging from cells to organs.[4)]

Meanwhile circadian rhythm is adjusted by specific external time cues (called zeitgeber in German and time giver in English). One of the strongest cues is known to be the light-dark cycle in addition to the temperature and redox cycle. When the time of exposure to light is altered by seasonal variation and/or sleep pattern changes, circadian rhythm is also titrated according to such alterations in external signals. This helps the body to be well in tune with external environmental changes. Radical changes in the patterns of external cues such as rotating-shift work, night-overtime or jet lag destroy the normal circadian rhythm and may lead to various disease states.

The circadian rhythm change of various clinical indicators can be observed through clinical studies. Blood pressure rapidly ascends in the morning peaking during the daytime and descends in the evening reaching its lowest at night.[5] In standard fasting conditions, responses to glucose tolerance testing are significantly greater in the morning than in the evening.[6,7] In addition, hormone levels and lab test results are also known to differ according to the circadian rhythm.[4] Therefore, it is important to maintain a constant test schedule and subject life style for reliable result when conducting studies in medicine and biology. Also fluctuation of the signs and symptoms of various diseases and occurrence of events leading to death show differences in a 24-hour period.[8,9]

The reduction in pain level is a priority target in the management of chronic pain. Although numerous therapeutic methods are being applied to control pain, limitations are still evident and especially so in the case of chronic pain. A variety of clinical and experimental studies showed that subjective and measured pain intensity is not constant during the day.[10] Based on such facts, some authors suggest that the cause of unsuccessful pain control is failure to notice pre-existing pain patterns and the absence of treatment strategies considering the circadian rhythm.

The purpose of this review is to examine the pain pattern of chronic pain in the orofacial region by contemplating on previous articles. The understanding of pain patterns and its generation mechanism will provide rationale for the establishment of clinical treatment strategies that will lead to better prognosis of the orofacial pain patient and future researches in this untouched field.

CIRCADIAN RHYTHM AND PAIN PERCEPTION

1. Somatic Pain

Somatic pain is a type of pain generated by the reaction of normal neural receptors to noxious stimulation. Animal models used to evaluate somatic pain measure the response to various painful stimuli—heat, cold, pressure, etc. Frederickson et al.[11] examined the circadian rhythm of pain response through the mouse hot plate test. The pain threshold was observed to show a distinct diurnal rhythm being higher in the late afternoon. Animal models used to study pain in the muscles and joints—areas where chronic pain is frequently present—usually induce inflammation to cause pain in the target muscle and joint by injecting chemical irritants or forcing excessive exercise.[12,13] But, experimental studies of the circadian rhythm of joint and muscle pain using animal models do not exist yet.

Toothache which is the most common type of pain that the dentist encounters does not occur in a random fashion during a 24-hour period. Pöllmann[14] examined the duration of local anesthesia on tooth pain after dental surgery. As a result, the longest duration was found to be in the afternoon (around 15:00) while the shortest was in the early morning and at night. Also the pain threshold of teeth to electrical stimulation was lowest during the later part of the night.[10] These observations are consistent with clinical finding that show toothache mainly occurs in the early morning and also in line with results of studies concerning other body parts.

Pains of musculoskeletal origin constitute the most common form of chronic pain. This type of pain also shows time-dependent rhythms in pain intensity. It is reported that rheumatoid arthritis patients experience more severe pain in the morning.[15,16] Conversely, osteoarthritis patients generally feel the greatest level of pain in the evening time.[17,18] However, such pain patterns are not applicable to all joints as patients with hand osteoarthritis reported least pain in the afternoon which is a pattern more similar to that of rheumatoid arthritis patients.[19] Few studies reported on the pain pattern of patients with temporomandibular disorders (TMD). In their study, van Grootel et al.[20] instructed 133 patients with myogenous TMD to record their pain intensity 4 times a day during a 2-week period. The majority of patients (79%) experienced a peak in their level of pain in the evening while only a minority of patients (21%) had maximal pain in the morning. Data showing a similar pattern was published by Glaros et al.[21] on patients with various types of TMD. However, variability within different TMD groups was significant and the pattern was not strongly linear. This discrepancy in findings of the 2 studies concerning the circadian pain pattern of TMD patients seems to be related to the variation in study subjects affected with TMD of various etiologies and suggests the possibility that the pain pattern may differ according to distinct subgroups of TMD.

2. Neuropathic Pain

Neuropathic pain is a type of pain that originates from within the nervous system itself, and has been defined by the International Association for the Study of Pain as "pain caused by a lesion or disease of the somatosensory system" in 2011.[22] Most animal models of neuropathic pain are performed by causing damage to a peripheral nerve—usually the tibial or common peroneal branch—or by continuously constricting the sciatic nerve by applying loose sutures.[23]

Takada et al.[24] investigated the pattern of neuropathic pain in mice after sciatic nerve ligation. Pain was evaluated by the measurement of hind paw withdrawal latency time after applying heat stimulus 4 times at a 6-hour interval. Overall the experimental group showed a significantly lower thermal pain threshold than the control group at all time points. In the control group, the hind paw withdrawal latencies at 14:00 and 20:00 were significantly higher than those at 8:00 and 2:00. In contrast the latencies at 2:00 and 8:00 were significantly higher than those at 14:00 and 20:00 in the experimental group. Such results suggest that the change in pain thresholds show a circadian rhythm and presence of neuropathic pain could alter such pain patterns. Based on these findings we may conclude that the intensity of neuropathic pain is minimal in the morning, increases during daytime, and decreases at night.

Early clinical studies regarding neuropathic pain suggest that pain can worsen during the night resulting in significantly impaired sleep.[25,26] Odrcich et al.[27] investigated the diurnal pain pattern in patient with diabetic neuropathy (DN) and post-herpetic neuralgia (PHN). The patients were divided into four groups according to their prescription drugs (placebo, gabapentin, morphine, gabapentin and a morphine combination) and all patients recorded their pain intensity using a numeric rating scale 3 times a day. The pain intensity of all patients steadily increased throughout the daytime. Interestingly the circadian rhythm in the pain pattern was maintained even after the overall pain intensity was decreased during treatment with medication. Such consistency in the circadian rhythm of pain despite medication was also reported by Gilron et al.[28]

The pain pattern in burning mouth syndrome (BMS) has been handled in a few studies. The pathophysiology of BMS is yet to be fully elucidated; however, the possibility of a major neuropathic component has been strongly suggested. Forssell et al.[29] instructed patients with BMS to complete a 2-week pain diary and record pain intensity three times a day (morning, 8:00-12:00; afternoon, 12:00-18:00; evening, 18:00-bedtime). The results show that pain intensity was lower in the morning compared to that in the afternoon and evening. Lopez-Jornet et al.[30] conducted a similar study using pain diaries in patient with BMS and found a significant discrepancy in pain intensities recorded at different periods. Pain was reported to generally increase as the day progressed into the evening. Braud et al.[31] used a neuropathic pain questionnaire to evaluate 17 BMS patients. All patients completed the questionnaire and recorded their pain intensity using a visual analog scale every hour. Eleven BMS patients who complained of continuous pain reported that their pain increased throughout the daytime. Collectively these findings suggest that the pain intensity of BMS patients generally show a progressive increase during the daytime. Such facts should be considered when managing BMS pain. Unfortunately there was no study dealing with the nocturnal pain pattern of BMS patients.

POSSIBLE MECHANISMS OF CIRCADIAN VARIATIONS IN PAIN

1. Extrinsic Factors

Extrinsic factors—the summation of tactile sensation and physical activity—are possible explanations to the circadian rhythm in pain patterns. For example, DN most commonly occurs in both lower extremities. Thus, physical activities including walking could exacerbate the pain in patients with DN. Gilron et al.[28] suggest that the pain rhythmicity during daytime is more distinctive in DN than in PHN, and this could be explained by the temporal summation of painful stimuli occurring during the day. Parafunctional oral habits are commonly identified in patients with BMS[32,33] and such irritation might result in subclinical inflammation and neuropathic changes of the oral mucosa that ultimately lead to the burning sensation.[34,35] It has already been reported that the regulation of oral parafunctional habits or the usage of topical lubricants may reduce the burning sensation.[36] Based on such results it appears that the pattern of increasing pain throughout the day in BMS patients may be generated by summation of mechanical irritation caused by parafunctional movement. In the case of TMD, clenching and grinding habits and excessive use of the jaw could influence pain patterns.

However, one study reported that there was no relationship between the pain pattern and the presence of allodynia which would have been a major cause of additional pain stimulus in patients with DN and PHN.[28] It has also been reported that the diurnal pain rhythmicity in patients with TMD were not influenced by the presence of bruxism.[22] More research is required to further explain the contribution of extrinsic factors to the generation of pain rhythmicity.

2. Intrinsic Factors

Intrinsic factors include the following networks, substances, and genes: (1) endogenous opioid system influencing pain perception, (2) melatonin and clock genes that make up the master clock network, and (3) numerous substances exhibiting circadian rhythm in their expression and action (e.g., immune and inflammatory mediators).

Endogenous opioids play a significant part in pain modulation. Takada et al.[24] investigated the mRNA expression level of various opioid receptors in the frontal cortex, periaqueductal gray (PAG), thalamus and spinal cord—anatomical regions known to be responsible for pain perception and modulation—in mice after sciatic nerve ligation. Unlike other regions time-variation of mu-opioid receptor mRNA expression was observed in the PAG area which plays a critical role in descending pain control. In the control group, mRNA expression was significantly greater at 14:00 and 20:00 compared to at 8:00, and in the experimental group the mRNA expression level was significantly greater at 2:00 than that at 14:00 and 20:00. A correlative tendency between pain thresholds and mu-opioid receptor mRNA expression was observed in both groups.[24]

Some articles reported on the circadian rhythm change of the endogenous opioid system in humans. The results suggest that the plasma level of beta-endorphine is highest at 8:00 and lowest at 20:00,[37] and enkephaline-like and beta-endorphine like immunoreactivity of human parotid saliva were highest in the morning.[38] Based on these findings we could speculate that such variation in the level of endogenous opioids may influence the pain pattern.

Various studies have shown the relationship between melatonin and pain disorders. Firstly pain could affect melatonin activities. Early clinical studies reported that patients with chronic pain disorders had a lower urine and plasma melatonin concentration than controls.[39] Also Odo et al.[40] reported that sciatic nerve injury led to changes in the expression pattern of melatonin receptor mRNA level in the hypothalamus of mice. On the other hand studies exist which show the pain relieving effects of melatonin. In various experimental studies, regardless of the manner of stimuli and melatonin administration, melatonin shows analgesic effects.[41] Meanwhile the therapeutic use of melatonin has shown to be effective in the pain relief of fibromyalgia,[42,43] irritable bowel syndrome,[44,45] and migraine.[46,47]

Various studies have attempted to reveal the mechanism underlying melatonin's antinociceptive actions. Zurowski et al.[48] has studied the analgesic effects of melatonin through an animal neuropathic pain model (chronic constriction injury model). Rats with nerve injury first showed mechanical allodynia and thermal hyperalgesia and the administration of melatonin resulted in a partial increase of the pain threshold to mechanical stimulus. Various medications—naloxone (opioid antagonist), prazosin (melatonin-3 receptor antagonist), luzindole (melatonin 1, 2 receptor antagonist), picrotoxin (GABA antagonist), and flumazenil (benzodiazepine antagonist)—have been administered in combination with melatonin. As a result naloxone completely attenuated the antinociceptive action of melatonin, and luzindole, flumazenil and picrotoxin also significantly reduced the antinociceptive action of melatonin. Such findings suggest that melatonin may act to increase the pain threshold to mechanical stimulus and this analgesic effect may be mediated via activation of the opioid system and benzodiazepine—GABAergic pathways. Beta-endorphine[49] and the nitric oxide-arginine pathway[50] have been proposed as candidate molecules involved in such mechanisms but their specific mode of operatoin is yet to be clearly identified.

Finally, various kinds of cytokines and chemokines which are known to directly and indirectly influence nociception could alter pain levels[51,52] but the evidence to support their specific role in circadian pain pattern generation is still insufficient.

CONSIDERATION OF CIRCADIAN RHYTHM IN THE MANAGEMENT OF CHRONIC OROFACIAL PAIN

1. Pain Diary

Various kinds of chronic pain disorders show unique circadian pain rhythms. But inter-individual variations do exist. In the study of Forssell et al.,[29] the overall pain intensity of BMS patient's showed a tendency to increase during the day. However, 8 patients reported that their pain peaked in the morning. Eight patients experienced most severe pain in the afternoon while seven patients reported a constant level of pain all day long. Also, Levi et al.[17] reported that half of the patients with osteoarthritis complained of two peaks in their level of pain during the day compared to the general tendency of such patients to have a higher pain level in the evening. As mentioned above the pain pattern of TMD patients could be divided into 2 types, namely the morning and evening peak type.[20,21]

A pain diary is a record of pain level, disability level, medication intake, and other pain related facts that are written by the patient. Since considerable variations in pain rhythmicity among patients with chronic pain were identified it is crucial for the patient to keep a pain diary. Such records will help both the patient and doctor to identify the unique pain rhythmicity of a specific patient and this will eventually lead to tailored treatment planning and better treatment outcomes. The observation of a specific pain pattern in a BMS patient by using a pain diary might enable the application of an individualized treatment strategy concerning medication protocols and control of contributing factors. For example, BMS patients who complain of worse pain as the day progresses could benefit by avoiding aggravating factors that add up during the daytime.[31] Also pain diaries could help to classify patients according to pain patterns. In this context, Grushka[53] has already proposed three subgroups of BMS characterized by pain patterns. Such approaches may enhance the understanding of chronic pain disorders including BMS and eventually improve treatment prognosis.

2. Chronotherapeutics

Generally the principle of pain medication application is to take a stepwise approach in the order of weak non-opioid analgesics to strong opioids. Also, medication should be prescribed following a schedule rather than by patient's demands. Given the circadian changes of the internal milieu, it is not surprising that analgesic effect could be affected by the circadian rhythm. Chronotherapeutics is the concept that reflects the circadian change in efficacy of analgesia and the purposeful delivery of analgesics to maximize pain relief and minimize undesirable effects.[4] Chronotherapeutics should be considered in (1) disease pathophysiology, (2) human circadian time structure, and (3) chronopharmacology—chronokinetics and chronodynamics.

Animal and human researches addressing chronopharmacology reveal that the pharmacokinetics of nonsteroidal anti-inflammatory drugs (NSAIDs) show a circadian rhythm. Bioavailability of NSAIDs is highest in the morning, and plasma levels of ketoprofen and indomethacin after 7:00. administration are 50% to 58% higher than after evening administration.[54,55] Another study also reported that the pharmacokinetic changes range between 20% to 70%.[56] Frequency in side effects differed according to administration time. The occurrence rate of gastric mucosal lesions or gastrointestinal disturbance produced by taking aspirin or ketoprofen in the morning was two-fold greater than that by taking the same medication in the evening.[57,58]

Time of administration could affect analgesic effect. Levi et al.[17] investigated the relationship between efficacy of analgesics and administration time in patients with osteoarthritis. The effectiveness of the drug did not differ according to time. However, significant differences were found when the pattern of pain was considered. Taking the medicine in the evening was most effective in patients who complained of the severest pain in the night, while morning or noon administration was most effective in patients who complained of the severest pain in the afternoon or evening.

Von Korff et al.[59] studied whether there were differences in dosage and side effects of opioid depending on method of administration—time-scheduled versus pain level dependent. Surprisingly, patients receiving pain-contingent dosing decreased the dosage and showed lower side effect rate.

CONCLUSION

In summary, various types of chronic pain disorders have demonstrated circadian variations in pain intensity, and the efficacy of analgesics are also influenced by drug dosing time. Thus, it is important to understand the circadian rhythm in changes of pain intensity when treating chronic pain of the orofacial region. In clinical setting, the clinician must identify individual pain patterns, and be able to establish an appropriate treatment plan. However, few studies have been conducted on the pattern of pain in the orofacial region, and there is limited evidence for the mechanism of pain patterns. Also, there is no research dealing with treatment strategies for orofacial pain considering chronotherapeutics. Further research is needed on pain patterns and related treatment planing of orofacial pain disorders.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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