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Research Article

Circadian Variation of Pain as a Measure of the Analgesia Requirements during the First 24-Postoperative Hours in Patients using an Opioid Patient Controlled Analgesia Delivery System

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Abstract

Circadian rhythms have governed the everyday life of every single organism that has lived on Earth. The present study addresses the rhythms of cortisol and melatonin, their analgesic properties and the potential circadian rhythm of pain as a driver of the frequency of self-administered analgesia in postoperative patients with an opioid Patient Controlled Analgesia (PCA) delivery system. It aims to determine if acute 24-hour post-operative pain displays a circadian variation by analysing the number of times that patients self-administered morphine for pain relief and incidentally to determine if gender has any association with the frequency of self-administered analgesia. For that purpose, the frequencies of self-administered analgesia were divided into four periods of six hours each (three of them approximately corresponded to the day and 1 to the night). A Multi-level Poisson regression analysis compared frequencies during period 4 (night) to all others (1, 2 and 3). The results show that there was a statistically significant difference between the frequencies of self-administered opioids in the night period compared to any other day period (p-value of <0.001, for periods 1, 2 and 3 respectively compared to period 4). Differences in terms of gender were also statistically significant (p<0.001) with men's opioid consumption almost double that of women'sbutwithmuchsteeper rate of decline (p<0.001). These results may be partly explained by the rhythms of melatonin, cortisol and ß-Endorphin, morphine's chromo pharmacology and possibly by oestrogen and progesterone.

Keywords: Circadian Rhythms; Opioids; Patient-Controlled Analgesia; Postoperative Pain;

Introduction

Circadian Rhythm: Overview

A circadian rhythm refers to a period of approximately 24 hours. The biological master clock, which governs the pace, is located in the Supra Chiasmtic Nuclei (SCN) in the anterior hypothalamus [1] and it is driven by light. Light stimulates/suppresses the expression of certain CLOCK genes who will then control basic behaviors such as wakefulness, sleep and temperature [2].

Circadian Rhythm in Pain Perception

The idea that pain perception might display a circadian rhythm pattern is not new. Some studies date back to 1975 when [3] evaluated the potential relationship between the intensity of pain and a specific hour of the day. Their study included patients with cancer pain, herpetic neuralgia, phantom limb pain, atypical facial pain and Complex Regional Pain Syndrome (CRPS). The entire sample displayed a circadian pattern with the maximum pain sensitivity registered at 22:00. In another study, [4] analysed 14 patients suffering from Rheumatoid Arthritis (RA) and found pain to display a circadian variation with the highest registered intensity during the morning around 7:00 - 8:00. These studies

show that the pain threshold and its intensity might depend on the pathophysiology of the different kinds of pain. In all cases however, the pain experienced did display a 24-hour rhythm [5,4,6,3,7]. Cancer pain sufferers appear to experience more Breakthrough Pain (BTP) during the late morning around 9:45 - 10:15 [8,9]. Consistent with these results, [10], evaluated the use of an opioid-PCA for the treatment of BTP in adults with cancer pain. They found that opioid analgesia was least demanded from 22:00 to 6:00 compared to any other time of the day with a significant 34% less self-administered opioid within these hours.

Inflammatory, autoimmune pain displayed the highest intensity during the early morning at 7:00 [4]. Visceral pain (colic pain) peaks around midnight [11] whereas neuropathic pain increases during the day to reach a peak at 22:00 [7]. Migraine pathophysiology is believed to have a vasogenic origin associated with platelet aggregation and ischaemia which are mechanisms that are also involved in angina pectoris. Interestingly, [12,13,14] arrived to the same conclusion regarding the daytime incidence of these two pain related disorders. Finally, post-operative pain was also worse during the early morning [6].

The present study aims to determine if acute post-operative pain, indicated by the patients' opioid requirements (by an opioid PCA delivery system), displays a circadian rhythm city during the first 24 post-operative hours. We hypothesised that the pain would display a consistent pattern of variation that is related to the circadian rhythm. We also aimed to identify whether there was an influence of gender in the frequencies of self administered opioids for postoperative pain relief.

Materials and Methods

The study was an observational prospective study conducted at the University College Hospital London (UCLH). All post-operative patients older than 18 years on an opioid PCA delivery system, including opioid naive patients were included in the study. Patients receiving an epidural or any form of regional analgesia, those with a cancer, hematological, psychiatric diagnosis, chronic pain syndrome and opioid dependent or chronic opioid use were excluded. Also excluded were all incomplete cycles (patients with less than a 24-hour cycle of PCA therapy). A continuous period of 24 hours following surgery was recorded for each patient. The patient must have recovered consciousness and the pain be controlled before he or she is discharged from the Recovery Ward (RW) The PCA delivery system is installed and ready to be used once the patient leaves the RW. The following data were collected: age, gender, surgical procedure, concomitant administered drugs at the time of the measurement, the type of opioid, the dose, and the time of day and time since surgery at which it was self-administered, the presence or absence of clinician boluses and the PCA status - either PCA-only or PCA + Continuous Infusion. The data collection was performed in London, UK during the months of June and July. The day was defined as the period between 5:00 and 22:59 and night that between 23:00 and 4:59. This timing reflects London's latitude of 51° 32' north where the sun rises at 5:00 and complete darkness occurs at 23:00.

The PCA pumps used at UCH were made by Smiths Medical ASD, Inc. (St. Paul, MN 55112 USA) and are regularly tested for electrical safety. The data were collected every day from each patient's PCA pump at 8:00.All pumps have a standardised protocol of usage, which includes a lockout period of 5 minutes following the administration of an intravenous dose of 1 mg of morphine delivered by the patient. All patients were informed about the study and provided oral consent before their data was captured from the PCA pump.

Statistical Analyses

The mean number of presses each hour was calculated and formed the basis of the primary outcome measure. To determine if there was a particular period of the day on which the demand for analgesia was more prevalent, the 24-hour day was divided into 4 periods as follows: Period 1 from 5:00 to 10:59, period 2 from 11:00 to 16:59, period 3 from 17:00 to 22:59 and period 4 (night) from 23:00 to 4:59. A generalised linear mixed model with Poisson link regressed frequency of demanded analgesia on period of the day, gender and time since surgery was performed. Potentially confounding variables included the type of operation (degree of invasiveness) and the time at which surgery was performed (morning, afternoon, evening and night).

Results

In total, data for 16 patients (8 men and 8 women) were included; 18.75% were between 18 and 30 years old, 37.5% between 40 and 65 and 43.75% were older than 65. All patients used a morphine PCA delivery system, 31.25% (5 patients) had a continuous infusion, 2 of them at a rate of 0.5mg/h and three of them at 1mg/h; 62% were also having oral paracetamol for pain relief and 31.25% were receiving ibuprofen. Other oral medications that were administered during the 24-hour cycle included antibiotics, antihypertensive, anticoagulation and fat lowering therapy. Only 1 patient was on prednisolone. The mean number of presses for all 16 patients is displayed as a bar chart for all 24 hours recorded for each patient (Figure 1). Relatively low frequencies are seen during the night (Figure 2).

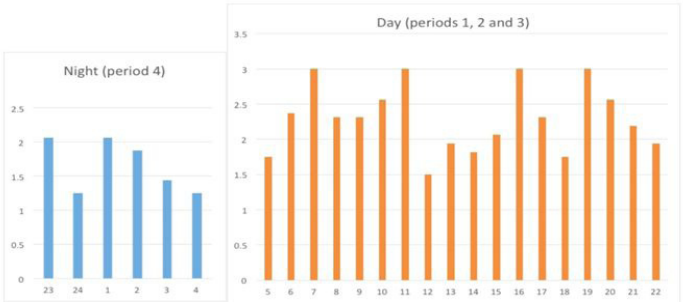

Figure 1: Mean frequency for every hour (pressed button/hour). In yellow is depicted the day-hours and in blue the night-hours.

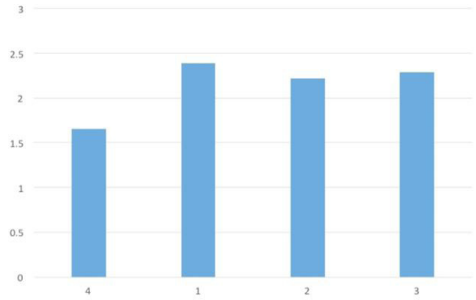

Figure 2: Mean rate of administrations of pain relief for each period: Period 1: 05:00 - 10:59, period 2: 11:00 - 16:59, period 3:17:00 - 22:59 and period 4 (night): 03:00 - 4:49.

Source	F	df1	df2	p-value
Corrected Model	11.511	9	374	0.001
Period	10.3	3	374	0.001
Gender	16.455	1	374	0.001
Period*gender	3.073	3	374	0.028
Post_op_hrs	35.278	1	374	0.001
Gender*post_op_hrs	16.584	1	374	0.001

Table 1: Significance tests of fixed effects terms in the statistical model for 'times pressed button' (using Poisson distribution and log link function).

In addition to period, time since operation (hr), gender and interactions were included in the model. All main effect terms and interaction period*post-op-hours were statistically significant with p<0.001, interactions of period*gender with p=0.028. Table 1.Contrasts of differences between mean presses at period 4 (night time) and periods 1, 2 and 3 show higher daytime values and are statistically significant with p-values <0.001.Results for secondary factors were of a strong effect of time since operation, gender and their interaction. These effects are illustrated in Figure3.

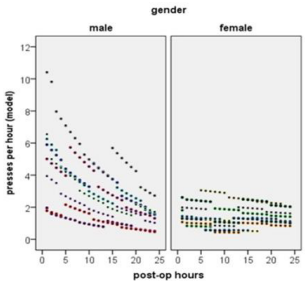

Figure 3: Trajectories of pressing rate by post-op hours for 8 males and 8 females (from fitted statistical model).

The results indicated in Figure 1 and Figure 2, suggest that the alternative hypothesis is true and that there is a circadian rhythm in pain with more incidence during the day compared to time during the night. The trajectory plot, Figure 3, shows the mean frequencies for the demanded analgesia as a function of the postoperative period. It is clear (and was expected) that as time passed, pain reduced. This result suggested a possible confounding effect from the time of the operation. However, including the hour of the day at which the surgery was performed in the statistical model found no noticeable effect. With regard to differences between the frequencies of self-administered doses in terms of gender, there was a statistically significant difference (p-value of <0.001) Figure 3 with men taking almost double the self-administered opioid analgesia compared to women.

Discussion

Acute pain as a measure of patient's opioid requirements does display a circadian rhythmicity during the first 24-postoperative hours. It is less prevalent during the night compared to the day. In terms of gender, women self-administered less opioid for pain relief compared to men under the same post-surgical background. The circadian behavior of pain and analgesia observed herein could be partly explained by the circadian rhythms of analgesic hormones such as cortisol, melatonin and ß-Endorphine.

Cortisol, Melatonin and ßEND and Their Circadian Rhythms on Pain and Analgesia.

Human studies have proven the existence of a diurnal cortisol rhythm by measuring cortisol present in saliva of healthy volunteers [15-18], studied the circadian variation in serum cortisol in 33 healthy participants demonstrating that the cortisol levels peaked at 08:32 and were lowest at 00:18.If cortisol is influenced by light; is it alsoinfluenced by melatonin? Could melatonin drive the circadian rhythm of cortisol? Can these variables explain the circadian rhythmicity in postoperative pain in this study?

Melatonin, Cortisol and ßEND

Melatonin appears to drive the secretion an important endogenous analgesic: ßEND. performed a study in rats in which they evaluated the role of melatonin as a regulator of the secretion of ßEND in rats and whether its secretion was related to analgesia by changes in pain behaviors. The suppression of melatonin secretion was correlated with an increase in the production of endogenous ßEND. The high concentrations of ßEND were then correlated to an increase in the time latencies on a hot plate providing proof of an analgesic effect for these rats. The authors concluded that 'there is an inverse phase relationship between melatonin and ßEND resulting from a feedback mechanism between the opioid and the pineal system'. It is important to highlight the fact that ßEND and ACTH come from the same macro molecule: the POMC (Proopiomelanocortin), and that the increase in ßEND via POMC would also raise ACTH. ACTH would then promote the secretion of cortisol via adrenals and would also provide analgesic effects.

Some authors claim that melatonin has an analgesic effect of itself [19,20]. This property would explain the decreased demand for analgesia during the night. If patients suffer less from pain at night and if ßEND levels are known to be low at that point, then the explanation of the decrease in pain intensity (and hence of the analgesic requirements) could be attributed to the analgesic properties of increased melatonin serum concentrations at night.

Surgery and it's Influence on Cortisol's and Melatonin's Circadian Rhythms

Cortisol is the most important stress hormone and its secretion increases rapidly once surgery has started. Most importantly, during the immediate postoperative period both hormones (ACTH and cortisol) remain constantly high [21,22,23] found that during PO day 1, cortisol and ACTH levels were both high, while during PO day 2, cortisol levels were still high but in a context of low ACTH. Cortisol was also found by [24-29] to be increased after surgery.

[25] Gogenuret al. (2007) evaluated alterations in melatonin secretion after major surgery. They measured melatonin in PO patients and found two statistically significant differences in melatonin: Its rhythm was preserved but was shifted to a later time of the night and its concentration augmented froma mean preoperative value of 51 pg/ml to 68 pg/ml on PO day 2. The shift in time was present from PO day 1 persisting onto PO day 2 manifested as a delay in melatonin's peak onset from 22:46 to 23:54.

It is therefore reasonable to conclude that the stress of surgery keeps cortisol levels high during at least the first 2 PO days in the body's attempt to deal with the physical stress but also in a way to provide the appropriate setting for repair, recovery and analgesia. Melatonin levels after surgery are also affected; this alteration is initially manifested as a delay on the onset of its rhythm and afterwards as an increase in its concentration. Surgical procedures appear to blunt the circadian pattern of activity of cortisol and melatonin with a marked increase in their concentrations compared totheir basal state. See Figure 4 for summary.

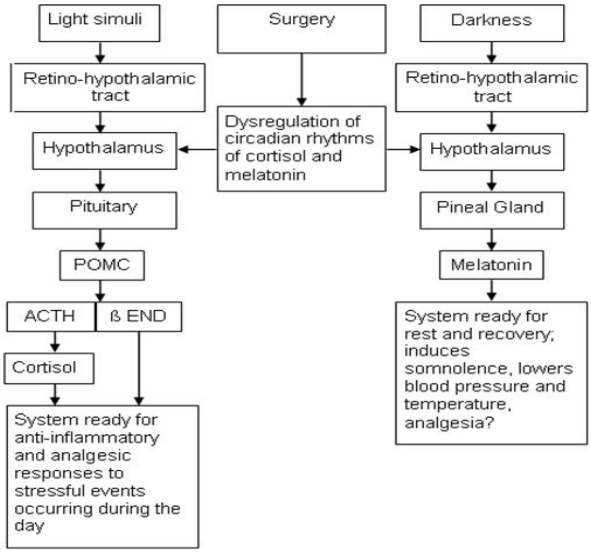

Figure 4 : Summary of how light, darkness and surgery affect the circadianrhythm of cortisol and melatonin.

Morphines Chromo Physiology and Pharmacology

Chromo pharmacology refers to the study of a drug's pharmaco dynamics and pharmacokinetics as a function of time. Apart from the circadian variation in the secretion of endogenous Opioids and other hormones that in fluence those, the daytime variability in the expression of Opioids receptors, as well as their bioavailability, can partly account for the rhythmicity of post-operative pain intensities. If morphine is better absorbed and better distributed during the night and if this circumstance coincides with the time at which Mu opioid receptors are at their highest expression, then the analgesia would be much more efficient during the night compared to the day.

[30] Takada et al. (2013) evaluated the circadian variations in pain sensitivity in mice subjected to a pain model (lesioned mice) compared to control (healthy) mice whilst measuring the potential variations in the expressions of Mu-receptor mRNA in different brain regions (including the Periaqueductal Grey mater (PAG). They observed that the pain behavior was at its highest between 14:00 and 20:00 in the lesioned-mice (tested by the hot plate); the same period of time on which the lowest expression of Mu-receptor mRNA in the (PAG) was documented in these mice. In contrast, control-mice showed a greater latent period in the hot plate between 14:00 and 20:00 which also corresponded to the highest levels of mRNA Mu opioid receptor in the PAG in these healthy mice. Their results show two important facts: Firstly,

that pain behaviors can be explained in terms of the availability of Mu opioid receptors in pain regulating areas. Secondly, there is a rhythm in opioid receptor expression and this rhythm is subject to changes as a consequence of a stress full event: an invasive lesion or surgery.

Differences in Pain Perception as a Function of Gender

The idea that pain tolerance and pain thresholds are different between men and women is not new and recent studies not only support that idea but also have obtained the same results as the present study. [31] Chia et al (2002) evaluated the morphine requirements in postoperative patients who were on PCA analgesia. They found out that the most important factors influencing the self-administration of morphine was gender (and pain upon movement). With a total of 2298 patients analysed, women consumed significantly less morphine during the first 3 postoperative days compared to men (23% to 43% more morphine consumption in men). [32,33] McQuay et al. (1980) also arrived to the same results whilst comparing the demanded analgesia in the postoperative period between men and women on an opioid PCA.

[34,35] Miaskowski and Levine (1999) performed a systematic review to establish if there were any differences in gender relative to postoperative pain and the use of an opioid PCA. Of the 18 studies analysed, 56% showed more opioid consumption by men in the immediate postoperative period. However, the author also remarks that many of these studies did not measure pain intensity (i.e. with a validated pain scale: VAS) and relied on analgesic consumption to account for these differences. Pain and analgesia are two different things but they risk being mixed together. To highlight this difference is crucial and can be exemplified as follows: If women consume fewer Opioids than men while they are in pain, it can be said that Opioids are more efficient for pain relief in women as compared to men but it can also be explained by arguing that women suffer less from pain than men.

Conclusions

The literature as well as the present study points toward a circadian rhythm in pain that might depend on many complex variables that pose a challenge to their quantification such as the drug's variation of its bioavailability, the expression of opioid receptors and their location and the variability in the expression of such receptors as a consequence of invasive procedures. While the circadianrythmas of melatonin and cortisol get disrupted by surgery, their high level scan not explain the diminished frequency in self-administered analgesiat night [36].

The fact that women self-administered less morphine than men suggests either that Opioids work better in this group or that women suffer from less pain than men. Either way, the pain is there and if pain is to be prevented rather than treated, then the way to provide analgesia will need a system capable of delivering the exact amount of dose at its most efficient time while considering the time at which the pain is most probable to occur.

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