Circadian variation of IV PCA use in patients after orthognathic surgery – a retrospective comparative study

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Background: An understanding of the features of postoperative pain is essential for optimal analgesic dosing strategies. Using a visual analogue scale (VAS) score and patient controlled analgesia (PCA) infusion pattern analysis, an anesthesiologist can estimate when and how severely patients suffer from pain. Several reports have been published about circadian changes in the pain threshold. Postoperative pain was analyzed retrospectively in 250 patients who underwent orthognathic surgery.
Methods: A total of 250 patients were allocated into two groups according to the time of recovery from anesthesia. Patients in the early group (group E) recovered from anesthesia before 06:00 p.m. Patients in the late group (group L) recovered from anesthesia after 06:00 p.m. All patients received intravenous patient controlled analgesia (IV PCA) at the end of the operation. The VAS score of pain intensity was measured. Self-administration of bolus analgesic from the IV PCA device was also analyzed according to actual time and elapsed time.
Results: VAS scores showed no difference between the two groups except 36 hours after recovery from anesthesia. On POD1, there were two peaks for self-administration of bolus analgesics in group L and one peak in the morning for group E. Two peaks each in the morning and in the afternoon were shown in both groups on POD2.
Conclusions: Diurnal variance in pain should be considered for effective dosing strategies.

Key Words: Circadian; Orthognathic surgery; Patient controlled analgesia; Postoperative pain.

INTRODUCTION

To date, several studies have reported diurnal variations in pain perception. Patients with rheumatoid arthritis seem to suffer more from pain in the morning [1]. Biliary colic and labor pain also show a circadian rhythm [2, 3]. Cancer patients appear to require extra doses of pain medication between 10:00 a.m. and 10:00 p.m., and they require higher pain control during the day [4]. Postoperative pain is similar to rheumatoid arthritis pain due to inflammatory features [5]. Because of the chronopharmacokinetics of opioids and nonsteroidal anti- inflammatory drugs, it would be useful for dosing strategies to incorporate circadian pattern and drug type [6-8].

The time of day that an operation is conducted influences the need for postoperative analgesic pain control [9]. In our study, patients who underwent two-jaw orthognathic surgery were allocated according to time of recovery from anesthesia. Patients were asked about pain intensity with a VAS score and their demand for analgesics was investigated. We investigated the circadian pattern of postoperative pain and whether the timing of anesthesia influences pain level.

MATERIALS AND METHODS

1. Patient Characteristics

The institutional review board of Seoul National University Dental Hospital approved this study (Seoul, Republic of Korea.). A total of 250 patients undergoing orthognathic surgery from March 2007 to February 2008 were enrolled. Information was compared retrospectively. Patients were allocated into two groups, an early group (group E) and a late group (group L). In group E, anesthesia for the operation ended before 18:00 in the evening. In group L, anesthesia ended after 18:00 in the evening. Six different surgeons performed the orthognathic operations.

2. Anesthesia

All patients fasted from midnight, and no patient received any premedication on the day of surgery. Monitoring for general anesthesia was started. High flow (5 L/minute) oxygen was delivered via a face mask. Intravenous induction began with administration of 2 mg/kg of 1% propofol or 5.0 mcg/ml target site concentration with 2% propofol and 5.0 ng/ml target site concentration with remifentanil that was diluted to 100 mcg/ml via a target controlled infuser (Orchestra® Base Primea, Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany). After confirming loss of consciousness, 0.6 mg/kg rocuronium was administered. Invasive arterial pressure monitoring was started after cannulation with a 20-G cannula in the dorsalis pedis artery. Full relaxation was confirmed through neuromuscular monitoring, and intubation was performed with a nasotracheal tube. Electrocardiography, pulse oximetry, end-tidal carbon dioxide partial pressure, noninvasive blood pressure, and invasive blood pressure were continuously monitored during the operation. When patients received total intravenous anesthesia with propofol and remifentanil with target-controlled infusion, the Bispectral index (BIS) was monitored until anesthesia recovery. Targeted BIS scores were between 40 and 60.

3. Patient controlled analgesia

In intravenous patient controlled analgesia (IV PCA) devices with a target VAS score of 3, 700 mcg fentanyl and 150 mg ketorolac were diluted with 120 ml normal saline. The IV PCA device (Accumate 1000®, Acemedical, Seoul, Korea) was programmed to infuse analgesics with a basal infusion rate of 1.0 ml/hour, a 1-ml bolus dose on demand, and a lockout time of 10 minutes. With these infusion settings, a patient cannot receive another additive bolus within 10 minutes of pushing the button for a bolus infusion. The PCA device time was synchronized with Korea Standard Time at the national metrology institute. At the end of the operation, IV PCAs were connected to patients through an intravenous line. The time of starting the device, the number of bolus attempts, the amount of bolus drug delivery, and the end of device usage was saved according to standard time. If pain was too severe to control with PCA infusion, 50 mcg fentanyl was administered as a rescue drug.

4. Pain intensity with visual analogue scale and IV PCA report

Pain intensity was obtained directly from patients at discharge from the post-anesthesia care unit (PACU) and 6 hours, 12 hours, 24 hours, 36 hours, 48 hours, 60 hours, and 72 hours after recovery from anesthesia. Information regarding patient self-administration of analgesia via a patient-activated infusion device was downloaded to personal computers with an IV PCA device specific download program, Eventlog Viewer version 1.0 for Accumate1000 (Wooyoung medical, Inc., Seoul, Korea).

5. Statistics

Statistical analysis was conducted with Sigmaplot for Windows version 13.0 (Systat Software, Inc., San Jose, CA). Data are expressed as the mean ± standard deviation (SD) for normally distributed continuous variables, median (range) for non-normally distributed continuous variables, and count for categorical variables. A simple moving average was used to smooth out fluctuations and

show up cycles of number of bolus attempts over time. Three successive values were calculated for meaning. Student t-tests were used to calculate differences in counts of bolus attempts and bolus infusions. Analysis of VAS scores from the two groups was done with the Mann-Whitney rank sum test due to failure of the normality test. Nonlinear regression analysis was done for trends of bolus attempts. Residuals from the nonlinear regression analysis were calculated with the one-way t-tests. Graphs were depicted using GraphPad Prism 5.01 (GraphPad Software, Inc., La Jolla, CA).

RESULT

1. Patient characteristics

Patient characteristics are presented in Table 1. There were no significant differences in age, sex, ASA physical status, body weight, height, BMI, time of finishing anesthesia, total volume of infused PCA, and total number of bolus attempts and infusions. However, anesthesia duration

in group L was significantly longer than in group E.

2. VAS score after operation

The VAS score in group L was significantly higher 36 hours after the operation than the VAS score in group E ($P < 0.05$). Other than that, there were no differences in VAS scores between the two groups. The mean value
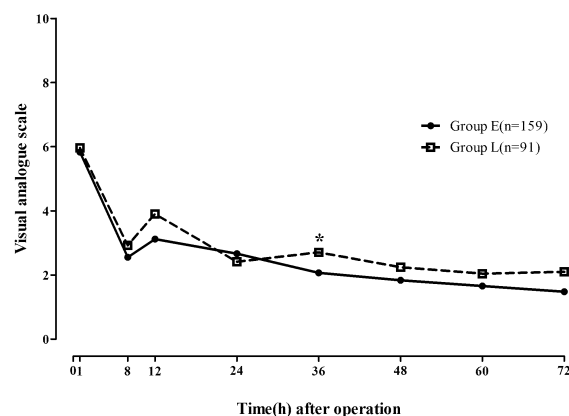

Fig. 1. Visual analogue scale score of pain intensity. Visual analogue scale (VAS) scores of pain intensity between group E and group L are compared over time. VAS score data are expressed as medians. X-axis values are expressed as elapsed time. VAS score of 36 hours after surgery is significantly higher in group L. $^{*}P < 0.05$.

Table 1. Patient characteristics

	Group E (n=159)	Group L (n=91)
Age, years	23.2 ± 6.1	23.9 ± 6
Sex (M/F)	69/90	48/43
Weight, kg	59.2 ± 11.8	61.7 ± 14
Height, cm	165.81 ± 10.25	168.5 ± 11
BMI	21.4 ± 2.8	21.5 ± 3.3
ASA PS 1/2	151/8	87/4
Time of anesthesia start	08:10:00 (08:05:00-08:21:15)	08:20:00 (08:10:00-11:10:00)
Time of anesthesia end	15:35:00 (13:50:00-16:50:00)	19:25:00 (18:52:30-20:00:00)
Duration of anesthesia, minutes	392.6 ± 124.7	590.2 ± 145*
Total infused PCA volume, mL	89.5 ± 26	97.9 ± 37
Count of bolus attempt	16 ± 25	21 ± 33
Count of bolus delivery	9 ± 12	12 ± 15

Data are expressed as mean±SD, median (range) or count and compared using the two-sample t-test or Mann-Whitney rank-sum test as appropriate. ASA PS: American Society of Anesthesiologists of Physical Status, BMI: Body mass index.
$^{*}P < 0.001$ vs. group E.

Table 2. Average number of infusion attempts and infusion delivery per hour

	Group E		Group L	
	Attempts	Delivery	Attempts	Delivery
POD0	0.891 ± 0.560	0.503 ± 0.26	1.457 ± 0.400*	0.741 ± 0.33¶
POD1	0.149 ± 0.067	0.0879 ± 0.03	0.273 ± 0.149*	0.170 ± 0.08*
POD2	0.0825 ± 0.070	0.0437 ± 0.03	0.129 ± 0.087†	0.082 ± 0.04*

Data are expressed as mean ± SD or median (range). For POD0, 1, and 2: Student t-test was used.
$^{*}P < 0.001$ vs. group E. $^{†}P = 0.002$ vs. group E. $^{¶}P = 0.005$ vs. group E.

of real time 36 hours after the operation in group L was about 7:36 a.m. on the second morning after operation day. Fig. 1, shows the median values of VAS scores between the two groups according to time after operation.

3. Information from PCA device

The total infused volume of analgesics through the IV PCA was not significantly different between the two groups. Total counts of bolus infusion and bolus attempts were not different between group L and E.

However, the counts of bolus attempts recorded every hour according to actual time between the two groups were significantly different. In Table 2, patients in group L demanded a bolus infusion more frequently than patients in group E on operation day, POD1 and POD2. Bolus infusions were delivered more frequently in patients of group L than for patients in group E.

In Fig. 2, average values of bolus attempts in group E and group L are depicted according to actual time recorded in PCA devices (left graph) and elapsed time after surgery (right graph). Both graphs show decreasing patterns over time.
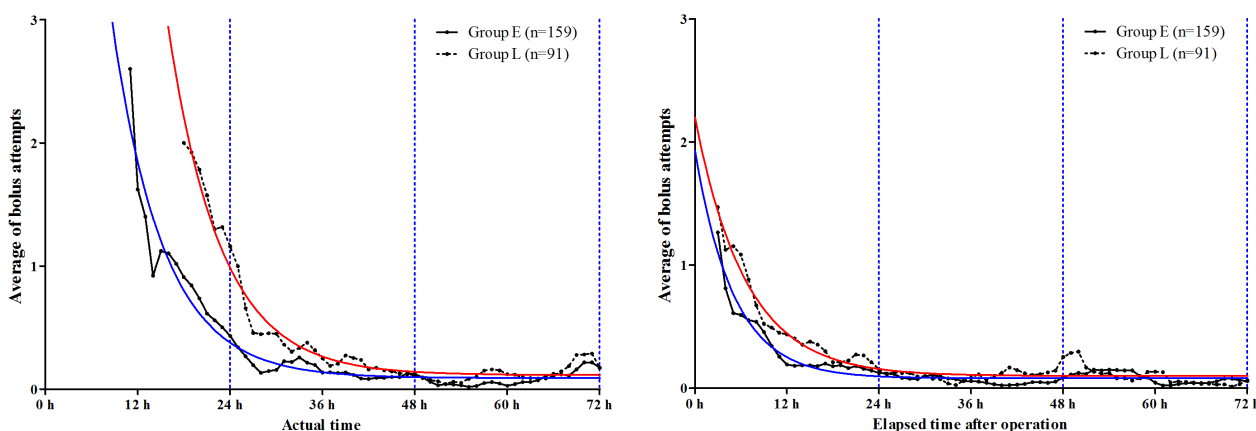

Fig. 2. Comparison of bolus attempts over time. Data are expressed as mean of bolus attempts every hour. X-axis values are expressed as elapsed time (right graph) and actual time (left graph). Mean values of bolus attempts between group E and group L decreased over time. Red and blue lines are nonlinear regression curve of group L and group E. Average values for attempts on the left graph on POD1 and POD2 show similar in group E and group L. Nonlinear regression equation: $f(t) = (Y0 - \text{Plateau}) \cdot e^{-kt} + \text{Plateau}$. Covariant: $Y0 = 1.928$, $k = 0.1983$, Plateau $= 0.08079$ (elapsed time in group E). $Y0 = 2.198$, $k = 0.1503$, Plateau $= 0.0994$ (elapsed time in group L). $Y0 = 9.310$, $k = 0.1509$, Plateau $= 0.09091$ (actual time in group E). $Y0 = 25.14$, $k = 0.1459$, Plateau $= 0.1133$ (actual time in group L). Ranges in 95% confidence intervals: $0.1731 < k < 0.2235$ (elapsed time in group E), $0.1333 < k < 0.1672$ (elapsed time in group L), $0.1310 < k < 0.1707$ (actual time in group E), $0.1309 < k < 0.1609$ (actual time in group L). The gradient of regression curve, k-values were statistically different ($P < 0.05$) in elapsed time graphs between two groups.
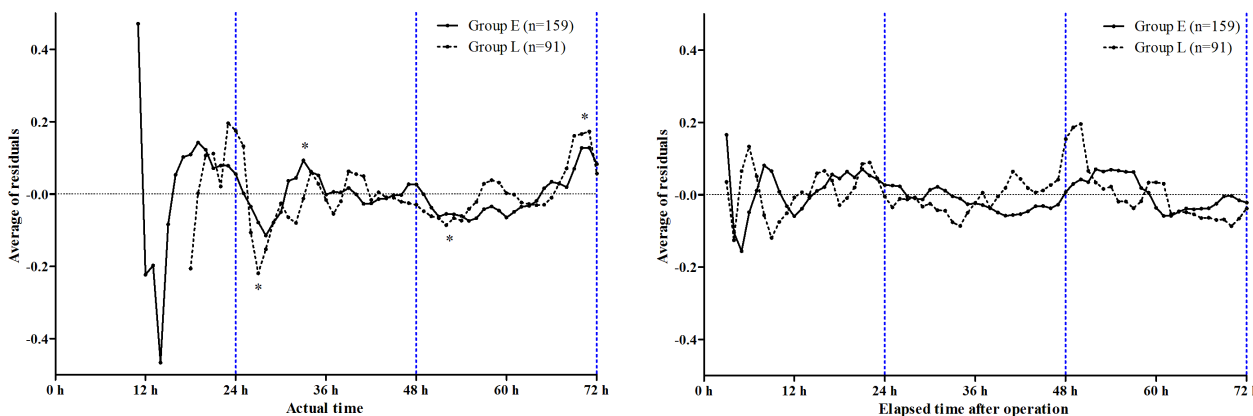

Fig. 3. Comparison of residuals of bolus attempts from nonlinear regression curve. Data are expressed as mean residuals in group E (black linear line) and group L (black dotted line) according to actual time and elapsed time after operation. Residuals were analyzed used with one-way t-test. 4 points marked with asterisks were significantly different in both groups from trends of nonlinear regression. *: $P < 0.05$

In Fig. 3, peak and deep patterns were similar in both groups when the averages of residuals were presented according to actual time. On POD1 and POD2 patients felt significantly less pain at dawn. In the morning on POD1 and in the evening on POD2, patients felt more pain (P < 0.05).

DISCUSSION

In post-anesthesia care units, patients whose orthognathic surgeries finish late at night tend to complain of more severe pain. There are several reasons for this. The operations in group L were prolonged compared to those in group E. When operations finish early in the afternoon, caregivers are around more than at night, and they are also more active. Therefore, pharmacological and behavioral treatment can be achieved immediately. Disturbances in the circadian rhythm of patients due to invasive procedures can also cause more severe pain. In our study, the VAS scores between two groups showed no significant difference, except 36 hours after operation. Data regarding attempted boluses is a surrogate method for determining pain severity. In addition to VAS scores, data regarding bolus attempts and bolus infusions were collected hourly for meticulous and quantifiable analysis. There were significantly more attempts and infusions in group L on POD0, POD1 and POD2. The attempt count of patients in group L indicates that these patients seemed to suffer more intense pain than patients in group E. Due to the infusion of more analgesics through patient-activated bolus devices, pain intensity expressed as VAS scores is likely similar between groups.

On POD0, the patients in group E received IV PCA earlier, and a higher dose of analgesics was estimated to be accumulated. On POD1, there were two peaks each in the morning and in the afternoon in group L. Group E only had a peak on the morning of analgesic administration. However, on POD2 both groups showed a similar pattern of two peaks for self-administration of analgesics. The difference in time of recovery from anesthesia was less significant over time.

Pain intensity indicated by VAS scores had a decreasing pattern. On POD1 and POD2, there were self-administration peaks with different overall patterns than during the day. There have been several reports on the chronopharmacokinetics of morphine and diurnal variation in pain intensity [6]. However, fentanyl clearance does not seem to change with circadian patterns [10]. In our PCA medication, in addition to fentanyl ketorolac is contained. Changes in the pharmacokinetics of non-steroid anti-inflammatory drugs during the day have been reported. Ketoprofen clearance increases during the day, and circadian variation in the mean plasma concentrations of ketoprofen after intravenous administration has been reported. When ketoprofen was administered orally around 1:00 a.m., the time to peak concentration took much longer after drug administration. The lag time was significantly longer at 1:00 a.m. than at 13:00 p.m. Several studies indicate why there are peaks in bolus demand during the day [8,11]. There are changes in protein binding capacity throughout a day, increased drug clearance, and changes with activities such as walking, eating, and sleeping. Because of these changes, pain intensity and attempts to cope with pain vary over time.

Chronobiology and circadian rhythm clearly influences the pharmacokinetic and pharmacodynamic features of analgesics [12]. By understanding these patterns with postoperative pain, anesthesiologists and surgeons can control patient pain with an effective dosing strategy. Our study found a circadian pattern expressed as peaks during the day, and diurnal variance in pain should be considered. Further research on the influence of circadian rhythms on general anesthesia and postsurgical pain is needed.

CONCLUSION

Postsurgical pain intensity decreased over time. In decreasing pattern of VAS, additive analgesics and pain

assessment might be needed in the morning and in the afternoon for better pain control.

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