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Chronobiology of Subarachnoid Fentanyl for Labor Analgesia

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Background: **Chronobiology studies the recurrent biologic rhythms that directly affect how an organism interacts with its environment and how its environment affects the organism. The purpose of this study is to determine whether the time of administration influences the analgesic duration of the commonly used subarachnoid fentanyl for labor analgesia.**

Methods: **After institutional review board approval and informed consent were obtained, 77 healthy nulliparous women in active labor requesting neuraxial analgesia were assigned to one of two groups, based on the time of combined spinal–epidural analgesia placement: the day group, for the time period from 12:00 to 18:00, and the night group, for the period from 20:00 to 02:00. Combined spinal–epidural analgesia was performed with 20 μg subarachnoid fentanyl. An epidural catheter was inserted but not dosed until patients requested further analgesia. Dynamic data were recorded at 5-min intervals for 20 min initially and then every 15 min. The analgesic duration was defined as the time from subarachnoid fentanyl injection to the time the patient requested further analgesia.**

Results: **Seventy evaluable patients completed the study, with 35 per group. Patient demographics, visual analog pain scale scores, and labor characteristics were similar between groups, but the duration (mean ± SD) for subarachnoid fentanyl labor analgesia was 92 ± 34 min for the day group and 67 ± 21 min for the night group ($P < 0.001$).**

Conclusions: **The results indicate that chronobiology of subarachnoid fentanyl plays a significant role of up to 27% difference in labor analgesic duration between the two administration time periods studied. Chronobiology should be incorporated in future comparative studies or analysis of previous studies on subarachnoid fentanyl.**

CHRONOBIOLOGY studies the recurrent biologic rhythms that directly affect how an organism interacts with its environment and how its environment affects the organism.[1,2] Chronopharmacology studies the effect of the moment of drug administration on its response according to the temporal structure of the organism receiving it.[1,2] These rhythms are ubiquitous in nature and can have both extrinsic controls, such as sunlight, and intrinsic controls, such as circadian rhythms.[2,3] Several reviews underlined the importance of the chronobiologic process; the effectiveness and toxicity of many drugs and the pain threshold to noxious stimuli may vary significantly depending on the relation between the time of administration and the circadian rhythm of biochemical, physiologic, and behavioral processes.[4–10] In mammals, the suprachiasmatic nucleus of the hypothalamus is the central regulation of chronobiologic rhythmicity, and light is the input synchronizer connecting the internal clock to the external environment.[2] Chronopharmacology for local anesthetic has been demonstrated with its time-varying toxicity and potency. Some possible mechanisms proposed are the rhythmic changes in membrane permeability and access to channels, and the temporal variations of distribution, protein binding, and metabolism, which have been well documented in mice.[2] Before the discovery of the newer agents propofol, desflurane, and sevoflurane, many studies, mostly in animals, also reported temporal changes in toxicity and efficacy among general anesthetic agents.[2]

However, there is a limited number of studies examining the effects of chronobiology on labor analgesia.[11–13] Debon *et al.*[12] reported significant chronobiologic variations in analgesic duration with epidural ropivacaine when administered for labor analgesia. In particular, the maximal analgesic duration occurred when epidural ropivacaine was administered between 13:00 and 19:00, and the least analgesic duration occurred when epidural ropivacaine was administered between 19:00 and 01:00.[12] A significant amount of research has been focused on determining the optimal dose of subarachnoid opioids used in combined spinal–epidural analgesia (CSEA) for labor analgesia. Subarachnoid fentanyl and sufentanil emerged as the most common and most useful.[14,15] Debon *et al.*[13] recently also reported that the analgesic duration of 10 μg sufentanil exhibited a 12-h ultradian cycle (a cycle that is shorter than 24 h) when administered into the subarachnoid space to parturients of mixed parity in active labor. Despite the many pharmacokinetic and clinical differences between fentanyl and sufentanil,[16,17] it has not been previously studied whether the analgesic duration of subarachnoid fentanyl would also exhibit chronobiologic variations. Furthermore, most previous studies on evaluating the optimal analgesic duration of subarachnoid fentanyl did not account for chronobiologic effects,

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potentially subjecting the results to bias and erroneous conclusions if significant chronobiologic effects exist with subarachnoid fentanyl analgesia. We hypothesized that the time of administration of subarachnoid fentanyl significantly affects the analgesic duration of action when used for labor analgesia.

Materials and Methods

After institutional review board approval (Forsyth Medical Center and Wake Forest University, School of Medicine, Winston-Salem, North Carolina) and informed consent were obtained, 77 parturients were enrolled. The parturients were healthy, had an American Society of Anesthesiologists physical status of I or II, were nulliparous, were aged 18 yr or older, had a singleton vertex pregnancy at term gestation ($\geq$ 37 weeks), and were in spontaneous active labor with the cervix dilated between 2 and 5 cm. Enrolled patients requesting neuraxial labor analgesia were assigned to one of two groups, based on the time period when the CSEA was administered: the day group, for hours between 12:00 and 18:00, and the night group, for hours between 20:00 and 02:00. These two time periods were chosen based on the epidural ropivacaine study of Debon *et al.*[12] that showed the maximum difference in labor analgesic duration occurring between two similar time periods and the logistics of performing this study at our site during certain hours of the day. Exclusion criteria included opioid analgesics within 1 h before administration of CSEA, contraindications to regional anesthesia, weight greater than 114 kg, abnormal fetal heart rate tracing, and allergies to any study drug. All patients received an intravenous infusion of 250–500 ml lactated Ringer's solution within 15 min of the CSEA placement. With the patient in the sitting position, placement of the CSEA was performed at the L3–L4 or L4–L5 level, using loss-of-resistance-to-air technique with a needle-through-needle approach. A 17-gauge Weiss epidural needle, a 27-gauge Whitacre 4-11/16-in spinal needle, and a 19-gauge closed-end, triple-holed, epidural catheter were used for each patient. Each patient was given a 20-μg subarachnoid fentanyl dose, which was prepared with a 1-ml tuberculin syringe, mixed with 0.6-ml normal saline to a total volume of 1 ml, and then transferred to a 3-ml syringe for subarachnoid injection. Cerebrospinal fluid (CSF) was confirmed with aspiration before and after injection of subarachnoid fentanyl. If CSF return was not obtained either before or after the injection of subarachnoid fentanyl, the patient was excluded from the study. After removal of the spinal needle, the epidural catheter was inserted 4–6 cm inside the epidural space. After the epidural catheter was secured with tape and it was confirmed that there was no blood or CSF return from aspiration of the catheter, the patient was placed supine with a slight left tilt. The epidural catheter remained untested until the patient requested additional analgesia, at which time the visual analog pain scale (VAPS) score and the cervical dilation were rechecked. The duration of subarachnoid labor fentanyl analgesia was defined as the time from subarachnoid fentanyl administration until the patient requested additional analgesia.

Visual analog pain scale score, pruritus, blood pressure, heart rate, respiratory rate, fetal heart rate, frequency of uterine contraction, level of sensory and motor blockade, and presence of emetic symptoms were obtained before CSEA placement; at 5, 10, 15, and 20 min after subarachnoid injection; and subsequently every 15 min thereafter until the patient requested additional analgesia. If the VAPS score did not decrease to less than 20 mm by 20 min after subarachnoid injection of fentanyl, the patient was excluded from the study. Hypotension was defined as a decrease in systolic pressure of 20% or more from baseline and was treated with a fluid bolus and intravenous ephedrine in 5- to 10-mg increments, as needed. Pruritus was treated with 25 mg intravenous diphenhydramine, if needed.

Statistical Methods

For statistical analysis, Sigma Stat 3.01 was used (SPSS Inc., Chicago, IL). A previous power analysis revealed that an estimated minimal sample size of 34 patients/group was required to achieve a power of 0.9 and an α of 0.05 to detect a difference of 20 min in subarachnoid analgesic duration between groups, with a SD of 25 min. We considered a 20-min difference clinically significant, which represents a 20–30% difference in analgesic duration of subarachnoid fentanyl in previous studies.[18] Categorical data were assessed by Fisher exact test, chi-square test, or Mann–Whitney rank sum test as appropriate. Continuous data were analyzed with an unpaired *t* test or analysis of variance as appropriate. Continuous data were expressed as mean $\pm$ SD, and categorical data were expressed as median and mode. A *P* value less than 0.05 was considered to be statistically significant.

Results

A total of 77 patients were enrolled. All enrolled patients reported their usual routine daily activities as normally getting up in the morning and sleeping at night. Seven patients were excluded: one because of no CSF return on aspiration, three with inadequate pain relief from subarachnoid fentanyl administration, and three with protocol violations due to one premature administration of epidural medication and two CSEAs administered at the hour outside the two studied time periods. The remaining 70 evaluable patients constituted 35 patients each in the day and night groups. Patient demographics were similar between the two groups (table 1).

Table 1. Patient Demographics and Labor Characteristics

	Day Group (12:00–18:00) (n = 35)	Night Group (20:00–02:00) (n = 35)
Age, yr	26 (6)	26 (6)
Weight, kg	86 (16)	81 (16)
Height, cm	165 (8)	164 (5)
Gestational age, wk	40 (1)	39 (1)
Fetal weight, g	3,487 (471)	3,453 (558)
Cervical dilation before CSEA, cm	3.5 (0.8)	3.4 (0.9)
Median	3	3
Cervical dilation when patients requested additional analgesia, cm	5.1 (1.5)	5.2 (1.7)
Median	5	5
Fetal heart rate before CSEA, beats/min	132 (7)	131 (11)
Fetal heart rate at 15 min after CSEA, beats/min	134 (8)	133 (9)
Uterine contraction frequency before CSEA, min/contraction	2.3 (0.7)	2.4 (0.6)
Uterine contraction frequency at 15 min after CSEA, min/contraction	2.3 (0.5)	2.4 (0.7)
Incidence of cesarean delivery, %	20	16.7

There was no significant difference in all variables between groups. Values are presented as mean (SD) unless otherwise indicated.
CSEA = combined spinal–epidural analgesia.

Duration of Analgesia

The overall labor analgesic duration (mean ± SD) of subarachnoid fentanyl for all 70 patients was 80 ± 31 min. The analgesic duration (mean ± SD) of fentanyl differed significantly ($P < 0.001$) between the day group (92 ± 34 min) and the night group (67 ± 21 min). The 25-min average difference represented a 27% reduction in analgesic duration between groups (fig. 1).

Oxytocin Augmentation

We had 54% and 51% subsequent oxytocin augmentation in the nulliparous patients during the study period in the day and night groups, respectively. We further stratified the patients into groups with or without subsequent oxytocin augmentation in addition to the day and night group stratification, and applied analysis of variance (with pairwise multiple comparison by Holm-Sidak method) to compare among groups. Comparing analgesic duration (mean ± SD) only in patients with subsequent oxytocin augmentation between the day and night groups showed a significant difference (97 ± 43 min [day group] *vs.* 73 ± 19 min [night group]; $P < 0.01$, power = 0.86). Likewise, comparing only patients without augmentation between the day and night groups yielded a similar significant difference (86 ± 18 min [day group] *vs.* 61 ± 23 min [night group]; $P < 0.01$, power = 0.86). The analgesic duration (mean ± SD) was 86 ± 35 and 73 ± 24 min for all patients with subsequent oxytocin augmentation (n = 37) and without augmentation (n = 33), respectively ($P < 0.09$).

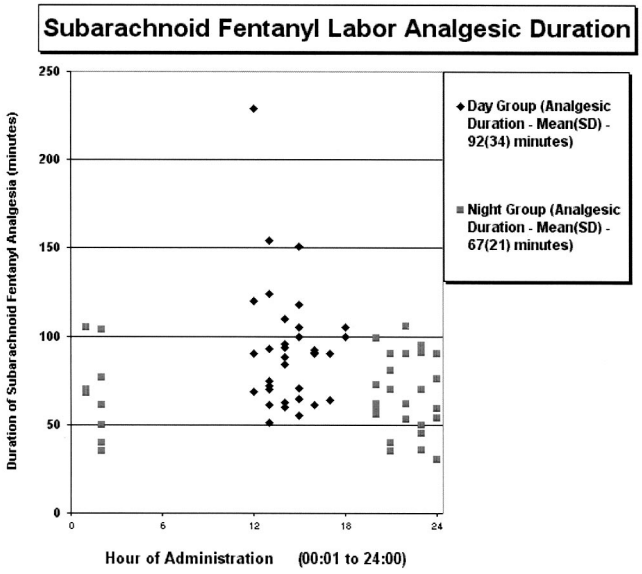

Fig. 1. Time of administration and the duration of subarachnoid fentanyl analgesia in laboring parturients.

VAPS Score, Cervical Dilation, Sensory Level, Opioid Use, Cesarean Delivery, and Side Effects

The VAPS score and sensory blockade level before CSEA, 15 min after CSEA, and at the time of requesting additional analgesia *via* epidural catheter were all similar between groups. Both cervical dilation and the frequency of uterine contraction (minutes/contraction) before CSEA placement and at the time of requesting additional analgesia were similar between groups. No patient had a cervical dilation greater than 8 cm when requesting additional analgesia. The incidence of opioid use more than 1 h and less than 4 h before CSEA placement and the incidence of cesarean delivery were not different between groups. The overall incidence of pruritus for all patients was 83% (86% for the day group, 80% for the night group). Only 27% of patients with pruritus requested treatment. The incidence of emetic symptoms was 3%, excluding subjects who already had emetic symptoms before CSEA placement. Maternal hemodynamics, incidence of hypotension, and fetal heart rate were comparable between groups both before and after administration of subarachnoid fentanyl. No serious ad-

Table 2. Labor Analgesia Characteristics

	Day Group (12:00–18:00) (n = 35)	Night Group (20:00–02:00) (n = 35)
VAPS score before CSEA (0–100 mm)	80 (16)	74 (17)
VAPS score at 15 min after CSEA (0–100 mm)	1 (2)	2 (5)
VAPS score when patients requested additional analgesia (0–100 mm)	54 (21)	52 (21)
Sensory blockade dermatome to temperature at 15 minutes after CSEA		
Median	T6	T6
Mode	T6	T6
Incidence of pruritus, %	86	80
Incidence of pruritus necessitating treatment, %	23	31
Incidence of emetic symptoms after CSEA, %	3	3
Incidence of hypotension after CSEA, %	6	3
Incidence of opioid use* $>$ 1 h and $<$ 4 h before CSEA placement,	46.7%	43.3%
Amount of butorphanol administered, mg	1.07 (0.3)	1.15 (0.4)

Values are presented as mean (SD) unless otherwise indicated. There were no statistically significant differences in all variables between day and night groups.

* Opioid use consisted of intravenous butorphanol.

CSEA = combined spinal–epidural analgesia; VAPS = visual analog pain scale.

verse untoward event, such as respiratory depression, cardiopulmonary arrest, high spinal blockade, or severe hypotension necessitating significant resuscitation and neurologic injury, was noted in the study (tables 1 and 2).

Discussion

Our study demonstrated that the time of day affected the analgesic duration of subarachnoid fentanyl in nulliparous, spontaneously laboring parturients with cervical dilation between 2 and 5 cm. The average analgesic duration of 80 min from 20 μg subarachnoid fentanyl for all patients was similar to that reported in other subarachnoid fentanyl studies in the past.[18,19] The 27% difference in average analgesic duration between the day and night groups was significant, both clinically and statistically. Many previous studies compared the efficacy of different subarachnoid drugs with or without adjuvant for labor analgesia and found maximum differences of only 20–40% in analgesic duration among different drug combinations.[20] Not considering the chronobiologic variations may potentially create significant bias, variability, and inaccuracy in the results and conclusions from past or future studies.

Although fentanyl is one of the most commonly used subarachnoid opioids for labor analgesia in the United States,[14,15] there are no published data on whether subarachnoid fentanyl analgesic duration exhibits chronobiologic variations during labor analgesia. The two time periods of administration we studied were based on the epidural ropivacaine study of Debon *et al.*[12] showing maximum analgesic duration differences between two similar time periods and also due to the feasibility of patient enrollment at our site during those hours. We can be criticized for not studying patients during all 24 h of administration, but our goal was to show that chronobiology exists and significantly affects subarachnoid fentanyl labor analgesic duration, not necessarily to determine the exact time of peak and trough of the chronobiologic variations. Our results with subarachnoid fentanyl were similar to the subarachnoid sufentanil study of Debon *et al.*[13] in that both showed significant variations in analgesic duration with time of administration of subarachnoid opioid during labor. The study of Debon *et al.*[13] further characterized the variations with two peak subarachnoid sufentanil durations of action around 12:00 and 24:00. Our study showed that the 12:00 h was within the time period of the day group with the longer subarachnoid fentanyl analgesic duration, but it did not show, nor was it designed or powered to show, the rhythmic variation with a second peak around 24:00 h for subarachnoid fentanyl. Instead, our result showed that the 24:00 h was within the time period (night group) when the average analgesic duration was significantly shorter than the day group. Although both study designs were similar in some ways, there were a number of factors that might have contributed to the differences in the results. The opioids and relative doses we studied were different. Nelson *et al.*[19] showed a 4.3:1 ratio between subarachnoid fentanyl and sufentanil. The 10 μg subarachnoid sufentanil used in the study of Debon *et al.* would be equivalent to more than twice the 20 μg fentanyl we studied. Significant differences have been shown between fentanyl and sufentanil in their pharmacokinetic behaviors, volume of distribution in CSF, spinal cord and epidural space, transfer rate from CSF to epidural space, and relative potency ratio when administered intravenously *versus* in the subarachnoid space.[16–19] It is not clear, nor has it been shown, whether all or any of these differences could have altered the chronobiologic characteristics between these two opioids. Furthermore, our study consisted of only nulliparous patients, and the studies of Debon *et al.*[12,13] consisted of both nulliparous and multiparous patients.

The use of oxytocin may affect analgesic duration. Although our study was not designed or powered to

detect the 13-min difference in analgesic duration noted between patients with oxytocin augmentation and those without, our data consistently showed a trend of longer average analgesic duration in patients with subsequent oxytocin augmentation. Whether oxytocin increases visceral pain threshold or affects chronobiology of subarachnoid fentanyl and at what dose (especially during labor) is not clear.[21] Although the uterine contraction frequency and cervical dilation were similar between groups (including between patients with and without subsequent oxytocin augmentation) at the time before CSEA placement and at time of additional analgesic request, one may postulate that patients' subsequently requiring augmentation may be in part due to a less intense and slower labor and therefore potentially less pain and longer analgesic duration, independent of whether oxytocin has any effect on chronobiology or pain threshold.

In our study, one patient in the day group had an analgesic duration of 229 min, a highly unusual, long duration of action and possibly an outlier among the data. The VAPS score, cervical dilation, cervical dilation changes, progress of labor, and frequency of contraction for this patient were all similar and consistent with other patients. Nevertheless, there would still have been a statistically significant difference between groups even if this patient were excluded. After exclusion of this patient from data analysis, the analgesic duration (mean ± SD) was 88 ± 25 and 67 ± 21 min for the day and night groups, respectively ($P < 0.001$).

Recently, Aya *et al.*[11] reported a chronobiologic difference in labor pain perception in an observational study showing daytime pain scores of 75.6 ± 15.1 *versus* 85.7 ± 14.1 in the nocturnal group. Even though this may contribute to differences in analgesic duration between our groups, our data demonstrated no significant difference in cervical dilation, frequency of uterine contractions, or the corresponding VAPS score between the day and night groups both immediately before CSEA placement and at the time when patients requested additional analgesia *via* the epidural catheter.

In conclusion, this study demonstrated that subarachnoid fentanyl analgesic duration during labor was affected significantly by the time of administration, with a mean difference of 27% between the two 6-h administration time periods (12:00–18:00 *vs.* 20:00–02:00). Future study designs with subarachnoid fentanyl or other opioids and the analysis of past and future studies should take the time of drug administration into consideration. Further research is warranted to identify the mechanism of chronobiologic effects on subarachnoid opioids, the difference in chronobiologic effects between different opioids, their route of administration, the addition of subarachnoid local anesthetic to opioids, and the effects of oxytocin augmentation of labor on chronobiology of subarachnoid opioids.

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