folia medica

Folia Medica 64(1):49-54
DOI: 10.3897/folmed.64.e59831

Original Article

Circadian Effects on Neural Blockade of Levobupivacaine and Fentanyl Intrathecal Administration for Caesarian Section

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Received: 19 October 2020 ♦ **Accepted:** 8 Feb 2021 ♦ **Published:** 28 Feb 2022

Citation: Nikouli E, Chloropoulou P, Karras G, Kiamiloglou B, Tsigalou C, Vogiatzaki T. Circadian effects on neural blockade of levobupivacaine and fentanyl intrathecal administration for caesarian section. Folia Med (Plovdiv) 2022;64(1):49-54. doi: 10.3897/folmed.64.e59831.

Abstract

Introduction: Circadian variations in biological rhythms affect the pharmacological properties of many anaesthetic agents, suggesting circadian patterns of local anaesthetics' activity in labour pain analgesia, with important differences among diurnal and nocturnal phases.

Aim: We examined whether a rhythmic variation of the effect of intrathecal mixture of levobupivacaine and fentanyl exists throughout the day period regarding caesarean sections.

Materials and methods: Eighty parturients presented for caesarean section, both urgent and/or elective, were assigned to five equal groups (A, B, C, D, and E) according to the time-point of the intrathecal drug administration. The same levobupivacaine and fentanyl dose was given to all patients. Pinprick or cold test, the four-point modified Bromage scale (0-3), and the numerical scale (NRS 0-10) were used respectively for the assessment of sensory and motor blockade, and post-anaesthetic pain. The duration of sensory and motor blockade, analgesia duration and pain score at first analgesic request were recorded.

Results: Statistically significant differences were found among the studied groups in the duration of motor and sensory blockade and pain score at first postoperative analgesic request. Prolonged duration of motor blockade in groups A, B and C ($p<0.001$) and prolonged duration of sensory blockade and analgesia in groups A, B ($p<0.001$) were observed. Higher pain scores at first postoperative analgesic request were recorded in group E ($p<0.001$).

Conclusions: The present study highlights the significant effects of circadian rhythm on the efficacy of a mixture of local anaesthetics, levobupivacaine and fentanyl, during caesarean delivery.

Keywords

caesarian section, circadian effects, local anaesthetics, pain, spinal anaesthesia

INTRODUCTION

Pharmacokinetics and pharmacodynamics of local anaesthetics are subject to circadian variations, profoundly affecting their efficacy and toxicity.[1-4] In order to establish if neuraxial local anaesthetics present time-dependent effects, numerous chronobiological studies were conducted in labour pain analgesia.[5-8,13] Although only two studies reported that time of day did not appear to influence the duration of analgesia during labour produced by intrathecal local anaesthetics or opioids[9,10], the results of most studies were able to produce a consistent picture with peaks in the morning or at noon.[4,5,7,8] The pharmacological effect regarding intrathecal or epidural administration of local anaesthetics was longer in the diurnal period[4,8,13], and the latency period was longer at night[6]. A temporal pattern in the duration of analgesia with a peak around noon[5,7,8] was also observed. In addition, a study on orthopaedic anaesthesia also revealed that the time of intrathecal administration of local anaesthetics influences the duration of anaesthesia.[14]

AIM

Due to contradictory published data, we designed our study to determine whether the time-point of intrathecal levobupivacaine administration influences the duration of spinal anaesthesia and the intensity of post-anaesthetic pain.

MATERIALS AND METHODS

This study was approved by our hospital scientific committee (acting also as ethics committee, ref. number: 14/4th/27-4-2015); written informed consent was obtained from all study participants. Our protocol was conducted for three months, during the winter season (December to February 2015-2016) in constant temperature, humidity, and light conditions. Eighty parturients, primiparous to multiparous, ASA I-II, presenting for urgent or elective caesarean section under spinal anaesthesia were assigned to five groups, namely group A (08:00 am–12:00 am), B (12:00 am–4:00 pm), C (4:00 pm–8:00 pm), D (8:00 pm–12:00 pm), and E (12:00 pm–08:00 am). The five time periods chosen for patient enrolment throughout the day period were in accordance with social markers (morning, noon, afternoon, evening, and night). Four groups (A, B, C, D) of equal duration of four hours and a fifth group (E) of eight hours duration were built, due to practicality of performing the study. Considering the low rate of urgent caesarean sections performed at night, the sample size in each group was decided according to the number of nocturnal caesarean sections usually performed for three months in our hospital. Sixteen subjects were included in each group. All participants followed regular feeding and sleeping schedule, including regular bedtime routine at consistent time each night, seven to eight hours of sleep, awakening up around the same time each day, and regular meal times (breakfast, lunch, dinner). Night-shift workers, patients with a history of levobupivacaine allergy, sleep disorders, abnormal coagulation profiles, morbid obesity or chronic pain syndromes were excluded from the study. Preoperative (24 hours before surgery) alcohol consumption, caffeine intake, use of tobacco or sleeping medication were additional exclusion criteria.

All participants received a mixture of 12 mg levobupivacaine (5%) and 0.10 mg fentanyl intrathecally at different time points throughout the day. The intrathecal injection was performed at the L3–L4 interspace, using a 25-gauge Quincke needle, in sitting position. Vital signs were recorded using non-invasive blood pressure monitoring, pulse oximetry, capnography and electrocardiography. Sensory and motor assessments were performed at 1-min intervals until the beginning of the surgery. Side effects such as hypotension, bradycardia, nausea, vomiting, and shivering were recorded. Post-caesarean section further evaluation was then done at 15-min intervals in the post-anaesthesia care unit until complete recovery of sensory and motor blocks. Sensory block was evaluated with the hot/cold test and by response to pinprick stimulation. Motor block was evaluated with the four-point modified Bromage scale (0, full flexion of the knees and feet; 1, just able to flex knees, full flexion of feet; 2, unable to flex knees, flexion of feet; 3, unable to move legs or feet, full motor block). Pain score was assessed with numerical scale (NRS 0-10).

Statistical analysis

Statistical analysis of the data was performed using the Statistical Package for the Social Sciences (SPSS), version 19.0 (IBM). The normality of quantitative variables was tested with Kolmogorov-Smirnov test. All quantitative parameters were expressed as mean ± standard deviation (SD). For the statistical evaluation of the difference in the indicators between the five different groups, analysis of variance (ANOVA) was used. Multiple comparison was performed using the least significant difference (LSD) test with corrected significance level at $\alpha=0.005$ according to Bonferroni's correction. All statistical tests were two-sided and the results were considered statistically significant for $p<0.05$.

RESULTS

Eighty participants were included in the study. The demographic characteristics of all participants were comparable between the five groups **(Table 1)**. In the sequence, the duration of motor block to Bromage 0, the recovery time of sensory block to touch sensation and pinprick, the time to first postoperative analgesic request and pain scores at analgesic request were compared between the five groups of patients **(Table 2)**. Kolmogorov-Smirnov test revealed that the values of the duration of motor block, recovery time of sensory block, time to postoperative analgesic

Table 1. Characteristics of patients according to the time of enrolment throughout the day period (group A: 08:00 am–12:00 am, group B: 12:00 am–4:00 pm, group C: 4:00 pm–8:00 pm, group D: 8:00 pm–12:00 pm, and group E: 12:00 pm–08:00 am)

Groups	A (n=16)	B (n=16)	C (n=16)	D (n=16)	E (n=16)	*p*
Age (yrs)	28.27±6.54	28.47±6.78	26.87±6.33	28.47±7.72	26.80±5.81	0.908
Weight (kg)	79.60±12.41	80.20±14.58	77.07±9.67	87.60±16.25	83.60±12.00	0.231
BMI	29.38±4.62	29.51±5.13	28.73±3.48	32.85±5.40	31.31±4.09	0.101
Height (m)	1.65±0.05	1.65±0.04	1.64±0.05	1.63±0.05	1.63±0.04	0.802
Duration of operation (min)	29.38±4.62	29.51±5.13	28.73±3.48	32.85±5.40	31.31±4.09	0.287

Table 2. Duration of motor block and sensory block, time to first postoperative analgesic request and pain score of patients according to the time of enrolment throughout the day period (group A: 08:00 am–12:00 am, group B: 12:00 am–4:00 pm, group C: 4:00 pm–8:00 pm, group D: 8:00 pm–12:00 pm, and group E: 12:00 pm–08:00 am)

Groups	A (n=16)	B (n=16)	C (n=16)	D (n=16)	E (n=16)	*p*
Duration of motor block (min)	203.20±54.19	195.60±37.29	173.00±34.58	161.20±29.60#	135.47±38.22*	<0.001
Recovery time of sensory block (min)	270.60±44.26	296.67±48.72	219.00 ±26.20*	210.20±32.81*	188.67±31.37*	<0.001
Time to postoperative analgesic request (min)	243.40±50.72	269.27±50.24	202.00±33.69@	186.20±28.90*	173.33±32.22*	<0.001
Pain score at first analgesic request	4.53±1.06	4.73±1.03	4.73±0.99	5.01±0.06	6.57±0.85$	<0.001

Statistically significant difference: # compared to group A; @ compared to group B; * compared to groups A and B; $ compared to groups A, B, C and D.

request and pain score at analgesic request were normally distributed within each group (Group A: p=0.987, 0.989, 0.999, and 0.418; Group B: p=0.426, 0.716, 0.698, and 0.428; Group C: p=0.990, 0.963, 0.778, and 0.362; Group D: p=0.975, 0.931, 0.877, and 0.707; Group E: p=1.000, 0.890, 0.611, and 0.203). Moreover, Levene's test indicated equal variances of the duration of motor block (p=0.231), recovery time of sensory block (p=0.058), time to postoperative analgesic request (p=0.097), and pain score at first analgesic request (p=0.996).

ANOVA revealed statistically significant intergroup differences in the duration of motor (p<0.001) and sensory (p<0.001) block, the time of study drug administration to first postoperative analgesic request (p<0.001) and the pain scores at analgesic request (p<0.001). In particular, in post-hoc analysis, the following statistically significant differences were observed: in motor block duration in group E versus groups A (mean difference ± standard error, −67.73±14.47 min, p<0.001) and B (−60.13±14.47 min, p<0.001), and in group D versus group A (−42.00±14.47 min, p=0.005); in sensory block duration in group C versus groups A (−51.69±13.74 min, p<0.001) and B (−77.67±13.74 min, p<0.001), in group D versus groups A (−60.40±13.74 min, p<0.001) and B (−86.47±13.74 min, p<0.001), and in group E versus groups A (−81.93±13.74 min, p<0.001) and B (−108.00±13.74 min, p<0.001); in time from study drug administration until first postoperative analgesic request in group C versus group B (−67.27±14.70 min, p<0.001), in group D versus groups A (−57.20±14.70 min, p<0.001) and B (−83.07±14.70 min, p<0.001), and in group E versus groups A (−70.07±14.70 min, p<0.001) and B (−95.93±14.70 min, p<0.001); in pain scores at analgesic request in group E versus groups A, B, C, D (all p<0.001). We found 30%-33% longer motor block duration in groups A and B compared with group E and 30%-36% longer sensory block duration in groups A and B compared with group E. Higher pain scores by 31%-45% were recorded in group E.

DISCUSSION

Our findings suggested time-related differences in the efficacy of intrathecal levobupivacaine and fentanyl during caesarean delivery. We found 30%-33% longer motor block duration and 30%-36% longer sensory block duration in groups A and B (morning/noon groups) compared with group E (night group). Higher pain scores at first analgesic request by 31%-45% were recorded in group E. Interesting outcomes were shorter anaesthesia duration during nocturnal caesarean delivery and maximal analgesia duration at noon.

Our results were in accordance with the findings of earlier protocols on labour pain analgesia, based on the epidural or spinal drug administration, at different time points. Debon et al.[5] observed significantly longer effect of epidural ropivacaine during the first stage of labour in the diurnal period. Costa-Martins et al.[6], using patient-controlled epidural analgesia, observed longer pharmacological effect during daytime and longer latency period at night. Chassard et al.[7] found temporal pattern in the duration of intrathecal plain bupivacaine with a 25% variation during daytime, with a peak around noon. Moataz Morad El-Tawil[8] depicted shorter duration of analgesia in the evening and night compared to the morning when bupivacaine was administered intrathecally during labour. On the contrary, Scavone et al.[9] and Shafer et al.[10] reported that time of day did not appear to influence the duration of analgesia produced by intrathecal local anaesthetics or opioids. Our data consistently showed a trend of higher pain scores at night. Similar findings have been reported by other authors. Pan et al.[11] investigated the temporal relation in the analgesic duration of intrathecal fentanyl for spinal labour analgesia and found difference in visual analogue pain scores (VAPS) between day and night periods, especially lower VAPS in the morning. Aya et al.[12] showed that VAPS were lower in the morning than in the afternoon, evening and night periods. Desai et al.[13] displayed that parturients with labour onset and neuraxial analgesia request in the evening and night experienced higher pain scores. Costa-Martins et al.[6] also presented significantly higher pain scores in the night group in women receiving patient-controlled epidural analgesia.

A variety of factors could influence the results of the chronobiology protocols, and this might explain the discrepancies between the published data. Keeping constant all possibly known confounders is the gold standard (constant routine protocols) in order to establish if a change in the rhythm is endogenously generated or a result of a change in the environment.[15] It is important to note that temporal variations in cycles of light-dark, rest-activity, fasting-eating, and other environmental factors defined as *synchronizers* (zeitgebers), give the organism temporal markers and impose their period on biological rhythms.[16] Ultradian (<24 hr), circadian (~24 hr), and infradian (>24 hr) rhythms exist.[17] Light is the strongest zeitgeber, but also oxygen levels, stress, anxiety-like behaviour, seasonal changes, alcohol, nicotine, caffeine, shift work and medications can alter the parameters characterizing a biological rhythm and should be considered as cofactors that can mask or unmask any circadian effects of drugs.[18] Circadian rhythms are controlled by an internal central clock, which is endogenous, self-sustained, temperature compensated, freely running/generating rhythms even in the absence of zeitgebers.[19] The regulation of rhythmicity necessitates clock mechanisms (at cellular and systemic level), inputs from the external environment to clocks (zeitgebers) and output signalling pathways that modulate physiology. The central circadian pacemaker is located in the suprachiasmatic nucleus of the hypothalamus.[20] Circadian clocks in different individuals may entrain differently to zeitgebers, especially to light, which results in different chronotypes (genetic polymorphisms in clock genes) and significant variability of therapeutic responses.[15] The circadian system has profound effects on pharmacokinetics and pharmacodynamics of drugs. Circadian variations of distribution, protein binding, and metabolism, membrane permeability and access to channels may partially explain temporal changes in local anaesthetic efficacy and kinetics drugs.[21]

Higher pain scores at night, could be explained partly by the fact that during night urgent caesarean delivery was performed. Participants had less time and knowledge for psychological preparation preoperatively. Pre-existing pain, anxiety, exhaustion or sleep deprivation, could result in increased post-operative pain.[12] In addition, the nocturnal reduction of hormones that modulate pain incidence (endogenous opioids, melatonin, cortisol, progesterone, catecholamines) could have contributed to the diurnal variation in pain perception observed in our study, because they decrease the pain perception threshold. Specific obstetrical factors (stage of cervical dilation, and pharmacological induction of uterine contractions and their frequency) and other factors such as age, parity, previous caesarean sections, could complicate the assessment of the postoperative pain.[4,12]

The strength of our study is the attempt to minimize the impingement of parameters that affect circadian rhythmicity by enrolling patients with common everyday lifestyle and regular feeding and sleeping schedule, and by performing the study in the same season in order to better detect endogenous rhythms. The limitations of our study included the lack of synchronization of the subjects' circadian time organization by not checking cortisol or melatonin plasma levels (rhythm markers), or the identification of an individual's innate circadian phenotype. The speed of onset of the effects of local anaesthetics was also not examined and pre-existing pain was not investigated. Finally, postoperative pain intensity was measured in all groups where both elective and urgent caesarean sections were performed, except one (night group).

CONCLUSIONS

Our findings suggested a circadian variation of spinal block's duration, with lowest duration noted at night, maximal duration in the daytime period, and maximal analgesia duration at noon. We assume that the time of administration contributes to anaesthesia duration when local anaesthetics are administered intrathecally and that the intensity of postoperative pain after anaesthesia's regression is partially related to circadian conditions. Due to the lack of recently published data, further research is needed to confirm our findings. Determining how spinal anaesthesia affects the internal clock is not only of scientific interest but also holds potential clinical relevance. The administration of local anaesthetics based on the circadian patterns of drug activity allows the optimization of the drug effect by adjusting the suitable dose during the day. Pain relief could also be increased by manipulation of the timing of drug administration.

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Циркадные эффекты невральной блокады с интратекальным введением левобупивакаина и фентанила при кесаревом сечении

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Дата получения: 19 октября 2020 ♦ **Дата приемки:** 8 февраля 2021 ♦ **Дата публикации:** 28 февраля 2022

Образец цитироания: Nikouli E, Chloropoulou P, Karras G, Kiamiloglou B, Tsigalou C, Vogiatzaki T. Circadian effects on neural blockade of levobupivacaine and fentanyl intrathecal administration for caesarian section. Folia Med (Plovdiv) 2022;64(1):49-54. doi: 10.3897/folmed.64.e59831.

Резюме

Введение: Циркадные вариации биологических ритмов влияют на фармакологические свойства многих анестетиков, предполагая циркадные паттерны активности местных анестетиков при обезболивании родовой боли с важными различиями между дневными и ночными фазами.

Цель: Мы исследовали, существует ли ритмическая изменчивость эффекта интратекальной смеси левобупивакаина и фентанила перед дневным периодом в условиях кесарева сечения.

Материалы и методы: Восемьдесят рожениц поступили на операцию кесарева сечения, как в экстренном, так и в плановом порядке, и были разделены на пять равных групп (A, B, C, D и E) в зависимости от времени интратекального введения препарата. Всем пациентам вводили одинаковые дозы левобупивакаина и фентанила.

Для оценки сенсорной и моторной блокады и боли после анестезии применяли укалывание и холодовую пробу, четырёхбалльную модифицированную шкалу Bromage (0–3) и цифровую шкалу (NRS 0–10). Регистрировали продолжительность сенсорной и моторной блокады, продолжительность обезболивания и исход болевого синдрома при первом запросе на обезболивание.

Результаты: Выявлены статистически значимые различия в исследуемых группах по длительности двигательной и сенсорной блокады и баллам боли при первом послеоперационном запросе на обезболивание. Отмечено увеличение продолжительности моторной блокады в группах А, Б и С ($p<0.001$) и увеличение продолжительности сенсорной блокады и обезболивания в группах А, Б ($p<0.001$). Более высокие показатели боли при первом запросе на послеоперационное обезболивание были зарегистрированы в группе Е ($p<0.001$).

Заключение: Настоящее исследование сосредоточено на значительном влиянии циркадианных ритмов на эффективность местного анестетика левобупивакаина и фентанила во время кесарева сечения.

Ключевые слова

кесарево сечение, циркадные эффекты, местные анестетики, боль, спинномозговая анестезия