Chronotherapeutics of Intrathecal Fentanyl Added Bupivacaine for Labour Analgesia

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Abstract

Chronotherapeutics is the optimization of pharmacotherapies, taking into consideration rhythm-dependence in the kinetics and dynamics of medications plus predictable-in-time variability in the manifestations and severity of human disease. The aim of the present work was to determine whether the efficacy and side-effects of intrathecally administered mixture of a small dose of fentanyl and bupivacaine, to relieve labour pain, is influenced by the hour of administration.

One hundred parturients requesting neuroaxial labour analgesia were assigned to one of four equal groups based on the time period when the intrathecal mixture was administered. Group E= evening, group N= night, group M= morning and group AN= afternoon. Maternal demographic and obstetric data, and the characteristics of the intrathecal blocks were recorded. Demographic data, gestational age and cervical dilatation were similar in the four groups.

The incidence of oxytocin use was lower in E & N groups than M & AN groups. The base-line visual analog pain score (VAPS) was higher in E & N groups than in M & AN groups. The onset of analgesia was delayed in E & N groups than M & AN groups [8.6 (3.4), 8.2 (3.1) Vs 6.5 (2.5), 6.6 (2.6), mm respectively].

There were no significant cant differences between groups as regard the upper sensory level, the number of parturients with detectable motor block or side effects.

The duration of analgesia was shorter in groups E and N than in groups M & AN [75 (22) & 71 (19) Vs 108 (33) & 102 (31) mm respectively]. Maternal and midwife satisfaction scores were lower in groups E & N than in groups M & AN but no significant difference at 30 mm and at reinjection.

Conclusion: Fentanyl and bupivacaine exhibit a temporal pattern of kinetics and dynamics when administered intrathecally for labour analgesia and this should be considered in future comparative studies and in analysis of previous studies and clinically to administer the suitable dose over the 24 hours of the day.

Introduction

Chronobiology is the study of biologic rhythms and biologic time structure. Medical chronology in particular is concerned with circadian (24-h) influences on human diseases such as their occurrence or variation in severity over 24-h and/or the effects of medical treatments (1).

Body rhythms affect the pharmacokinetics and pharmacodynamics of medications. A major goal of medical chronobiology is chronotherapeutics, the optimization of pharmacotherapies, taking into consideration rhythm-dependencies in the kinetics and dynamics of medications plus predictable-in-time variability in the manifestation and severity of human disease (2).

The induction of labour analgesia with intrathecal (IT) 25 ug fentanyl and 2.5 mg bupivacaine has gained much popularity with the introduction of the combined spinal epidural (CSE) technique (3,4).

These small doses of fentanyl and bupivacaine provided complete and satisfactory analgesia during labour with less adverse effects on the mother and fetus. (5)

The rational is that these agents work at two distinct sites - the local anesthetic at the nerve axon and the opioid at the spinal cord receptor- to eliminate pain via a combined and possibly synergistic mechanism. (6)

A temporal pattern (circadian rhythm) of the kinetics and dynamics of local anesthetics is demonstrated in dental and skin anesthesia, and of opioids is demonstrated in analgesic effects, with an important variation of action related to the hour of administration (7).

The aim of this prospective study was to
determine whether the efficacy and side effects of intrathecally administered mixture of a small doses of fentanyl and bupivacaine to relieve early labour pains is influenced by the hour of administration, i.e. is there a temporal pattern?

**Methods**

After obtaining written and informed consent from patients and agreement from the Ethical Committee of Hospital, we enrolled 100 women with the following inclusion criteria: ASA 1-2, nulliparous, singleton term pregnancy, vertex presentation, active labour with cervix <5 cm, requesting labour analgesia, and the patients were socially synchronized with diurnal activity from 7:00 AM to midnight and nocturnal rest, meaning that patients normally got up in the morning and slept at night.

Exclusion criteria included patients with complicated pregnancies, had abnormal fetal heart rate tracings, receiving antihypertensive drugs and patients had already received analgesics within 12 hours prior to administration of combined spinal-epidural (CSE) analgesia. The 100 parturients requesting neuroaxial labour analgesia were assigned to one of four equal groups based on the time period when the CSE was administered; and according to Aya et al\(^8\) observational study on chronobiology of labour pain perception.

Group E= evening: for time period between 19:01 to 1:00, Group N= night: for time period between 1:01 to 7:00, Group M: morning: for time period between 7:01 to 13:00, and Group AN: afternoon: for time period between 13:01 to 19:00.\(^8\)

Each parturient received an intravenous infusion of 500 ml lactated ringer’s solution over 10mim before induction of intrathecal (IT) analgesia. Each patient received bupivacaine 2.5 mg, and fentanyl 25 ug IT using a combined spinal-epidural technique (CSE). The CSE procedure was performed with the Braun Escopan (R) combination needle (Braun Medical SA, Boulogne, France). Patients were placed in the sitting position, and an 18-gauge Touhy needle was inserted by using the loss of resistance to air technique. After insertion of a 27-gauge pencil-point needle and intrathecal (IT) bupivacaine and fentanyl injection (Zero time), a 20-gauge multiorifice catheter was inserted in the epidural space. The epidural catheter was left in position, without other drug administration until patients requested further analgesia while the patient slept on her left side.

The maternal demographic data were recorded (age, height, and weight) and obstetric data (Gestational age, cervical dilatation, oxytocin use, and base-line visual analog pain scores (VAPS) were also recorded).

The onset of analgesia (t\(_1\)) is defined as the time from IT injection (zero time) to the time of the first comfortable uterine contraction (freedom from pain regardless of block height).

The duration of analgesia (t\(_2\)) is defined as the time from IT injection to the time when patients requested additional analgesia. Subsequent analgesia was maintained using 10 ml of (bupivacaine 0.125% + fentanyl 1 pg/ml) via the epidural catheter and repeated when needed.

The blood pressure, heart rate, arterial oxygen saturation, and fetal heart rate were monitored before the IT injection and thereafter throughout the procedure, using a non invasive monitor. The incidence of maternal hypotension, bradycardia and hypoxia, and fetal bradycardia was recorded if occurred, where hypotension was defined as a decrease in systolic arterial pressure >20% of baseline, and was treated with a 6 mg intravenous (IV) ephedrine bolus as necessary.

Maternal bradycardia was defined as heart rate less than 60 beat/min and was treated with 0.4 mg artopine I.V. Hypoxia was defined as a decrease in \(\text{SPo}_2\) less than 94% on room air and was treated by \(\text{O}_2\) inhalation.

Fetal bradycardia was defined as FHR <100 beats/mm, and was managed accordingly.

At 15 and 30 mm after injection, the upper sensory level was determined by loss of discrimination of cold sensation in the midclavicular line using an alcohol swab, and motor block was assessed simultaneously using the modified Bromage score (0 = able to straight leg raise the whole lower limb at the hip, 1 = able to flex the knee but unable to straight leg raise, 2= able to move the foot but unable to flex the knee,3= non movement of the lower limb), the number of parturients with detectable motor block i.e. modified Bromage score >0 was recorded.\(^9\)
Assessment of labour pain intensity was made on a visual analog pain scale (VAPS), each patient was presented with a line 100 mm long and was told that the left end represented no pain (0) and the right end represented the worst pain imaginable (100). They were then asked to mark a mark on the line to indicate the intensity of their pain at the peak of contraction.\(^9\) The VAPS was recorded before IT injection as a baseline, at 15 and 30 mm of IT injection, and at reinjection in the epidural catheter.

**NB.** If pain relief was unsatisfactory (VAPS >30 mm) by 15 mm after IT injection, the cases were then excluded from data collection.

The incidences of nausea, vomiting and pruritis were assessed by direct questioning of the parturients at 5-mm intervals in each group and cases were recorded and treated if necessary.

Maternal and midwife satisfaction scores were assessed and recorded at the end of IT analgesia by asking the patient and the midwife respectively to mark a mark on a 0-100 mm line, 0 mm = unsatisfied and 100 mm = full satisfaction,\(^9\)

Non-parametric data were analyzed using the Chi-square or Mann-Whitney U tests, and parametric data were analyzed with the Student’s \(t\) test, using SPSS version 8. P <0.05 was considered statistically significant.

**Results**

One hundred patients completed the study. There were no failures in locating the epidural space or obtaining CSF in any patient. There were no significant differences between the four equal groups as regard the age, height, weight, gestational age and cervical dilatation (Table 1). The number of parturients received oxytocin was lower in group E and N than in group M and AN i.e. 7 and 8 versus 11 and 10 respectively (Table 1). The base-line VAPS was significantly higher in groups E and N than in groups M and AN i.e. 84 [67-92] and 85 [72-93] versus 72 [61-89] and 73 [69-90] mm respectively (Table 1).

The onset of analgesia was significantly delayed in groups E and N than M and AN 8.6 (3.4) mm and 8.2 (3.1) min Vs 6.5 (2.5) min and 6.6 (2.6) min respectively (Table 2).

At 15 and 30 mm although the upper sensory level (to cold) was higher and the number of parturients with detectable motor block was lower in groups E and N than in groups M and AN there were no significant differences between the four groups (Table 2).

The VAPS was significantly higher in groups E and N than in groups M and AN at the base line and at 15 mm, but no significant differences at 30 mm or reinjection (Table 2).

The duration of analgesia was significantly shorter in groups E and N than in groups M and AN 75 (22) min and 71(19) min versus 108 (33) min and 102 (31) mm respectively (Table 2).

Maternal satisfaction scores and midwife satisfaction scores were significantly higher in groups E and N than M and AN (Table 2).

**Discussion**

In the present study we demonstrated that the frequency of oxytocin use, the base-line VAPs, the onset of analgesia, the duration of analgesia and the maternal and midwife satisfaction score obtained after administration of the same dose of fentanyl and bupivacaine varied significantly according to the time of drug administration.

We observed a rhythmic variation of labour analgesia characteristics when we used 25 ug fentanyl plus 2.5 mg bupivacaine throughout the day period with a 6 hour component.

In agreement with our study Debon et al\(^{10}\) showed that epidural ropivacaine for labour analgesia exhibits a temporal pattern with important differences among diurnal and nocturnal phases, and that the largest intraday variation of analgesia duration among groups reached 28%.

In another study, Debon et al\(^{11}\) demonstrated that the duration of analgesia obtained after administration of the same dose of intrathecal sufentanil varied significantly according to the time of drug administration.

They observed a rhythmic variation of analgesia duration of intrathecal sufentanil throughout the day period with a 12-h component. The mean duration of analgesia in
their study were 109. ± 5 and 76.9 ± 5 minutes at morning and night, respectively, demonstrated that the daily variation was approximately 30% of the 24-h mean.

Pan et al.\textsuperscript{(12)} found that the duration (mean ± SD) for intrathecal fentanyl labour analgesia was 92 ± 6 minutes for daylight period group and 69 ± 5 minutes for dark night period group (P<0.01).

We can understand and explain the circadian rhythm of various physiological processes and chronotherapeutics by reviewing the studies of Akashi et al.\textsuperscript{(13)} They reported that a cell-autonomous circadian gene is fundamental for the generation of circadian rhythm through two transcriptional elements, one for rhythm generation and the other for control. Also Ishida et al.\textsuperscript{(14)} revealed that light is a powerful synchronizer for the circadian rhythm and that light induces gene expression in the adrenal gland via the sympathetic nervous system. Moreover, this gene expression accompanies the surge of plasma and central nervous system corticosterone levels. Again Mishuk and Saiapin\textsuperscript{(15)} while explaining the endocrine mechanisms of the pathogenesis of nocturnal asthma stated that there was a shift in the maximum secretion of estradiol from daylight to night hours, accompanied by presence of hypoprogesteronemia and absolute and relative adrenal cortical glucocorticoid deficiency at night.

These endocrinal differences may be the cause of more uterine contractility (labour pain intensity) at night hours, than daylight hours and explain the cause of the higher VAPS, the less use of oxytocin, the delayed onset and shorter duration of analgesia, and the less satisfaction of parturients and midwives at night-hours. Also Hastings et al.\textsuperscript{(16)} stated that the pineal gland transducers photic information into an endocrine signals and that photo period associated with increased pineal melatonin signals potentiate the function of endogenous opioids, which are probably related to chronopharmacologic differences in the effects of exogenous intrathecal opioids and local anesthetics. Other mechanisms are thought to be involved in toxicity and efficacy of intrathecal local anesthetics circadian rhythm. First, circadian changes in membrane nerve cell permeability to ions were reported by Njus et al.\textsuperscript{(17)} In the same way, Moore Ede et al.\textsuperscript{(18)} showed that the cell potassium concentration and the K⁺ efflux from cells has a circadian rhythm. Also Reinberg et al.\textsuperscript{(19)} reported a circadian rhythm of catecholamine release, where norepinephrine is an inhibitory neurotransmitter in the central nervous system by stimulating the \(a_2\) adrenergic receptor increases the pain threshold and is cardiovascular stimulant where it increases the arterial blood pressure by stimulating the \(a_1\) adrenergic receptors in blood vessels.

Ke and Lukas\textsuperscript{(20)} found that nicotinic acetylcholine receptors (nAChR) are potential targets for steroids, where acute or short term (5 mm) preexposure to steroids such as progesterone, estradiol, corticosterone, or dexamethasone inhibits function of human nAChR in the nervous system and stated that nAChrs are diverse members of the ligand-gated ion channel superfamily of neurotransmitter receptors and play critical roles in chemical signaling throughout the nervous system. In addition Vidar et al.\textsuperscript{(21)} stated that prostaglandins are important mediators of pain. By inhibiting the phospholipase enzyme, the glucocorticoids block both the cyclooxygenase and the lipoxygenase pathway in the inflammatory chain reaction thus, these compounds may be effective in reducing the incidence and intensity of pain. From these previously mentioned studies we can explain the results of our study as following:

Daylight is accompanied by an increased secretion of endogenous opioids, corticosterone, progesterone, catecholamines and melatonin and the reverse occur at night and these hormones modulate pain incidence and intensity.

We concluded that the hour of drug injection contributes to analgesia onset, duration and satisfaction when the same dose of fentanyl add to bupivacain were administered intrathecally during labour.

Opioids and local anesthetics exhibit a temporal pattern of kinetics and dynamics when administered intrathecally, with a delayed onset, shorter duration and less satisfaction in the night period compared with the diurnal phase. Chronobiology of intrathecal opioids and local anesthetics should be incorporated in future comparative studies and in analysis of previous studies. Also chronotherapeutics of opioids and local anesthetics...
when given intrathecally should be considered to administer a suitable dose (smaller) at day time and another suitable dose (larger) at night time, to optimize effects and reduce side effects.

References
### Table 1. Maternal demographic and obstetric data:

<table>
<thead>
<tr>
<th></th>
<th>Group E n=25</th>
<th>Group N n=25</th>
<th>Group M n=25</th>
<th>Group AN n=25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>21.8 (4.64)</td>
<td>22.7 (4.22)</td>
<td>23.7 (4.6)</td>
<td>22.0 (4.72)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161.0 (6.69)</td>
<td>163.3 (5.38)</td>
<td>159.7 (6.34)</td>
<td>161.9 (6.87)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74.7 (11.17)</td>
<td>72.1 (10.11)</td>
<td>73.3 (13.25)</td>
<td>72.9 (12.70)</td>
</tr>
<tr>
<td>Gestation (week)</td>
<td>39.9 (1.3)</td>
<td>39.3 (1.2)</td>
<td>39.6 (1.1)</td>
<td>39.7 (1.5)</td>
</tr>
<tr>
<td>Cervical dilatation (cm)</td>
<td>4.3 (0.96)</td>
<td>4.1 (1.12)</td>
<td>4.5 (1.11)</td>
<td>4.2 (1.03)</td>
</tr>
<tr>
<td>Baseline VAPS (mm)</td>
<td>84 67-92 *</td>
<td>85 72-93 *</td>
<td>72 61-89</td>
<td>73 69-90</td>
</tr>
</tbody>
</table>

- Results are expressed as mean (SD), median [interquartile range], and count as appropriate
- n= number
- VAPS= visual analog pain score
* p<0.05

### Table 2. Characteristics of block in patients given the studied drugs intrathecally

<table>
<thead>
<tr>
<th></th>
<th>Group E n=25</th>
<th>Group N n=25</th>
<th>Group M n=25</th>
<th>Group AN n=25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of analgesia (mm)</td>
<td>8.6 (3.4)*</td>
<td>8.2 (3.1)*</td>
<td>6.5(2.5)</td>
<td>6.6 (2.6)</td>
</tr>
<tr>
<td>at 30 mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of parturients with detectable motor block (n)</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Bromage score &gt;0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at 15 min</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>at 30 min</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>VAPS (mm)</td>
<td>84[67-92]*</td>
<td>85[72-93]*</td>
<td>72[61-89]</td>
<td>73[69-90]</td>
</tr>
<tr>
<td>Baseline</td>
<td>7 [0-15]*</td>
<td>8 [0-15]*</td>
<td>5[0-10]</td>
<td>5 [0-10]</td>
</tr>
<tr>
<td>at 15 mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at 30 min</td>
<td>5[0-10]</td>
<td>6[0-10]</td>
<td>3[0-10]</td>
<td>4[0-10]</td>
</tr>
<tr>
<td>Duration of analgesia (min)</td>
<td>75 (22)</td>
<td>71(19)</td>
<td>108 (33)*</td>
<td>103 (31)*</td>
</tr>
<tr>
<td>Pruritis(n)</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Nausea &amp; vomiting (n)</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Maternal hypotension required Ephedrine (n)</td>
<td>8</td>
<td>7</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Maternal bradycardia required Atropine (n)</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Maternal respiratory depression (n)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fetal bradycardia</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Maternal satisfaction score</td>
<td>73 [70-80]</td>
<td>76 [70-80]</td>
<td>87 [80-95]*</td>
<td>85[80-90]*</td>
</tr>
<tr>
<td>Midwife satisfaction score</td>
<td>76 70-80</td>
<td>78 [75-85]</td>
<td>90 85-95 *</td>
<td>87[80-95]*</td>
</tr>
</tbody>
</table>

Results are expressed as mean (SD), median [interquartile range], and count as appropriate; n=number; VAPS= visual analog pain score; E= evening, N= night, M= morning & AN afternoon.
* p <0.05