Duration of Spinal Anesthesia with Bupivacaine in Chronic Opium Abusers Undergoing Lower Extremity Orthopedic Surgery

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Background: It has been demonstrated that chronic opium abusers have lower thresholds for pain. Spinal anesthesia is a common procedure in anesthesia, which is performed through administration of drugs (usually local anesthetics) in the intrathecal space, to produce temporary pain relief. The aim of this study was to determine whether chronic opium abuse could have any possible effect on the duration of spinal block by bupivacaine.

Methods: In a case-control study, 50 opium abusers and 50 nonabusers undergoing lower extremity orthopedic operations were selected from the patients admitted in Taleghani Hospital in Tehran for elective surgery. The study parameters were assimilated as much as possible, including the method of anesthesia.

Results: No statistically significant difference was noted between the two groups regarding the age, sex, and duration of surgery; while, the duration of sensory block was much shorter in the opium abusers (86.6 ± 15.7 minutes) compared with the nonabusers (162 ± 22.1 minutes) (P < 0.0001).

Conclusion: The study suggests a shortened duration of spinal block with bupivacaine in opium abusers. The results can propose a number of possible mechanisms including cross-tolerance mechanisms between local anesthetics and opioid compounds at the level of spinal neurons. Further molecular studies at the level of spine are suggested.

Keywords: Bupivacaine • cross-tolerance • opium abuse • pain receptor • spinal anesthesia

Introduction

We have observed many times in our practice that the duration of spinal anesthesia in opium abusers is shorter than nonabusers. This finding led us to a previous investigation which had compared the duration of spinal block with lidocaine in opium abusers with nonabusers for lower abdominal surgical operations. The current study was designed to compare the duration of sensory and motor spinal block with bupivacaine in opium abusers with nonabusers undergoing lower extremity orthopedic procedures.

The opioid analgesics, exemplified by morphine, are common treatment for severe acute and chronic pains (both malignant and nonmalignant). Prolonged use of opioids is associated with a state of progressive need for higher doses to achieve a constant analgesic effect; a phenomenon known as analgesic tolerance, the exact underlying mechanisms of which are not fully understood. Although some hypotheses have been proposed, including changes in the shape, function, or the concentration of the opioid receptors, a change in the endogenous opioid peptides, which can interfere with exogenous opiates, has been considered as an important proposed hypothesis.

New insights into pain and its regulation in...
opium or opioid abuser patients have been introduced, especially regarding the cross-interaction and cross-tolerance between local anesthetics and opioid compounds at the receptor level of the spinal cord. These effects have been observed in clinical practice as shorter than normal duration of spinal anesthesia for the opium abusers, which needs supplemental analgesics and sedatives for the operations.

The clinical phenomenon studied here could be linked to a number of previously observed conditions attributed to a change in the spinal neuronal activity, their related mediators, and the neuronal cellular channels and receptors, in the presence of exposure to repeated doses of opioids. These findings demonstrate that the neuroplastic changes elicited by opioid exposure includes adaptive changes in a way to promote increased pain transmission and consequent diminished antinociception, appeared clinically as opioid tolerance. Also, opioids could ensue in a number of adaptive mechanisms in the pain system, which induces exaggerated pain sensation due to descending facilitation, up-regulation of spinal dynorphin, and enhanced, evoked release of excitatory transmitters from primary afferents; in response to continuous and repetitive exposure to opioids. These adaptive changes happen to indicate the need for more sophisticated assessment of the clinical consequences of long-term opioid administration.

This study was planned to compare the duration of effect of intrathecal administration of 0.5% bupivacaine in opium abuser and nonabuser patients undergoing lower extremity operations. The opium abusers, if proved to have a lower duration of action of intrathecal bupivacaine should be managed in a way to lengthen the duration of anesthesia and analgesia, either by adding intrathecal opioid adjuvants or adding supplemental intravenous or inhalational anesthetics to the spinal anesthesia to be suitable for the operation.

Materials and Methods

The proposal of the study was confirmed by Ethics Committee, Deputy of Research Affairs, Taleghani Hospital, Shaheed Beheshti University of Medical Sciences, Tehran, Iran.

In a descriptive-analytical case-control study, the target population was considered as all the patients admitted in the operating room of the Taleghani Hospital during a six-month period. Of these patients, 100 patients who were candidates for elective lower extremity orthopedic surgery were selected according to the following inclusion and exclusion criteria. The selected patients were allocated into two groups according to their history of opium addiction. The included patients were those who signed the written informed consent, were scheduled for elective lower extremity orthopedic surgery, were in the age range of 18 – 65 years, and were in the height range of 150 – 185 centimeters. Those patients enrolled in the study as the case group had been chronic opium abusers, using opium preparations orally or by an inhalation route, as a regular habit, at least for one year. In addition, they described subjective symptoms of withdrawal with drug cessation. The patients in the control group, by self report, had no history of opium use for any reason for the preceding two years.

The excluded patients were those who refused subarachnoid block, abused or illicitly used other substances, had preexisting cardiac or pulmonary diseases, or had any sign or history denoting past or present neuropathy.

All the patients, regardless of their group, were visited the night before the surgery by the same anesthesiologist (among the authors), and were informed about the study and the enrollment process to make them certain regarding their treatment status and the process of the study. Also, a premedication dose of promethazine was prescribed (0.05 mg/kg intramuscular) one hour before the surgery, accompanied by a 10 mg diazepam tablet per 70 kg body weight. The patients in the case group were recommended to use their usual daily dose of opium. This was discussed in a private room with each opium abuser patient by the anesthesiologist who had visited the patient the evening prior to the surgery.

All the patients were Non Per Os (NPO) (nothing by mouth) for eight hours before the scheduled operation time.

The anesthesiologist who had visited all the study patients the evening prior to the surgery was not the same individual who performed the subarachnoid block and documented the sensory and motor level. After initiating standard monitoring (electrocardiography, pulse oxymetry, noninvasive blood pressure, and heart rate), the patients received 500 mL Ringer’s solution over 10–15 minutes. Subarachnoid blocks were performed in the sitting position under sterile
conditions. The L3-L4 interspace was selected and a 25 gauge Whitacre spinal needle was inserted via a midline approach. The needle bevel was oriented cephalad while 20 mg (4 mL) of 0.5% preservative-free hyperbaric bupivacaine was injected at a rate of 1 mL every five seconds. The patient’s position was changed to neutral supine after drug injection. All patients received 1 mg intravenous midazolam for sedation after spinal administration of the drug and a T8 to T10 level of anesthesia was gained with the help of position maneuvers. For confirmation of the effective performance of spinal anesthesia technique and also for monitoring the level of anesthesia, the skin pinprick test was used after drug administration to document the subarachnoid sensory block. The level of anesthesia was checked by the pinprick test, every 10 seconds for the first minute and every minute thereafter until 10 minutes. Then, the level of anesthesia was checked and documented every 10 minutes from the minute 10 to 180 after subarachnoid drug administration. If any patient had pain at any time during the operation, the anesthesia method would be changed without any additional intravenous analgesics to general anesthesia, by using an intravenous drug such as opioids, propofol, thiopental, or their combination, accompanied by an appropriate dose of relevant muscle relaxant drugs. Meanwhile, the subarachnoid effects of the local anesthetic drug (i.e., spinal anesthesia) were considered to be terminated and the exact time of spinal anesthesia termination was recorded. In those patients who did not experience pain during the surgery, the anesthesia method would be changed without any additional intravenous analgesics to general anesthesia, by using an intravenous drug such as opioids, propofol, thiopental, or their combination, accompanied by an appropriate dose of relevant muscle relaxant drugs. Meanwhile, the subarachnoid effects of the local anesthetic drug (i.e., spinal anesthesia) were considered to be terminated and the exact time of spinal anesthesia termination was recorded. In those patients who did not experience pain during the surgery, the total time for effective spinal sensory anesthesia was recorded from the time of drug injection up to the time that a two-segment regression in the level of block was detected and documented (using a pinprick test).

Also, from the minute 10 to 180, every 10 minutes, the patients were checked and the first time they could move any of their toes was considered as the termination of motor block.

The patients’ data were kept fully confidential, and the patients could decide to leave the study just by informing one of the researchers.

Data entry and analysis were performed by SPSS software (version 11.5). For data analysis, Student t-test and Chi-square test were used and P < 0.05 was considered significant.

Results

The two groups had no statistically significant differences regarding age, body weight, sex, and duration of the surgery (Tables 1 and 2). The duration of opium abuse in the cases group was 4.5 ± 2.5 years.

The duration of spinal anesthesia was significantly shorter in the abusers group (Tables 3 and 4). The duration of the sensory block was 86.6 ± 15.7 minutes (mean ± standard deviation) in the abusers and 162 ± 22.1 minutes in the nonabusers groups (P < 0.0001, Table 3). The duration of the motor block was 114.4 ± 9.2 minutes in the abusers and 185.7 ± 28.4 minutes in the nonabusers groups (P < 0.0001, Table 3).

Discussion

It has been mentioned that a number of factors can affect the duration of block in spinal anesthesia including the type of local anesthetic, drug dosage, and drug adjuvants such as opioids and epinephrine.2, 5 The authors had demonstrated the shortened duration of sensory block with intrathecal lidocaine in their previous study.1 The present study demonstrated shortened duration of sensory and motor block with intrathecal bupivacaine in chronic opium abusers.

The opioid receptor system signals and modulates a multitude of effects, and under certain conditions mediates hyperalgesia rather than analgesia.14 A multitude of studies, reviewed by Angst and Clark have tried to define the exact mechanisms creating opioid-induced hyperalgesia, which concluded that opioidergic mechanisms can act in a way contradictory to analgesic mechanisms.

Table 1. Distribution of age, body weight, and duration of surgery in the two groups. *

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Body weight (kg)</th>
<th>Duration of surgery (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic opium abusers</td>
<td>Nonabusers</td>
<td>P value (for t-test)</td>
</tr>
<tr>
<td>37 (14.3)</td>
<td>66.2 (9.7)</td>
<td>95.3 (19.3)</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± standard deviation (SD).

Table 2. Distribution of sex in the two groups.

<table>
<thead>
<tr>
<th></th>
<th>Chronic opium abusers</th>
<th>Nonabusers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>28</td>
<td>24</td>
</tr>
<tr>
<td>Female</td>
<td>22</td>
<td>26</td>
</tr>
</tbody>
</table>

Chi-square test, degree of freedom = 1, P > 0.05.
and enhance sensitivity to pain.\textsuperscript{14} The origin of such mechanisms have been proposed to be in the afferent neurons, spinal cord tissue, and supraspinal centers of the central nervous system.\textsuperscript{14} At the spinal level, excitatory amino acid neurotransmitters and receptor systems are implicated in pain sensitivity enhancement.\textsuperscript{14} Tonic activation of descending pain facilitation,\textsuperscript{2} possibly due to increased expression of mediators such as cholecystokinin,\textsuperscript{4 – 6} calcitonin gene related peptide (CGRP),\textsuperscript{1} and substance P in a number of spinal cord segments\textsuperscript{2, 15}, also, accompanied by pronociceptive neuroplastic changes within the spinal cord neurons have been proposed as the other possible mechanisms.\textsuperscript{3}

Taken together, these studies propose that there are a number of opioid-induced abnormal pain states, presented clinically and behaviorally as antinociceptive tolerance; these pain states are unrelated, both in their clinical appearance and in pain quality, to the original pain complaint for which opioid therapy was planned and executed.\textsuperscript{16}

Vanderah and colleagues demonstrated that administration of lidocaine in the rostral ventromedial medulla blocked opioid-induced pain.\textsuperscript{11} Allen and Dykstra, and Lai et al stated that N-methyl D-aspartate (NMDA) receptor antagonists could have an effective role in the prevention of a process leading to morphine development.\textsuperscript{13, 17} Lai and her colleagues proposed that there exists in many types of chronic pain, a critical role for voltage-gated sodium channels in many types of chronic pain.\textsuperscript{17}

Considering these studies and remembering the down-regulation of the opioid receptors and their related intracellular mechanisms in chronic opium abusers,\textsuperscript{14, 17} a synchronized drug tolerance to the effects of local anesthetics in the spinal cord during intrathecal administration of these drugs seems a possible mechanism for shorter duration of block in opium abusers in our study. This tolerance to the effects of intrathecal local anesthetics seems a cross-tolerance mechanism, which is a common finding for a number of other pharmaceutical products in the spinal cord.\textsuperscript{5 – 8}

Lower than normal thresholds of the neurons for pain sensitization and possible neuroplastic changes in spinal cord receptors of pain, possibly results in lower efficacy of the intrathecal local anesthetics; a finding which can be named as spinal cross-tolerance to the effects of local anesthetics.

It has been mentioned in some animal studies that there are a number of other receptors affected by opioids, besides the classic opioid receptors, both in the central and the peripheral nervous system.\textsuperscript{5 – 8, 14, 18, 19} Also, a number of studies have proposed some structural similarities between opioid and local anesthetic receptors in the spinal cord.\textsuperscript{18, 19} Even more interesting is the introduction of newer drugs that affect simultaneously both the opioid and local anesthetic drug receptors in the spinal cord.\textsuperscript{14 – 20} These findings suggest both structural and/or functional similarities between opioid and local anesthetic receptors at the spinal cord level. Would these similarities be proven, they could somewhat explain that in chronic opium abusers, decreased tolerance to opium compounds simultaneously creates a state of tolerance to local anesthetics at the level of the spinal cord.

The above-mentioned discussions are topics that could lead to further complementary studies to explain shorter duration of local anesthetic drugs block after intrathecal administration, which may help understanding more about transduction and processing mechanisms of pain in the central nervous system.\textsuperscript{14}

The findings of this study suggest a shorter duration of neural block, both sensory and motor, after induction of spinal anesthesia with intrathecal administration of bupivacaine in chronic opium abusers compared with other similar patients who are not currently abusing opium. So, such patients should be managed in a way to lengthen the duration of anesthesia and analgesia, either by adding intrathecal opioid adjuvants to the local

| Table 3. Duration of spinal anesthesia (sensory and motor block in minutes) in the two groups.* |
|---------------------------------|------------------|------------------|
|                                | Chronic opium abusers | Nonabusers | P value (for t-test) |
| Sensory block (min)            | 86.6 (15.7)        | 162 (22.1)      | <0.0001          |
| Motor block (min)              | 114.4 (9.2)        | 185.7 (28.4)    | <0.0001          |

*Data are presented as mean ± standard deviation.

| Table 4. Level of sensory block in the two groups. |
|---------------------------------|------------------|------------------|
|                                | Chronic opium abusers | Nonabusers |
| 8th thoracic level (T8)         | 8                 | 8               |
| 9th thoracic level (T9)         | 34                | 27              |
| 10th thoracic level (T10)       | 8                 | 15              |
| Total                          | 50                | 50              |
anesthetic solution or adding supplemental intravenous or inhalational anesthetics to the spinal anesthesia, in such a way to enhance the length of the operation.

Acknowledgment

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References


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