Effect of Fentanyl in Spinal Anesthesia With Bupivacaine in Opium Abusers

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Background: Spinal anesthesia is a common procedure in the anesthesia. In some studies it has been shown that chronic use of opioids is associated with shorter duration of spinal anesthesia when local anesthetics are applied.
Objectives: This trial was conducted in order to determine effect of fentanyl on the duration of spinal block by bupivacaine in chronic opium abusers who undergo spinal anesthesia and have lower thresholds for pain.
Patients and Methods: This study was a randomized clinical trial in which 50 opium abusers (25 patients in each group) undergoing lower extremity orthopedic surgeries with spinal anesthesia were selected. The patients were randomly divided into two groups. The study group received 15 mg hyperbaric bupivacaine 0.5% plus 25 μg fentanyl, while the control group received 15mg hyperbaric bupivacaine 0.5% plus 0.25 mL normal saline.
Results: All randomly selected cases were male (44.7 ± 13.6 year). The mean duration of sensory block was much longer in the study group (87.8 ± 7.22 minutes) in comparison with the control group (70.47 ± 5.45 minutes) (P < 0.001). There was no statistically significant difference between the two groups regarding their age and duration of surgery.
Conclusions: Bupivacaine administration in spinal anesthesia for spinal block has a shortened duration in comparison to the combination of bupivacaine and fentanyl in chronic opium abusers.

Keywords: Fentanyl; Anesthesia, Spinal; Bupivacaine

1. Background

Spinal anesthesia is a common procedure in the anesthesia field. It has been showed that chronic opium abusers have lower thresholds for pain. Factors affecting the block duration in spinal anesthesia among others include: type of the local anesthetic agent as well as the drug dosage and drug adjuvant such as opioids and epinephrine (1). Despite the fact that opioids are the primary medication for moderate to severe pain, their overuse is connected with the advancement of tolerance therefore higher dose is needed for pain relieving; however its mechanism has not completely cleared yet (2-4). By the way researchers have proposed some theories in regards to opioids receptors and the endogenous opioids peptides (5-8), it has recently been uncovered that cholecystokinin up-regulates in the rostral ventromedial medulla (RVM) when it get permanently exposed to opioids. Antiopioid and pronociceptive aspects of cholecystokinin are clear. Cholecystokinin can also activate pain relief mechanisms from the RVM upgrading nociceptive transmission at the spinal cord and induced hyperalgesia (4). In some studies it has been shown that chronic use of opioids is associated with shorter duration of spinal anesthesia when local anesthetics are applied. In chronic opioids users, higher doses of opioids are recommended for neuraxial block, because cross-tolerance between orally and epidural administered opioids has been described. Epidural lipophilic opioids (fentanyl, sufentanyl) appear to provide better postoperative pain relief than epidural morphine does in chronic opioids-consuming patients. Also fentanyl is a low molecular weight potent opioid, which make it a good candidate for the mentioned goal (9, 10).

2. Objectives

This randomized clinical trial was conducted in order to compare the duration of spinal anesthesia with bupivacaine alone and in combination with fentanyl in opium abusers undergoing lower extremity orthopedic elective surgical operations.

3. Patients and Methods

This is a double blind randomized controlled clinical

trial. The target population consisted of patients with a history of at least one year opium consumption that were referred to Imam Reza hospital due to recommended lower extremity orthopedic elective surgery from September 2012 to January 2013. The inclusion criteria were as follows: patients older than 25 years old were recommended lower extremity orthopedic surgery, chronic opium consumption (regular usage of opium preparations either orally or by inhalation for at least 1 year). Patients who were excluded from the study were the ones who refused subarachnoid blockage, abused or used other controlled illegal substances, had a preexisting cardiac or pulmonary history or any sign or clinical finding denoting a past or present neuropathy. Sample size was determined by means of a power analysis using the power analysis and sample size software: PASS 2005 (alpha = 0.02, beta = 0.2 and power = 0.8). Patients were divided into two groups of control (bupivacaine) and study group (bupivacaine plus fentanyl). Therefore, 25 patients were enrolled in each group. The patients were randomized by means of blinded opaque envelopes that had been sorted by computer-generated random allocation. In the first step, all patients were completely informed of the study protocol and its possible outcomes or side-effects. This study protocol was approved by the Ethics Committee of the Research Council, Mashhad University of Medical Sciences, Mashhad, IR Iran. A written informed consent was filled in by each patient prior to participation in the trial. All patients were then visited by a single anesthesiologist before their surgery. It was recommended to all patients to continue using their usual daily dosage of the drug. They were NPO (nil per os) for at least 8hrs before operation. Patients received 500-1000 mL of lactated Ringer's solution during 15-20 minutes after the first standard monitoring which consists of electrocardiogram, pulse oxymetry, noninvasive arterial blood pressure and heart rate measurements. Then subarachnoid blocks were performed on the patient in the sitting position considering the aseptic conditions. The L3-L4 or L4-L5 interspaces were entered and a 25-gauge Quincke spinal needle was inserted via a midline approach. The patients in the control group received 15 mg bupivacaine 0.5% with 0.25 mL normal saline; whereas, the study group received 15 mg bupivacaine 0.5% with 25 μg fentanyl.

The study drugs were prepared by a certain technician and delivered to the anesthesiologist; the patients were not aware of the type or the dosage of the used drugs. The total volume was 3.5 mL in both groups. The injection rate was 2 mL every 5 seconds. The patients were placed in the supine position after drug injection. All patients received 1mg IV (Intravenous) Midazolam for sedation after Spinal Anesthesia. A T6-T8 level of anesthesia was achieved with the help of positional maneu-

vers. The anesthesiologist who documented the sensory level was blinded to the patients' group; and also the intrathecal injection was performed by another blind anesthesiologist. The sensory level was assessed with pinprick testing and the level of anesthesia was checked and documented every 10 min up to 120 min after subarachnoid injection. General anesthesia would induce for the patients quickly if they encountered pain at anytime of the operation. Effective spinal anesthesia was calculated from the time the drug was injected (as the beginning point) up to the time a two-segment regression in the level of block (utilizing a pinprick test) was located. Finally the greatest level of sensory block, the time interval for reaching to the maximum level of sensory block and the time needed for achieving a two-fragment regression in the level of sensory block were compared between the groups. For the postoperative analgesia, intravenous pethidine was prescribed by the anesthesiologist to keep the patients pain below 3 of 10 based on visual analog scale (VAS).

3.1. Statistical Analyses

Data entry and analysis were performed by the SPSS software, version 14.0 (SPSS Inc., Chicago, USA). To evaluate the presence of differences between the two groups, unpaired Student's t-, $\chi 2$, or Mann-Whitney tests in cases of non-normal distribution of data were used and a P value < 0.05 was considered as significant.

4. Results

In this study, fifty patients participated and were randomly divided into two groups (Table 1). All randomly selected cases were male. Four patients from the control group did not achieve the desired block level; therefore, they underwent general anesthesia and were excluded from this study. In total, 84.1% of cases in the control group and 100% of those in the study group achieved the desired level of block, but no significant difference was observed between the two groups from this aspect (P = 0.11). There was no statistically significant difference between the two groups regarding their age and duration of surgery. Also the difference between the duration of opium usage was not significant between the two studied groups (P = 0.938). The average anesthesia duration, level of block, time required for reaching to maximum block level and time duration for two-segment regression in both groups have been shown in Table 2. The mean duration of sensory block was much shorter in the control group (70.47 ± 5.45 minutes) compared with the study group (87.8 ± 7.22 minutes) (P < 0.001). Also mean time of achieving to maximum level of block and Mean time of two-segment regression in studied group were significantly higher than control group (P < 0.01).

Table 1. Mean Age of Patients and Duration of Opium Usage Between Two Groups

Variable	Groups, Mean ± SD		P value
	Study Group	**Control Group**	
Age	43.04 ± 14.26	46.52 ± 12.94	0.371
Duration of opium Usage, y	8.08 ± 6.25	7.52 ± 5.53	0.938

Table 2. Mean Time of Anesthesia, Level of Block, Time of Achieving to Maximum Level of Block, Time of Two-segment Regression Between the Two Groups

Variable	Groups, Mean ± SD		P Value
	Control Group	**Control Group**	
Mean time of achieving to maximum level of block, min	17.38 ± 4.06	17.38 ± 4.06	< 0.001 [a]
Mean time of two-segment regression, min	54.76 ± 6.41	54.76 ± 6.41	< 0.001
Mean time of duration between injection until two-segment regression, min	70.47 ± 5.45	70.47 ± 5.45	< 0.001
Mean the maximum level of block (Dermatome)	8.28 ± 2.01	8.28 ± 2.01	0.014

[a] Result of Mann-whitney test.

5. 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 agent, drug dosage and drug adjuvant such as opioids and epinephrine (2, 5). Some studies, however, demonstrated shortened duration of subarachnoid block in those patients with a history of chronic opium abuse (11). They also suggested further investigation for evaluating the effect of additional intrathecal opiates in local anesthetics and as a consequence, its effect on the duration of spinal anesthesia in chronic opium abusers (11). In this study the duration of spinal anesthesia with bupivacaine alone or in combination with fentanyl in opium abuser patients undergoing similar surgical operations was compared and the final results showed that bupivacaine administration in spinal anesthesia for spinal block has a shortened duration in comparison to the combination of bupivacaine and fentanyl in chronic opium abusers. These results were also confirmed by Dabbagh et al. study (11) which demonstrated a shorter duration of neural block in chronic opium abusers who received intrathecal bupivacaine in comparison with nonopium abusers. In another study, Safari et al. (12) showed that the duration of anesthesia in the group to whom bupivacaine-midazolam were used was much longer than bupivacaine-fentanyl group, although they found that these groups had a longer duration of anesthesia than the plain bupivacaine group.

In spite of the fact that there was some trouble in getting some information about the history of opium abuse, this was somehow solved when the anesthesiologist became friend to the patients. Additionally, it had been conceivable to acquire objective documentation of opium abuse without moral considerations, more exact information in regards to the abuse must have been available, nonetheless, this was not conceivable and just subjective evaluations were acknowledged. Similarly, it was troublesome to survey the exact dosage and time interims of opium abuse. Administration of opioids ordinarily leads to absence of pain. However, the opioids receptor system signals and modulates a multitude of effects, mediates hyperalgesia rather than analgesia. The exact mechanism of opioids-induced hyperalgesia is under the investigation of researchers. Recently it has been found that, this mechanism is a complex one which contains numerous potential areas of pain amplification, including rostral ventromedial medulla descending tonic facilitation, pronociceptive spinal dynorphin release, and the excitatory amino acid neurotransmitters interactions with other receptors. Till now, there is a doubt about the pain facilitating processes role in local anesthetic tolerance. Some studies have demonstrated that there is a cross-tolerance of local anesthetics with opioids, while some others believe that some other factors such as voltage-gated sodium channel effects are concerned (5, 6). Notwithstanding the exemplary opioids receptors, various different receptors are influenced by opioids both in the central and the peripheral nervous system (7, 8, 13, 14). On the other hand various studies have shown structural similarities between opioids and local anesthetic receptors in the spinal cord in some parts (15-17). By the way we suggest for further studies for demonstration of the clinical finding of a shorter duration of intrathecal local anesthetic block in those with changed pharmacokinetics especially the opium abusers who can help to our comprehension

of pain control mechanism in the central nervous system and also transduction (18). The main limitation of the study was that the level of motor block after intrathecal anesthesia was not assessed due to surgical limitations. The findings of the present study suggest a shorter duration of neural block after induction of spinal anesthesia with intrathecal administration of bupivacaine in comparison to bupivacaine plus fentanyl in chronic opium abusers. Bupivacaine administration in spinal anesthesia for spinal block has a shortened duration when compared to the combination of bupivacaine and fentanyl in chronic opium abusers.

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Authors' Contribution

The contribution of the authors as mentioned below with their responsibility in the research; Ghasem Soltani: writing the manuscript, conception and designing; Nahid Javdani: obtaining findings; Nahid Zirak: writing the manuscript, final approval of the manuscript; Alireza Bameshki: critical revision of the article, provision materials, patients. Writing the manuscript, data collection, literatures search; Arash Peyvandi: critical revision of the manuscript, provision materials, patients, or resources; Alireza Sepehri Shamloo: writing the manuscript, administrative support, analysis and interpretation.

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