Intrathecal fentanyl with 0.5% bupivacaine heavy in chronic opium abusers

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Abstract

Background: Chronic use of opioids in opium abusers can cause poor pain control and increased analgaesic requirement. We compared the duration of spinal anaesthesia in chronic opium abusers and non-abusers.

Method: This prospective randomised study included 60 American Society of Anesthesiologists (ASA) Grade I or II adults undergoing surgery under spinal anaesthesia with 10 mg bupivacaine, and 25 µg fentanyl in non-opium abusers (Group A); and chronic opium abusers (Group B), and 40 µg fentanyl in chronic opium abusers (Group C). Patients were assessed for onset and duration of sensory and motor blockade and duration of effective analgesia.

Results: Mean time to onset of adequate analgesia in opium abusers was significantly longer in chronic opium abusers than in opium-naive patients. The duration of sensory block and motor block was significantly less in chronic opium abusers than in non-opium abusers. Duration of effective analgesia in groups A, B and C was 255.55 ± 26.84, 217.85 ± 15.15, and 268.20 ± 18.25 minutes, respectively; this difference was statistically significant.

Conclusion: In chronic opium abusers, the duration of spinal anaesthesia is significantly shorter than that in opium non-abusers. The duration of spinal anaesthesia with bupivacaine and fentanyl in chronic opium abusers can be improved by increasing the intrathecal fentanyl dose from 25 µg to 40 µg.

Introduction

The chronic use of opioids in opium abusers can cause poor pain control and increased analgaesic requirement in the postoperative period, as these patients have lower thresholds for pain. Prolonged use of opioids is associated with a state of progressive need for higher doses to achieve a constant analgaesic effect, a phenomenon known as analgaesic tolerance.[1-6] Opioid-induced hyperalgaesia (OIH) is a state of nociceptive sensitisation caused by chronic exposure to opioids, and is characterised by a paradoxical response whereby a patient can become more sensitive to painful stimuli.[7] OIH is a distinct, definable and characteristic phenomenon that explains the loss of opioid efficacy in some patients, and can be a possible cause for an increased perioperative analgaesic requirement.[7] New insight into pain has shown that in chronic opioid users, there is cross-interaction and cross-tolerance between local anaesthetics and opioid compounds at the receptor level of the spinal cord.[8,9] It has been observed that the duration of spinal anaesthesia with local anaesthetics in chronic opium abusers is shorter than that in non-abusers, and that there is also an increased need for supplemental analgaesics and sedatives in opium addicts.[5,10]

Discovery of opioid receptors in the spinal cord triggered the use of intrathecal opioids with local anaesthetics, in spinal anaesthesia.[5,6] Local anaesthetics administered with opioids demonstrate significant synergy. This improves intraoperative and postoperative analgesia, with a negligible incidence of adverse effects such as sedation, nausea, vomiting, pruritus, shivering and respiratory depression.[11]

The present study was designed to compare the duration of sensory and motor block in spinal anaesthesia with 10 mg bupivacaine 0.5% heavy (containing 8% dextrose) and 25 µg fentanyl in opium abusers and non-abusers, and to also study the possible benefit of increasing the intrathecal dose of fentanyl to 40µg in opium abusers who need to undergo lower extremity surgery.

Method

After obtaining written informed consent, a total of 60 patients (20 non-opioid abusers, and 40 opioid abusers) aged 20-80 years, belonging to American Society of Anesthesiologists (ASA) Grade I and II, and scheduled for elective lower extremity surgery under spinal anaesthesia, were divided in into three groups of 20 patients each.

The three groups were:
- Group A (non-abusers): Subarachnoid block with 0.5% hyperbaric bupivacaine 10 mg (2 ml) and fentanyl 25 μg (0.5 ml) diluted by adding normal saline to make a volume of 3 ml.
- Group B (abusers): Subarachnoid block with 0.5% hyperbaric bupivacaine 10 mg (2 ml) and fentanyl 25 μg (0.5 ml) diluted by adding normal saline to make a volume of 3 ml.
- Group C (abusers): Subarachnoid block with 0.5% hyperbaric bupivacaine 10 mg (2 ml) and fentanyl 40 μg (0.8 ml) diluted by adding normal saline to make a volume of 3 ml.

The patients enrolled in groups B and C were chronic opium abusers, using opium preparations such as afeem, morphine, heroin and codeine, taken orally, by injection, or by inhalational route, as a regular habit, and not as a prescription drug for at least last one year. The patients in the control group (Group A) had no history of opium use for any reason for the preceding two years. Exclusion criteria included a patient's refusal, as well as neurological or mental disorders, spinal deformities, local skin infection, a history of allergy to the drugs to be used, coagulation disorders, severe liver disease, impaired renal functions, morbid obesity, ASA physical status III or more, and an age of < 20 or > 80 years.

A routine pre-anaesthetic check-up, comprising a thorough general and systemic physical examination and relevant routine investigation, was performed a day before surgery on all patients. All patients were premedicated with oral diazepam 10 mg and ranitidine 150 mg a night before surgery, and oral diazepam 5 mg with ranitidine 150 mg, taken with a sip of water on the morning of the day of surgery. Patients were kept *nil per os* for at least six hours prior to surgery. On arrival in the operating theatre, monitoring of the patients' heart and respiratory rates, oxygen saturation, non-invasive blood pressure, and electrocardiography, were initiated. An intravenous line was secured, and preloading with isotonic saline 10 ml/kg body weight over a period of 15-20 minutes, was carried out.

Under strict aseptic conditions, a lumbar puncture was performed in the sitting position at L3-4 or L4-5 intervertebral space, using a 26 G spinal needle (Quincke's tip), after infiltrating the skin with 0.5-1 ml of 2% lidocaine. After obtaining a free flow of cerebrospinal fluid, 3 ml of a prefilled drug (not known to the anaesthetist performing the procedure), was injected into the subarachnoid space at approximately 0.2 ml/sec. The drugs to be administered were loaded by another anaesthetist, who was not involved in the intraoperative or postoperative care of these patients. Patients were then made supine immediately, on a perfectly horizontal operational table. Hypotension was defined as systolic blood pressure 20% lower than the baseline value, and was treated with incremental doses of mephentermine (3 mg) intravenously. Bradycardia was defined as a pulse rate 20% lower than the baseline value, and was treated with intravenous atropine (0.6 mg) bolus.

The level of sensory block was determined by a pinprick test, and motor block was assessed according to the modified Bromage scale, every two minutes for 10 minutes. The quality of intraoperative analgesia was assessed on a 0-10 linear visual analogue scale every 15 minutes, following intrathecal injection of the drug until the end of surgery. Patients with inadequate block, requiring supplemental general anaesthesia, were excluded from the study.

Table I: Demographic profile

	Group A	Group B	Group C	P-value
Age (years)	53.30 ± 19.36	62.55 ± 14.44	56.40 ± 14.94	0.09754
Body weight (kg)	69.1 ± 4.75	69.2 ± 11.81	70.95 ± 7.70	0.972168
Height (cm)	165 ± 5.25	166.75 ± 5.44	163.125 ± 4.57	0.307732
Mean duration of surgery (minutes)	67.40 ± 23.97	72.80 ± 39.76	79.45 ± 30.73	0.119329
Mean intraoperative heart rate (beats pressure/minute)	81.85 ± 7.83	83.20 ± 8.88	80.65 ± 9.50	0.188151
Mean intraoperative blood pressure (mmHg)	91.30 ± 12.08	90.25 ± 12.62	90.20 ± 12.15	0.602032
Mean intraoperative respiratory rate (beats/minute)	16.60 ± 1.70	16.60 ± 1.70	16.70 ± 1.98	0.962843

Values are given as mean ± standard deviation (SD)

Table II: Block characteristics

	Group A	Group B	Group C	P-value	CD
Onset of adequate analgesia (minutes)	2.99 ± 0.57	7.12 ± 0.96	6.18 ± 0.77	0.000221	2.5408
Time to attain maximum level of sensory block (minutes)	4.05 ± 0.70	6.97 ± 0.79	6.82 ± 0.47	0.000224	1.3567
Duration of sensory block (minutes)	170.90 ± 25.35	155.95 ± 25.97	180.30 ± 14.36	0.007031	16.8419
Duration of motor block (minutes)	184.30 ± 28.80	163.45 ± 25.74	187.25 ± 12.15	0.006889	16.8137
Duration of effective analgesia (minutes)	255.55 ± 26.84	217.85 ± 15.15	268.20± 18.25	0.004716	26.1841

Values are given as mean ± standard deviation (SD)

Table III: Side-effects

Side-effects	Group A	Group B	Group C	P-value		
				A vs. B	A vs. C	B vs. C
Nausea-	1 (5)	1 (5)	1 (5)	-	-	-
Vomiting	1 (5)	1 (5)	1 (5)	-	-	-
Pruritis	5 (25)	4 (20)	7 (35)	0.435769	0.239108	0.15532
Respiratory depression	0 (0)	0 (0)	0 (0)	-	-	-

Values are given as numbers, and values in parentheses denote percentage.

In the postoperative period, the duration of sensory blockade was noted by assessing the level of sensory block every 15 minutes until the time of regression to T_{12} level. Motor block was assessed by noting the time when the patient moved his or her big toe for the first time. The quality of postoperative analgesia was assessed by using a 0-10 linear visual analogue scale every 15 minutes until the first request for supplemental analgesia. Side-effects such as nausea, vomiting, pruritis, respiratory depression (respiratory rate < 10 breaths/minute or oxygen saturation < 90%), or any other complications, were noted and appropriately treated. The data were analysed statistically using the Z-test and analysis of variance (ANOVA) tests.

Results

Patients in all three groups were comparable with respect to age, body weight and height, duration of surgery, and intraoperative vital parameters, including heart rate, mean blood pressure and respiratory rate. The difference in values was statistically insignificant (see Table I).

Mean time to onset of adequate analgesia in groups A, B and C was 2.99 ± 0.57, 7.12 ± 0.96, and 6.18 ± 0.77 minutes, respectively, which showed a statistically significant difference. Similarly, the difference in the time to attain maximum level of sensory block (in minutes) in the three groups was statistically significant (p-value 0.000221). Duration of sensory block in groups A, B and C was 170.90 ± 25.35, 155.95 ± 25.97, and 180.30 ± 14.36 minutes, respectively. This difference was statistically significant.

Similarly, the difference in duration of motor block in the three groups was also statistically significant. Duration of effective analgesia in groups A, B and C was 255.55 ± 26.84, 217.85 ± 15.15, and 268.20 ± 18.25 minutes, respectively. This difference was statistically significant (see Table II).

The incidence of side-effects observed in patients in all three groups was comparable, and not statistically significant. These side-effects were not serious in nature, and were managed conservatively (see Table III).

Discussion

The findings of a study by Dabbagh et al suggest a shorter duration of neural block, both sensory and motor, after induction of spinal anaesthesia with intrathecal administration of bupivacaine in chronic opium abusers, compared with similar patients who are not currently abusing opium. Therefore, such patients should be managed to lengthen the duration of anaesthesia and analgesia, either by adding intrathecal opioid adjuvants to the local anaesthetic solution, or by adding supplemental intravenous or inhalational anaesthetics to the spinal anaesthesia, to enhance the length of the operative time.[6]

In this study, we used a combination of fentanyl with 0.5% bupivacaine for subarachnoid block in abusers and non-abusers of opium. An opium abuser is a person who has a craving for opium to experience the same euphoric effect again and again. Opium has been referred to as "hillbilly heroin" or "the poor man's heroin". Almost every country in the world is affected by drug abuse. Many people from a

rural background in India, particularly the Malwa region of Punjab state, are addicted to many forms of opium, mostly poppy husk.

We used a combination of 0.5% bupivacaine 10 mg with 25 μg fentanyl in opium non-abusers and abusers for spinal anaesthesia. As the patients addicted to opium have the problem of opioid tolerance and opioid-induced hyperalgaesia, in order to meet the higher requirement, we increased the dose of intrathecal fentanyl (40 μg) in Group C to investigate the possible advantage of a higher dose of fentanyl in opium abusers. We compared the onset of, and recovery time from sensory and motor block, the duration of effective analgesia, and associated side-effects in abusers and non-abusers.

The mean time for onset of analgesia in non-opioid abusers (Group A) was 2.99 ± 0.57 minutes, and in opioid abusers (Group B) was 7.12 ± 0.96 minutes. Therefore, there was a significant delay in the time for onset of analgesia in chronic opium abusers, compared to non-abusers. With an increased dose of intrathecal fentanyl (40 μg in Group C), the mean onset of analgesia in opioid abusers was rapid (6.18 ± 0.77 minutes), compared to 25 μg intrathecal fentanyl in Group B.

The time to attain maximum level of sensory block in opioid abusers (6.97 ± 0.79 minutes in Group B, and 6.82 ± 0.47 minutes in Group C), was significantly longer compared to non-opioid abusers (4.05 ± 0.70 minutes). Among the opium abusers, the statistical analysis revealed that the time to attain maximum level of sensory block was significantly shorter (p-value 0.000224), with a higher dose of fentanyl (40 μg).

Duration of sensory block was shorter in opium abusers, than in non-abusers. The mean duration of sensory block in Group A was 170.90 ± 25.35 minutes, in Group B 155.95 ± 25.97 minutes, and in Group C 180.30 ± 14.36 minutes, which was statistically significant (p-value 0.000224). Our results are consistent with the findings of Dabbagh et al. They showed that the duration of spinal anaesthesia was significantly shorter in the abuser group (86.6 ± 15.7 minutes in the abuser group, and 162 ± 22.1 minutes in the non-abuser group (p-value < 0.0001).[6]

Similarly, the duration of motor block was significantly shorter in opium abusers (163.45 ± 25.74 minutes in Group B), than in non-abusers (184.30 ± 28.80 minutes in Group A). However, the duration of motor block was comparable in opium abusers (187.25 ± 12.15 minutes in Group C), and non-abusers (184.30 ± 28.80 minutes in Group A), when the dose of fentanyl was increased to 40 μg in Group C. In their study, Dabbagh et al also showed that the duration of motor

block was 114.4 ± 9.2 minutes in the abuser, and 185.7 ± 28.4 minutes in the non-abuser groups (p-value < 0.0001).[6] Though significant, in our study, the difference in duration of sensory and motor blockade between opium abusers and non-abusers was not very big, compared to the subjects in the study by Dabbagh et al. This can be explained by the addition of fentanyl to bupivacaine in all the patients, which improved the quality of spinal anaesthesia. In their study of 100 patients scheduled for elective lower abdominal surgery using 100 mg of 5% preservative-free hyperbaric lidocaine with dextrose for spinal anaesthesia, Vosoughian et al showed that the duration of spinal anaesthesia was significantly shorter in the abuser group (60 ± 7 minutes) than in the non-abuser group (83 ± 10 minutes), p-value < 0.0001.[5]

In our study, the mean duration of effective analgesia in opium abusers (217.85 ± 15.15 minutes in Group B) was significantly (p-value 0.004716) less compared to non-abusers (255.55 ± 26.84 minutes in Group A), whereas by increasing the fentanyl dose to 40 μg in opium abusers (268.20 ± 18.25 minutes in Group C), the mean duration of effective analgesia was comparable to that in non-abusers.

In chronic opium users, decreased tolerance to opium compounds simultaneously creates a state of tolerance to local anaesthetics at the level of the spinal cord. This can be explained by the fact that both structural and functional similarities exist between opioid and local anaesthetic receptors at the spinal cord level.

Downregulation of the opioid receptors, and their related intracellular mechanisms in chronic opium abusers, and a synchronised drug tolerance to the effects of local anaesthetics in the spinal cord during intrathecal administration of these drugs, seem a possible mechanism for shorter duration of block in opium abusers in our study.[12,13] This tolerance to the effects of intrathecal local anaesthetics seems to be a cross-tolerance mechanism, which is a common finding for a number of other pharmaceutical products in the spinal cord.[8,10]

The opioid receptor system signals and modulates a multitude of effects, and under certain conditions, mediates hyperalgesia, rather than analgesia. Several mechanisms underlying OIH have been proposed. The most often cited is deranged excitatory amino acid (EAA) activation and metabolism, especially that of glutamate through the N-methyl-D-aspartate (NMDA) receptor with phosphokinase C (PKC) cascades, which leads to the modulation of cellular function.[14] It appears that the cellular sites of tolerance and hyperalgaesia may be communal at the level of EAA receptors.[14] The exact mechanism whereby opioids activate EAAs is currently unknown.

Sustained morphine exposure results in facilitatory neuroplasticity through the activation of the rostral ventral medulla (RVM).[15] This enhances the conduction of the pain impulse centrally. In addition, the RVM plays a role in activating the spinal dynorphin and calcitonin gene-related protein.

It has been proposed that a third mechanism works through spinal dynorphin. Dynorphin has been shown to have antianalgesic properties.[7] The systemic administration of opioids increases dynorphin release, and dynorphin appears to mediate the release of EAA from the afferent nerves.

Mao et al documented the occurrence of OIH in laboratory animals.[15] They examined the responses of rats to withdrawal tests in response to noxious stimuli after receiving intrathecal morphine. There was progressive reduction in baseline nocioceptive pain thresholds.[15] Similar findings have been seen in rats receiving fentanyl boluses, and in animals receiving repeated heroin administration.[16,17] These preclinical studies support the concept that there can be sensitisation to pain with concurrent administration of opioids.

Opioids have been, and continue to be used, for the treatment of chronic pain. Evidence supports the notion that opioids can be safely administered in patients with chronic cancer pain without the development of addiction or chemical dependency. However, over the past several years, concerns have arisen with respect to opioid administration for chronic pain treatment, particularly non-cancer pain.[18] The number of such patients receiving large doses of opioids and presenting for surgery is increasing daily. These patients need to be identified before surgery because they may also show shortened duration of spinal analgesia compared to the opioid-naive patient, and require opioid additives, along with intrathecal local anaesthetics.

Conclusion

The findings of this study suggest a shorter duration of spinal anaesthesia, both sensory and motor block, with the intrathecal administration of bupivacaine 10 mg and 25 µg fentanyl in chronic opium abusers, compared to similar patients who are not abusing opium. Therefore, such patients should be managed in such a way as to lengthen the duration of anaesthesia and analgesia, by increasing the intrathecal fentanyl dose to 40 µg.

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