Intrathecal fentanyl prolongs sensory bupivacaine spinal block

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The purpose of investigation was to study the effect of intrathecal fentanyl on the onset and duration of hyperbaric bupivacaine-induced spinal block in adult male patients. Forty-three patients undergoing lower extremity or genitourinary surgery were enrolled to receive either 13.5 mg hyperbaric bupivacaine 0.75% + 0.5 ml CSF it, *(Group I) or 13.5 mg hyperbaric bupivacaine 0.75% + 25 μg fentanyl* it, *(Group II) according to a randomized assessor-blind protocol. The onset and duration of sensory block were assessed by pinching the skin with forceps in the midclavicular line bilaterally every two minutes for first twenty minutes and then every five to ten minutes. Similarly, the onset and duration of motor block were assessed and graded at the same time intervals using the criteria described by Bromage. The time required for two sensory segment regression and sensory regression to L_1 dermatome was 74 ± 18 and 110 ± 33 min vs 93 ± 22 and 141 ± 37 min in Groups I and II, respectively ($P < 0.05$). Intrathecal fentanyl did not enhance the onset of sensory or motor block, or prolong the duration of bupivacaine-induced motor spinal block. Fewer patients demanded pain relief in the fentanyl-treated group than in the control group in the early postoperative period (19% vs 59%; $P < 0.05$). Episodes of hypotension were more frequent in the fentanyl-treated group than in the control group (43% vs 14%; $P < 0.05$). We conclude that fentanyl, 25 μg* it, *prolonged the duration of bupivacaine-induced sensory block (sensory regression to L_1 dermatone) by 28% and reduced the analgesic requirement in the early postoperative period following bupivacaine spinal block.*

Cette étude a pour objectif d'examiner l'effet du fentanyl sous-arachnoïdien sur le début et la durée de la rachianesthésie hyperbare à la bupivacaïne chez des patients adultes de sexe masculin. Quarante-trois patients opérés sur une extrémité inférieure ou sur l'appareil génito-urinaire sont répartis pour recevoir au hasard en rachianesthésie soit 13,5 mg de bupivacaïne hyperbare à 0,75% avec 0,5 ml de LCR (groupe I), soit 13,5 mg de bupivacaïne hyperbare à 0,75% avec 25 μg de fentanyl (groupe II). Le début et la durée du bloc sont évalués en coinçant la peau avec une pince sur la ligne médioclaviculaire bilatéralement à toutes les deux minutes pour les 20 premières minutes et à toutes les cinq à dix minutes par la suite. En même temps, le début et la durée du bloc moteur sont évalués et classé aux mêmes intervalles selon les critères de Bromage. Le temps requis pour la regression de deux segments sensoriels et la régression sensorielle jusqu'au dermatome de L_1 est de 74 ± 18 et 110 ± 33 vs 93 ± 22 et 141 ± 37 min dans les groupes I et II respectivement ($P < 0,05$). Le fentanyl sous-arachnoïdien n'accélère pas le début des blocs sensoriel et moteur ni ne prolonge la durée du bloc moteur produit par la bupivacaïne. Moins de patients ont demandé un analgésique dans le groupe fentanyl que dans le groupe contrôle à la période postopératoire immédiate (19% vs 59%, $P < 0,05$). Les épisodes d'hypotension sont plus fréquents dans le groupe traité au fentanyl que dans le groupe contrôle (43% vs 14%, $P < 0,05$). Les auteurs concluent que le fentanyl 25 μg sous-arachoïdien prolonge la durée du bloc senstif induit par la bupivacaïne (mesurée par la régression au dermatome de L_1) par 28% et diminue les besoins en analgésie dans le période postopératoire immédiate après une rachianesthésie.

Key words
ANAESTHETIC TECHNIQUES: spinal;
ANAESTHETICS, LOCAL: bupivacaine;
ANALGESICS: fentanyl, intrathecal.

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Neuraxial administration of opioids in conjunction with local anaesthetics improves the quality of intraoperative analgesia and prolongs the duration of postoperative analgesia.[1,2] Animal studies have also demonstrated antinociceptive synergism between intrathecal opioids and local anaesthetics during visceral and somatic nociception.[3-7]

Fentanyl (a lipophilic opioid) has a rapid onset and a shorter duration of action following intrathecal administration but its duration of action may be dose-dependent.[8,9] Hunt *et al.* reported that the addition of fentanyl ≥6.25 μg to hyperbaric bupivacaine reduced the intraoperative opioid requirement in patients undergoing

Caesarean delivery under spinal block.[2] Belzarena further demonstrated that low-dose fentanyl, 0.25 $\mu g \cdot kg^{-1}$ *it*, with bupivacaine 0.5% provided excellent surgical anaesthesia with few side effects. An increased dose of fentanyl, 0.5–0.75 $\mu g \cdot kg^{-1}$ *it*, was associated with increased incidence of adverse effects in patients undergoing Caesarean delivery.[10]

Datta *et al.* demonstrated faster onset of conduction blockade (increased sensitivity) in bupivacaine pre-treated nerve fibres in pregnant than in non-pregnant rabbits.[11] Given the suggested increased sensitivity to conduction blockade in parturients[12] and the paucity of comparable data in other population groups, this study was designed to evaluate the effects of intrathecal fentanyl 25 μg (0.3 $\mu g \cdot kg^{-1}$) on the onset and duration of hyperbaric bupivacaine-induced sensory and motor spinal block, and the early postoperative analgesic requirements in adult male patients undergoing lower extremity or genitourinary surgery.

Methods

Following institutional Human Investigation Committee approval, 43 adult men undergoing elective lower extremity or genitourinary surgery under spinal block consented to participate in this study. Patients were randomly assigned to receive either 1.8 ml (13.5 mg) hyperbaric bupivacaine 0.75% *it* + 0.5 ml cerebrospinal fluid (CSF) *it* (Group I) or 1.8 ml (13.5 mg) hyperbaric bupivacaine 0.75% + 0.5 ml (25 μg) fentanyl *it* (Group II).

After placement of routine non-invasive monitors, intravenous access was established and patients were preloaded with 700–800 ml lactated Ringer's solution. Intravenous infusion was maintained at 4–8 $ml \cdot kg^{-1} \cdot hr^{-1}$ during the intraoperative period. Midazolam, 1–4 mg *iv*, was administered to provide anxiolysis and sedation depending upon the preoperative status of the patient. Spinal block was performed with 25-gauge spinal needle at the L_{3-4} interspace in the lateral decubitus position and bupivacaine, 13.5 mg *it*, with or without fentanyl 25 μg *it*, was injected according to the random-assignment. The total volume of the subarachnoid injectate was 2.3 ml in both the treatment groups. Patients were immediately returned to the supine position after completion of the block procedure. Mean arterial pressure (MAP) was monitored every two to five minutes in the operating room and every ten to fifteen minutes in the post-anaesthesia care unit (PACU). Arterial haemoglobin oxygen saturation (SaO_2) and ECG leads II and V_5, were monitored continuously in the operating room and PACU. The onset and duration of sensory block were assessed by the same investigator blinded to the treatment groups, by pinching the skin with forceps in the midclavicular line bilaterally every two minutes for first 20 min and then every five to ten minutes. The time from intrathecal injection to the highest sensory level, regression of sensory level by two segments from the highest sensory level, and sensory regression to the L_1 dermatome were recorded. The highest level was recorded for unequal height of the sensory block on two sides. The onset and duration of motor block was assessed and graded at the same time intervals using the following criteria described by Bromage.[13]

0 = no impairment of movement of legs and feet;
1 = barely able to flex knees; no impairment of movement of feet;
2 = unable to flex knees and barely able to move feet;
3 = unable to move feet or knees.

Episodes of perioperative hypotension (MAP < 70 mmHg), bradycardia (HR < 50 bpm), and desaturation (SaO_2 < 90%) were also recorded. Hypotensive episodes were treated with boluses of fluid and increments of ephedrine, 5 mg *iv*, and bradycardia was treated with atropine, 0.2–0.4 mg *iv*. In addition, the number of patients experiencing nausea, itching, or shivering, or requesting pain relief during the early postoperative period (within four hours following intrathecal injection) were recorded. Patients were discharged from PACU either upon completion of the study period (four hours following intrathecal injection), or upon complete recovery of the sensory and motor function, whichever the longer of these two durations.

Data were analyzed using unpaired t test, Mann Whitney U rank sum test, and Fisher's exact test, with $P < 0.05$ considered statistically significant. Data are presented as mean values ± SD, median (range) values, and numbers (percent).

Results

The two treatment groups were comparable with respect to ASA physical status, age, weight, height, and the surgical procedures. Most, 64%, of the patients received midazolam, 1–4 mg *iv*, in the control group compared with 62% in the fentanyl-treated group (Table I).

The highest sensory levels achieved were T_8 (T_{5-10}) and T_7 (T_{6-8}) in Groups I (control) and II (fentanyl), respectively. The time intervals (durations) for sensory level to regress by two segments from the highest sensory level, and sensory regression to L_1 dermatome were prolonged in the fentanyl-treated patients (26% and 28%, respectively; $P < 0.05$) (Table II). Durations of Grade I, II, and III motor blocks were not prolonged in the fentanyl-treated group (Table III). The onset of bupivacaine-induced spinal block was not enhanced in the fentanyl-treated patients (Tables II and III).

There were no differences in the number of patients experiencing episodes of bradycardia, desaturation, shiv-

TABLE I Demographic characteristics of the two treatment groups

	Control	*Fentanyl*
Number of patients (*n*)	22	21
Age (yr)	62 ± 15	65 ± 11
Weight (kg)	81 ± 17	82 ± 13
Height (cm)	176 ± 6	174 ± 6
Preoperative sedation [n(%)]	14 (64%)	13 (62%)

Values are either numbers (*n*) or mean ± SD or numbers (percent) (*n*(%)).
No statistically significant differences.

TABLE II Characteristics of sensory block

	Control	*Fentanyl*
Highest sensory level (T) [median (range)]	T_8 (T_{5-10})	T_7 (T_{6-8})
Time from injection to highest sensory level (min)	7.1 ± 2.5	7.5 ± 3.2
Time for two segment regression from the highest sensory level (min)	74 ± 18	93 ± 22*
Time for sensory regression to L_1 from highest sensory level (min)	110 ± 33	141 ± 37*

Values are either median (range) or mean ± S.D.
*$P < 0.05$, considered significant (unpaired t test).

TABLE III Characteristics of motor block

	Control	*Fentanyl*
Onset to grade III motor block (min)	8.8 ± 3.3	8.6 ± 4.1
Duration of grade III motor block (min)	101 ± 42	112 ± 22
Duration of grade II motor block (min)	124 ± 43	139 ± 30
Duration of grade I motor block (min)	151 ± 46	169 ± 37

Values are mean ± S.D.
No statistically significant differences.

TABLE IV Characteristics of haemodynamic and other parameters

	Control	*Fentanyl*
Hypotension (MAP < 70 mmHg)	3 (14%)	9 (43%)*
Bradycardia (HR < 50 bpm)	4 (28%)	3 (14%)
Resp. depression (SaO_2 < 90%)	0	0
Shivering	2(9%)	0
Itching	0	2 (10%)
Nausea	1 (5%)	0
Request for pain relief (*n*/%)	13 (59%)	4 (19%)*

Values are numbers (percent).
*$P < 0.05$, considered significant (Fisher's exact test).

ering, itching or nausea between the two treatment groups. Episodes of hypotension were more frequent in the fentanyl-treated group than in the control group (43% vs 14%; $P < 0.05$). Fewer patients requested analgesic medication in the early postoperative period in the fentanyl-treated group than in the control group (21% vs 59%; $P < 0.05$) (Table IV).

Discussion

Results of our study demonstrate that the fentanyl, 25 μg *it*, prolonged the duration of bupivacaine-induced sensory blockade (sensory regression to L_1 dermatome) by 28%. This suggests a potential synergism between fentanyl and bupivacaine as reported in an animal study by Wang *et al.*[7] However, there was no prolongation of the duration of motor block.[2,3] Also, intrathecal fentanyl did not enhance the onset of bupivacaine-induced spinal block, as previously reported by Hunt *et al.* for parturients undergoing Caesarean delivery.[2]

Opioids and local anaesthetics exert their antinociceptive effect in the spinal cord by different mechanisms. The μ-agonist, fentanyl, exerts its action by opening K^+ channels and reducing Ca^{++} influx, resulting in inhibition of transmitter release. The μ-agonists also have a direct postsynaptic effect, causing hyperpolarization and a reduction in neuronal activity.[14,15] Local anaesthetic, bupivacaine, acts mainly by blockade of voltage-gated Na^+ channels in the axonal membrane.[16] Local anaesthetics may also interfere with synaptic transmission by a presynaptic inhibition of Ca^{++} channels in addition to their effects on nerve conduction.[16] A combination of these effects may explain the observed synergism between bupivacaine and fentanyl in our study group.

Our method of monitoring sensory and motor blockade was based upon the subjective patient responses. Monitoring of the somatosensory evoked potentials (SSEPs) during spinal block may be a better technique for assessing the degree of sensory and motor blockade; however, results obtained from various studies have not been conclusive.[17-19] Lund *et al.* found that isobaric bupivacaine, 18 mg *it*, despite complete motor block of the lower extremities and sensory blockade up to T_8 (by pin prick), did not reliably abolish SSEPs from electrical stimulation of the L_1 and S_1 dermatome. However, intrathecal bupivacaine had a strong depressant effect on neural afferent transmission and decreased the amplitude of SSEPs.[17] Therefore, further studies may be necessary to study the duration of bupivacaine-induced spinal block based on subjective patient responses compared to SSEPs.

In this study, 43% of the patients in the fentanyl-treated group experienced episodes of intraoperative hypotension compared with 14% in the control group. It has been reported that neuraxial administration of fentanyl with local anaethetics can lead to an increased incidence of hypotension.[20] Following co-administration of fentanyl

and local anaesthetic, the increased incidence of hypotension may be related to the higher sensory level achieved, as reported by Adkinsson *et al.*[21] However, in our study, the highest sensory levels achieved were T_8 (T_{5-10}) and T_7 (T_{6-8}) in the control and fentanyl groups, respectively. Therefore, this difference in highest sensory levels may not fully explain the increased incidence of episodes of hypotension. Animal studies have shown that fentanyl does not potentiate the effect of bupivacaine on efferent sympathetic pathways.[7]

Our study also demonstrated that fentanyl, 25 μg (0.3 $\mu g \cdot kg^{-1}$) *it*, reduced the analgesic requirement without increasing the incidence of episodes of desaturation, nausea, or pruritus during the early postoperative period. Belzarena found that fentanyl, 0.5 $\mu g \cdot kg^{-1}$ and 0.75 $\mu g \cdot kg^{-1}$ *it*, increased the duration of postoperative analgesia in parturients following Caesarean delivery (640 ± 142 min and 787 ± 161 min, respectively); however, this increased duration was associated with a decrease in the respiratory rate during the intraoperative period, and an increased incidence of sedation and pruritus related to higher doses of fentanyl. Also, consumption of supplemental analgesics decreased with increasing doses of fentanyl.[10] In contrast, Hunt *et al.* found that increasing the dose of fentanyl >6.25 μg did not increase the duration of analgesia following Caesarean delivery in parturients (192 ± 75 min); fentanyl, 6.25 μg *it*, was the optimal dose for effective perioperative analgesia.[2] Improved perioperative analgesia following co-administration of fentanyl and bupivacaine can be explained by a synergistic inhibitory action of these two agents on Aδ and C-fibre conduction.[7]

In conclusion, fentanyl 25 μg (0.3 $\mu g \cdot kg^{-1}$) *it*, prolonged the duration of bupivacaine-induced sensory spinal block and reduced the analgesic requirement during the early postoperative period. Our study demonstrates that intrathecal fentanyl acts synergistically to potentiate bupivacaine-induced sensory spinal block.

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