Regional Anesthesia and Pain

The addition of fentanyl does not alter the extent of spread of intrathecal isobaric bupivacaine in clinical practice

[En clinique, l'addition de fentanyl ne modifie pas l'importance de la diffusion de bupivacaine isobare intrathécale]

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Purpose: Fentanyl is commonly added to intrathecal local anesthetic solutions. *In vitro* data has shown fentanyl to render isobaric local anesthetics hypobaric, and alter the spread in artificial cerebrospinal fluid. This study examined whether the addition of fentanyl to isobaric bupivacaine with morphine leads to a clinically important alteration in the extent of spread of anesthesia.

Methods: Forty-four ASA I–III patients undergoing lower limb orthopedic procedures completed this double-blind, placebo-controlled trial. Patients were randomized into one of two groups, receiving intrathecal bupivacaine 15 mg and preservative-free morphine 200 µg without (Control group), or with the addition of fentanyl 0.02 mg (Fentanyl group). Patients were maintained at a slight head-up tilt. Variables studied over three hours included sensory level to cold and pinprick, motor blockade (Bromage scale), and circulatory data.

Results: No differences existed between the Fentanyl and Control groups with respect to highest level of block for cold: T4 (T2–T5) vs T3.5 (T3–T8) respectively (median, 95% confidence interval) or pinprick: T4 (T3–T6) vs T4.5 (T3–T8). Similarly, there was no difference in the time taken to reach maximum block height to cold (20 ± 9 vs 23 ± 13 min, mean $\pm$ SD) or pinprick (20 ± 9 vs 24 ± 13 min).

Conclusion: The addition of fentanyl 0.02 mg to 0.5% bupivacaine with morphine does not affect the maximal block height or time to maximal block in clinical practice.

Objectif : Le fentanyl est couramment ajouté aux solutions intrathécales d'anesthésiques locaux. Les données *in vitro* ont montré que le fentanyl rend hypobares les anesthésiques locaux isobares et modifient leur diffusion dans le liquide céphalo-rachidien artificiel. La présente étude voulait vérifier si l'addition de fentanyl à la bupivacaine isobare, accompagnée de morphine, provoque une modification d'importance clinique dans l'étendue de l'anesthésie.

Méthode : L'essai contre placebo et à double insu a été mené auprès de 44 patients d'état physique ASA I–III devant subir une intervention orthopédique aux membres inférieurs. Répartis au hasard en deux groupes, ils ont reçu une injection intrathécale de 15 mg de bupivacaine et 200 µg de morphine sans agent de conservation (groupe témoin) ou avec l'addition de 0,02 mg de fentanyl (groupe fentanyl). Les patients ont été maintenus en position de Fowler peu accentuée. On a testé pendant trois heures le niveau de l'insensibilité au froid et à la piqûre, le blocage moteur selon l'échelle de Bromage et les données circulatoires.

Résultats : Il n'y a eu aucune différence intergroupe quant au niveau le plus élevé d'insensibilité au froid : T4 (T2–T5) vs T3,5 (T3–T8) respectivement (médiane, intervalle de confiance de 95 %) ou à la piqûre: T4 (T3–T6) vs T4,5 (T3–T8). De même, il n'y a eu aucune différence quant au temps nécessaire pour atteindre la hauteur maximale de blocage neuromusculaire au froid (20 ± 9 vs 23 ± 13 min, moyenne $\pm$ écart type) ou à la piqûre (20 ± 9 vs 24 ± 13 min).

Conclusion : En clinique, l'ajout de 0,02 mg de fentanyl à la bupivacaine à 0,5 %, avec morphine, n'agit pas sur la hauteur maximale du bloc ni sur le temps nécessaire pour l'atteindre.

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S PINAL anesthesia is used for a wide variety of surgical procedures, necessitating variable levels of sensory block. The ability of the anesthesiologist to predict the height of sensory block is essential to providing adequate anesthesia with minimal side effects. Many factors can influence the degree of spread of local anesthetic solutions, including patient characteristics, physical properties of the cerebrospinal fluid (CSF), injection technique, and the dose and physical properties of the injectate.^{1,2} The baricity of a solution (ratio of the density of the solution to the density of CSF) is a primary determinant of the spread of solution after injection.

The addition of opioids to local anesthetic solutions for spinal anesthesia enhances surgical anesthesia and provides postoperative analgesia. Intrathecal morphine provides prolonged, good quality postoperative analgesia, while fentanyl has the advantage of decreasing visceral sensation and may prolong the duration of anesthesia.^{3,4} *In vitro* studies examining the effect of adding opioids to local anesthetics have shown morphine to cause minimal change in baricity of the final solution, whereas fentanyl decreases the density of 0.5% bupivacaine by up to 0.0011 g·mL⁻¹,^{5,6} where a difference of as little as 0.0006 g·mL⁻¹ in density alters the movement of local anesthetics in a spinal model.² In a more recent study, our group found that the addition of fentanyl to 0.5% bupivacaine made the resultant solution hypobaric within simulated CSF in a spinal model, leading to increased upward spread.⁷

The objective of the current study was to determine whether the addition of fentanyl to an isobaric spinal local anesthetic alters the level of sensory block in the clinical setting.

Methods

We conducted a double-blind randomized placebo-controlled study with two groups of patients. After Institutional Ethics Committee approval, written informed consent was obtained from 48 ASA I–III adult patients scheduled to undergo lower limb orthopedic procedures under regional anesthesia. Exclusion criteria included contraindication to spinal anesthesia, allergy to study drugs, previous lumbosacral spinal surgery, weight >110 kg, height <150 cm, neurological disease, diabetic neuropathy, and pregnancy.

Patients were randomly allocated by the hospital research pharmacist into one of two groups. The control group received intrathecal injections of 3.4 mL of solution containing: isobaric bupivacaine 15 mg (Marcaine 0.5%, Sanofi Canada, Markham, Ontario), and preservative-free morphine 0.2 mg (morphine LP, 0.5 mg·mL⁻¹, Sabex, Boucherville, Quebec). The fentanyl group received 3.8

mL of solution containing the above solution with the addition of fentanyl 0.02 mg (fentanyl citrate 0.05 mg·mL⁻¹, DBL, Laval, Quebec). Study injectates were prepared in identical 5-mL syringes, with the volume of solution blinded by a label wrapped around the syringe.

Monitoring consisted of noninvasive blood pressure and electrocardiogram (Model 90603A, Spacelabs, Redmond, WA) and pulse oximetry. An *iv* cannula was inserted and 500 mL of Ringers lactate solution was infused over ten minutes. Patients were positioned in the sitting position, and using standard sterile procedure, the intrathecal space was entered using a 24G Sprotte needle at the L2–3 or L3–4 interspace. The study solution was then injected over 60 sec, and confirmation of intrathecal placement was obtained at the beginning and end of the injections. In order to encourage upward spread of hypobaric solutions, patients were kept in the sitting position for 60 sec, then positioned supine on the operating table with a 6° head-up tilt, calibrated using a magnetic protractor.

Sensory block level was assessed at five, ten, 15, 20, 30, 45, 60, 90, and 120 min after injection, using thermal (cold alcohol swab), and pinprick stimuli. Muscle power was assessed using a modified Bromage scale (0=no block, 1=hip flexion blocked, 2=hip and knee flexion blocked, 3=complete block of hip, knee and ankle). Heart rate and blood pressure were recorded simultaneously. Hypotension, defined as greater than a 30% drop in resting systolic pressure or less than 90 mmHg, was treated with fluid resuscitation and ephedrine 5 mg *iv*. Bradycardia, defined as heart rate <50 beats·min⁻¹ was treated with atropine 0.6 mg *iv*.

Baseline demographic data included age, sex, weight, height, concurrent medications, and past medical and surgical history. The type and duration of surgery, the interspace used for intrathecal injection, and neurological assessments were recorded. Episodes of hypotension or bradycardia and the need to convert to a general anesthetic were documented.

Using mean and variability data from previous work,² sample size analysis indicated a need for a minimum of 17 subjects per group to demonstrate a dif-

TABLE I Patient data

Group	Fentanyl (n=22)	Control (n=22)
Age (yr)	65 ± 14	68 ± 13
Height (cm)	170 ± 11	172 ± 6
Weight (kg)	83.1 ± 12.1	81.4 ± 14.2
BMI	29.0 ± 4.4	27.5 ± 4.4
Male/female	12/10	17/5

Mean ± standard deviation. BMI=body mass index.

TABLE II Anesthetic block level

	<i>Fentanyl (n=22)</i>	<i>Control (n=22)</i>
Highest dermatome to cold	T4 (T2–T5; T1–T10)	T3.5 (T3–T8; T2–T10)
Highest dermatome to pinprick	T4 (T3–T6; T1–T10)	T4.5 (T3–T8; T2–T11)
Time to highest dermatome to cold (min)	20.4 ± 9.7	23.2 ± 13.3
Time to highest dermatome to pinprick (min)	20.0 ± 9.9	24.7 ± 13
Baseline systolic BP (mmHg)	144 ± 22	144 ± 18
Lowest systolic BP after block (mmHg)	104 ± 17	103 ± 20
Baseline heart rate (beats·min ⁻¹)	72 ± 14	80 ± 15
Lowest heart rate after block (beats·min ⁻¹)	60 ± 9	63 ± 11

Dermatome data presented as median (95% confidence interval of median; range). Other data are mean ± standard deviation.

FIGURE 1 Mean (± SEM) sensory block level to cold stimulus at all time periods for patients receiving intrathecal bupivacaine 0.5% and morphine with (Fentanyl group, closed squares) and without (Control group, open circles) the addition of fentanyl 0.02 mg.

ference in two dermatomes with a power of 0.80 and alpha error of 0.05. Data were analyzed using unpaired t tests for parametric data (change in blood pressure and heart rate), and Wilcoxon and Mann Whitney rank sums for between-group differences at each time point and maximal dermatomal block level. Incidence of adverse effects was compared using Chi-square test, and relationship of block level to patient demographic parameters using Spearman's rank order correlation.

Results

Four patients were withdrawn due to inability to achieve spinal anesthesia and need to convert to general anesthesia (one from Control group, three from Fentanyl group). Forty-four patients ($n=22$ in each group) thus

completed the protocol. The groups were similar with regard to demographic variables (Table I). The figure illustrates the block height for both groups at each time period (cold stimulus). There was no significant difference found between groups at any time period. Similarly, there was no difference in the maximal level of block to either pinprick or cold stimulus, or in the time to reach the highest dermatome (Table II). There was fairly wide distribution about the median in both groups for maximum block height (Table II). No significant relationship existed between maximum block level and either patient height or weight. Motor block was equal between groups (Bromage score 3 in all patients). Similarly, there was no difference between groups in incidence of hypotension or bradycardia after institution of spinal anesthesia (Table II), with eight patients being treated for hypotension (six control, two fentanyl).

Discussion

The current study demonstrated that, despite *in vitro* evidence, the addition of fentanyl to isobaric bupivacaine does not reliably alter the block height in the clinical situation. Furthermore, this study confirmed that wide interindividual variability in level of anesthesia can be anticipated despite using a consistent dose of intrathecal bupivacaine 0.5%. This is in keeping with previous studies that have described the "poor predictability" of isobaric bupivacaine, necessitating large volumes to give a reliable block level.⁸ Using variability data from previous studies, our sample size was calculated to demonstrate a potential difference in block height of two dermatomes. It is possible that a larger sample size might have made any difference between groups more apparent. However, the wide variability also implies that any difference found would not be predictable, and therefore would not be clinically reliable.

As opposed to studies utilizing a rigid and non-dynamic mechanical spinal model,^{7,9} a number of fac-

tors unique to the clinical situation are relevant to the wide variability in block level found. Although some patient factors such as height and weight showed no correlation with block level, other factors such as the volume of CSF in the lumbar space vary among individuals, and could be important in determining the degree of movement of solution within the CSF. However this was impossible to quantify or control in the current protocol.

A number of technical or procedure related factors may be relevant. Although some local anesthetics such as isobaric amethocaine have been shown to give more predictable spread with slower injection,¹⁰ no effect of injection speed was seen with 0.5% bupivacaine.¹¹ In the current study, injection was performed slowly and steadily over one minute to minimize this source of variability. Patient position during and following intrathecal injection is also important in determining block level, although theoretically less so with isobaric agents. All patients were sitting for placement of the spinal anesthetic, and remained so for 60 sec after intrathecal injection. Throughout the duration of surgery the patient was maintained in a 6 head-up tilt. These manoeuvres were used to enhance cephalad spread of the local anesthetic and emphasize any difference in baricity between groups, hypothesizing that fentanyl reduces the baricity of the local anesthetic solution.⁵ However even with this approach, no difference in height of block was found between the two groups. Some anatomical factors related to positioning may exist which are not possible to control, such as the degree of thoracic kyphosis. This could conceivably influence the movement of CSF within the spinal canal, particularly with the use of head-up tilt, and increase the interindividual variability seen.

With regard to the solutions injected, the dose of bupivacaine, morphine and fentanyl used reflects common clinical practice within our institution. Using formulas devised previously,⁵ the relative densities of the two solutions can be calculated. The change in density due to fentanyl may thus be calculated to be as low as 0.00040 or as high as 0.00067 g·mL⁻¹, depending on the reference values used.^{5,9} Since a difference of 0.0006 g·mL⁻¹ has been shown to influence the spread of local anesthetic in CSF,² it is possible that the dose of fentanyl used in this study did not affect the density sufficiently to consistently alter the movement of the solution in CSF. In addition, CSF density may vary, leading to variability in baricity of the injected solution among individuals. We did not analyze CSF density in the current study, although our subjects were nonpregnant and mostly healthy patients, whose CSF density would be expected to fall within a relatively narrow range.¹³

Morphine, in the dose used in the current study, does not substantially alter the density of a solution with bupivacaine 0.5%, or affect its characteristics in a CSF model.^{5,7} Thus the findings of this study would not likely be different had fentanyl been mixed with bupivacaine 0.5% alone. Finally, temperature of the injectate affects its spread, with solutions warmed to 37° showing different characteristics in CSF than room temperature solutions.^{2,14,15} Although we did not control the temperature of the injectate, the ambient temperature of the operating suite used during the study was kept within a narrow range.

In conclusion, unlike the results found in the laboratory setting⁵ and artificial spine model,⁷ the addition of fentanyl to isobaric 0.5% bupivacaine with morphine does not result in a predictable difference in the height of anesthetic block in patients undergoing lower limb procedures. This may be due to wide variability in block level, related to patient or operator characteristics, dynamics of CSF flow, or the relative densities of solutions used.

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