Laboratory Reports

Addition of opioids alters the density and spread of intrathecal local anesthetics? An *in vitro* study

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Purpose: To determine whether the addition of opioids alters the density and spread of intrathecal local anesthetics *in vitro*.

Methods: In Part I, the densities of hyperbaric bupivacaine 0.75% (HB), hyperbaric lidocaine 5% (HL) and isobaric bupivacaine 0.5% (IB) with and without morphine (M), and fentanyl (F) were measured at 22°C. In Part II a model was constructed utilizing a column containing a solution similar in composition to cerebrospinal fluid (CSF) at 37°C. The various local anesthetic-opioid solutions, coloured with crystalline methylene blue dye, were injected at 22°C into the column at a controlled rate through a spinal needle. The direction and extent of spread of the injectates were compared.

Results: The relative densities of the five solutions were: HB = HL > IB > M > F. The addition of fentanyl to IB reduced the density of the final solution ($P < 0.05$). In the model, IB alone and IB with morphine showed mainly downward spread, with the addition of fentanyl to IB resulting in upward movement ($P = 0.004$). The hyperbaric local anesthetics moved downward with or without opioids.

Conclusion: The addition of fentanyl reduces the density of IB *in vitro* and alters its movement in simulated CSF. This may prove to be important in predicting the level of spinal block in clinical practice.

Objectif : Déterminer si l'addition d'opioïdes a un effet sur la densité et l'étalement des anesthésiques locaux intrathécaux, utilisés *in vitro*.

Méthode : Dans la Partie I, les densités de la bupivacaine hyperbare 0,75 % (BH), de la lidocaïne hyperbare 5 % (LH) et de la bupivacaine isobare 0,5 % (BI) accompagnées ou non de morphine (M) et de fentanyl (F) ont été mesurées à 22 °C. Dans la Partie II, on a construit un modèle qui utilise une colonne contenant une solution dont la composition est similaire à celle du liquide céphalorachidien (LCR) à 37 °C. Les différentes solutions d'opioïdes-anesthésiques locaux, colorées avec du bleu de méthylène cristallin, ont été injectées à 22 °C dans la colonne à un débit contrôlé et au moyen d'une aiguille rachidienne. La direction et l'étendue de l'infiltration des solutions injectées ont été comparées.

Résultats : Les densités relatives des cinq solutions ont été : BH = LH > BI > M > F. L'ajout de fentanyl à la BI a réduit la densité de la solution finale ($P < 0,05$). Dans le modèle, la BI employée seule et la BI avec la morphine se sont étendues principalement vers le bas, mais la BI avec du fentanyl s'est propagée vers le haut ($P = 0,004$). Les anesthésiques locaux hyperbares s'étendent vers le bas, qu'ils soient avec ou sans opioïdes.

Conclusion : L'ajout de fentanyl réduit la densité de la BI *in vitro* et change son mouvement dans le LCR artificiel. Cette donnée peut se révéler importante pour prévoir le niveau de blocage rachidien en pratique clinique.

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THE ability to predict the ultimate level of block during spinal anesthesia is essential to providing adequate anesthesia while minimizing side effects. Many factors have been hypothesized to influence the spread of local anesthetic (LA) solutions within cerebrospinal fluid (CSF),^{1,2} including patient characteristics, physical properties of CSF, injection technique, as well as the dose and properties of the particular local anesthetic solution used. The density (defined as the weight in grams of 1 mL of solution) of the compounds used for intrathecal injection is believed to be a major determinant in controlling the extent of neural blockade. Baricity is the ratio of the density of the local anesthetic solution to the density of CSF, and thus determines the spread of the solution after injection. Since temperature has a considerable effect on density, the baricity of an agent may be related to the relative temperature of the injectate with respect to that of CSF.^{2,3}

The addition of opioids to local anesthetics for spinal anesthesia is increasingly common both to enhance surgical anesthesia and to provide post-operative analgesia. The effect of these agents on the final density of the intrathecal solution has recently been studied, demonstrating a reduction in density of bupivacaine 0.5% at 37°C when fentanyl is added.^{4,5} Since density differences as small as 0.0006 g·mL⁻¹ have been shown to influence the movement of local anesthetics in a spinal canal model,² we hypothesized that the addition of opioids may affect the spread of local anesthetic solutions after injection. In a previous study, our group determined that the addition of fentanyl to bupivacaine 0.5% altered the movement of the resulting solution in a spinal column model.⁶ However, the interpretation of these results is uncertain since the column temperature was maintained at 22°C rather than at body temperature, and contained fluid which did not adequately mimic the content of CSF.⁶

The objective of this two-part study was to determine whether the addition of opioids alters the density and spread of intrathecal solutions. In Part I, the densities of various solutions used for spinal anesthesia were measured at 22°C. In Part II, a model was utilized to compare the movement of various local anesthetic-opioid solutions in a column containing simulated CSF at 37°C.

Methods

Part I

Ten millilitre samples of undiluted local anesthetic solutions and opioids were measured using volumetric flasks, and weighed using a Mettler AJ100 top-loading balance (Fisher Scientific; Nepean, Ont) precise to

four decimal places. All measurements were conducted at 22°C. Five measurements were taken for each of the following solutions: HB: hyperbaric bupivacaine 0.75% with dextrose 8.25% (Marcaine Spinal, Sanofi Winthrop, Markham, Ontario), HL: hyperbaric lidocaine 5% with dextrose 7.5% (Xylocaine Spinal, Astra), IB: isobaric bupivacaine 0.5% (Marcaine, Sanofi Winthrop, Markham, Ontario), F: 0.05 mg·mL⁻¹ fentanyl (DBL, Dorval, Quebec), and M: 0.5 mg·mL⁻¹ morphine (Morphine LP Epidural, Sabex, Boucherville, Quebec). Density was also measured for various combinations of local anesthetic-opioid solutions mixed together in clinically used doses (Table). Crystalline methylene blue dye 0.002 g was dissolved into 20 mL of each solution (thereby increasing the density of each of the tested solutions by 0.0001 g·mL⁻¹) so that identical solutions could be compared in the *in vitro* model (Part II).

Part II: In Vitro Model

A column was constructed from clear polyvinylchloride (PVC) tubing (internal diameter 9.5 mm) 100 cm in length mounted vertically and marked with a scale extending 30 cm above and below the port of injection (Figure 1).⁷ The column was filled with 100 mL of a simulated CSF solution, created by adding 12 mL dextrose 5% in water and 7 mL albumin 5% to Ringer's Lactate to a total of 1000 mL.⁸ This solution was warmed to 37°C during filling of the column (System 250 Fluid Warmer, Level 1 Technologies, Rockland MA). A warm-air blanket was wrapped around the column (Life-air 1000, Progressive Dynamic Inc., Marshall MI), with its temperature adjusted to maintain the fluid between 36.5 and 37°C using temperature probes at two sites (Shiley Corporation, Carlsbad CA). Solutions drawn from the same batches as those prepared for Part I (at 22°C, coloured with methylene blue dye) were injected into the column. Injections were performed in the upright position using a programmable syringe pump (AS40A, Baxter, Deerfield, IL), which was set to inject a volume of 0.5 mL over one minute in order to minimize turbulence and tracking of the injectate along the wall of the column. The injectate was infused through a 24 gauge Sprotte spinal needle inserted perpendicular to the model's long axis to simulate a midline placement. The needle opening was directed sideways for each injection to avoid preferential upward or downward movement. After each injection, the model was drained and refilled with fresh solution. Three injections were carried out for each solution. Both the direction and extent of spread in the spinal model were recorded as the distance in cm from the injection site taken one minute after the end of each injection.

Statistical analysis

The densities of each of the LA-opioid mixtures were compared with those of the respective LA alone using analysis of variance (ANOVA). ANOVA was also used to compare the extent of spread of the different solutions injected into the spinal canal model. Tukey's test was employed post-hoc where ANOVA showed significance ($P < 0.05$).

Results

Part I

The measured densities of the undiluted solutions were consistent and reproducible using the volumetric method described. Overall, the relative densities of the five undiluted solutions were $HB = HL > IB > M > F$ (Table). The density of the simulated CSF solution was 1.0056 at 22°C and 0.9962 at 37°C.

Although the addition of opioids altered the densities for all three local anesthetic solutions studied, only the addition of fentanyl, alone or with morphine, to bupivacaine 0.5% resulted in a change in density, or in density relative to the solution contained in the spinal model (Table).

Part II

Figure 2 illustrates the comparative movement of the undiluted and mixed solutions after injections into the column. Figure 3 depicts actual injections of two different solutions. The hyperbaric local anesthetics moved downward with gravity, with no effect of adding opioids (as depicted in Figure 3A). Isobaric bupivacaine, 0.5% morphine, and a mixture of the two

also showed primarily downward movement. Fentanyl alone was clearly hypobaric; when added to IB, fentanyl resulted in upward movement compared with isobaric bupivacaine alone (Figure 3B, $P = 0.004$). One further observation was that the fentanyl/IB mixtures continued to travel upward to the top of the column after the one minute recording period was complete.

Discussion

The densities of various local anesthetics and opioids have been recorded in previous studies,⁹⁻¹¹ although the effect on density of adding opioids to local anesthetics has only recently been examined.^{4,5} We chose to study three commonly used spinal anesthetics, hyperbaric bupivacaine 0.75%, hyperbaric lidocaine 5%, and isobaric bupivacaine 0.5%, in combination with fentanyl or morphine in clinically relevant doses. This study was not an attempt to define reference values for the measured densities of these solutions, but rather to provide a comparative analysis of the measured densities, and to compare the movement of these solutions in a 37°C column. The most important finding was that the addition of fentanyl, but not morphine, to bupivacaine 0.5% at room temperature reduced the density of the final solution, and altered its spread in our *in vitro* model.

In the current study, the column in the spinal model was filled with a solution similar in composition

TABLE Density of opioid and local anesthetic solutions

Solution	Density ($g \cdot mL^{-1}$)
Fentanyl	0.9957 ± 0.0001
Morphine	1.0013 ± 0.0001
HB (3 mL)	1.0262 ± 0.0001
+ 0.3 mL F (0.3 mL)	1.0222 ± 0.0002
+ 0.7 mL M (0.7 mL)	1.0197 ± 0.0001
+ both F (0.3 mL) + M (0.7 mL)	1.0173 ± 0.0001
HL (2 mL)	1.0276 ± 0.0001
+ 0.3 mL F (0.3 mL)	1.0234 ± 0.0002
+ 0.7 mL M (0.7 mL)	1.0208 ± 0.0001
+ both F (0.3 mL) + M (0.7 mL)	1.0183 ± 0.0001
IB (3 mL)	1.0014 ± 0.0002
+ 0.3 mL F (0.3 mL)	1.0006 ± 0.0002
+ 0.7 mL M (0.7 mL)	1.0013 ± 0.0003
+ both F (0.3 mL) + M (0.7 mL)	1.0007 ± 0.0001

Measurements at 22°C. Mean $\pm$ SD. HB: hyperbaric bupivacaine 0.75%; IB: isobaric bupivacaine 0.5%; HL: hyperbaric lidocaine 5%, F: fentanyl (0.05 $mg \cdot mL^{-1}$), M: morphine (0.5 $mg \cdot mL^{-1}$).

FIGURE 1 Schematic diagram of the model used to simulate injections of the local anesthetic-opioid mixtures (at 22°C) into the spinal canal. The column was filled with fresh solution at 37°C prior to each injection and wrapped with a warm-air blanket (not depicted) to maintain temperature. The direction and extent of spread of the solutions, coloured with methylene blue dye, were determined.

FIGURE 2 Relative direction and extent of spread from the site of injection (zero point) of the various local anesthetic-opioid solutions in the model shown in Figure 1 (mean of three injections). HB: hyperbaric bupivacaine 0.75%, HL: hyperbaric lidocaine 5%, IB: isobaric bupivacaine 0.5%, M: morphine, and F: fentanyl. * indicates significance ($P < 0.05$) vs undiluted local anesthetic.

to human CSF which was maintained at 37°C,⁸ while the test solutions were measured and injected at 22°C in order to simulate the temperature effects involved in clinical practice. It is likely that the density of the injected solution decreased while being instilled into the simulated CSF due to an equilibration of temperature with the CSF. This could explain the pronounced upward movement of fentanyl, and the effect of adding fentanyl to IB. The effect of temperature on the distribution of intrathecal solutions is controversial. The densities of CSF and other dilute aqueous solutions exhibit a curvilinear decrease with increasing temperature.^{10,12} It has been postulated that warming a spinal solution may affect its spread in the subarachnoid space *in vivo*. Stienstra *et al.* found a difference between the segmental levels of sensory loss *in vivo* when bupivacaine 0.5% was injected at temperatures of 4°C and 37°C.² In contrast, Kristoffersen *et al.* found only small and non-significant differences in maximal cephalad spread of analgesia when bupivacaine 0.5% was injected at 19°C and 37°C.³ Beardsworth and Lambert found no effect on maximum spread of spinal anesthesia when bupivacaine 0.5% was injected at 20°C and 37°C, and concluded that other undetermined factors were more important in determining the level of anesthesia than the transient thermal effect on baricity.⁷ Thus thermal equilibrium was unlikely to have been an important factor in influencing the spread of the solutions, whereas rela-

FIGURE 3 Photographs of injections of solutions (coloured with methylene blue dye) into the spinal model. The warming apparatus has been removed for clarity. Solutions represented are A. hyperbaric lidocaine 5%; B. 0.05 mg·mL⁻¹ fentanyl.

tive density was most likely the predominant factor.

There are a number of potential limitations to extrapolating our results to the clinical setting. First, neither an anatomical configuration nor similar positioning of the spinal column during spinal anesthesia was attempted in our *in vitro* model since the aim was to compare the relative distributions of the different solutions. However, similar models have proved useful in previous studies examining the effects of various factors on local anesthetic movement.⁷ In addition, human CSF density has been reported to vary between individuals.⁵ Clearly, only the human model could allow the precise determination of the relative movement of these solutions in clinical practice. Second, a programmable syringe pump was used in order to achieve reproducible injections. To avoid the effects of turbulence, small volumes (0.5 mL) were injected over one minute. Thus, factors relating to the speed and technique of injection could potentially alter the spread of any solution.² The extent of movement of the solutions was documented one minute after injection since most of the preparations reached the extent of the column scale by this point (Figure 2). Finally, the precision of the instrumentation used in the density measurements limit their value as reference densities for the various solu-

tions, which have previously been studied at room temperature and at 37°C.^{4,5,13} However, the measurements did enable a useful comparative analysis of the densities of the various local anesthetic-opioid combinations at room temperature.

In conclusion, the addition of fentanyl and morphine to local anesthetics alters the density of the resulting solution. The addition of opioids to hyperbaric local anesthetics had no effect on movement in simulated CSF in our model. The addition of fentanyl altered the direction and extent of spread of isobaric bupivacaine 0.5%, leading to movement in an upward direction. This may have clinical relevance in predicting the spread of intrathecal solutions, and the effect of altering body position on the ultimate level of block. However, clinical trials are needed to determine the actual clinical effect of this altered baricity on the level of spinal blockade attained using local anesthetic-opioid mixtures.

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