Impact of Baricity of Bupivacaine on Intrathecal Fentanyl-Associated Pruritus during Combined Spinal/Epidural Anesthesia for Labor

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Citation

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Abstract

Background: Local anesthetics and dextrose independently decrease the incidence of pruritus when added to an intrathecal fentanyl solution. This study examines the incidence and severity of pruritus after administration of fentanyl with saline, hyperbaric local anesthetic, isobaric local anesthetic, or dextrose.Methods: 100 parturients were randomized in a double-blinded manner to receive an intrathecal injection of: (1) fentanyl 25 g in 0.25 mL normal saline; (2) fentanyl 25 g plus isobaric bupivacaine 1.9 mg; (3) fentanyl 25 g plus hyperbaric bupivacaine 1.9 mg; or (4) fentanyl 25 g plus dextrose 20 mg. Ten, 20, and 30-minutes after intrathecal injection, patients were asked to rate intensity of pruritus (face, arm, hand, or torso) and pain using a 100 mm visual analog scale. Highest sensory level of block achieved was measured.Results: There was significantly less pruritus in the hyperbaric bupivacaine group at 10 (p=0.002 vs control), 20 (p=0.002 vs control and p=0.03 vs. isobaric group), and 30 (p=0.002 vs control and p=0.03 vs. isobaric group) minutes. Sensory level was lowest in the hyperbaric group. Conclusion: Hyperbaric bupivacaine reduces both the incidence and severity of pruritus associated with intrathecal fentanyl in laboring parturients when compared to the isobaric formulation.

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INTRODUCTION

Pruritus is a frequent side effect of opioids administered into the intrathecal space. Although the exact mechanism is unclear, animal studies suggest that pruritus is mediated by activation of mu receptors supraspinally and in the dorsal horn [1]. An incidence as high as 95% has been reported following intrathecal fentanyl injection [2], and pruritus has long been considered to be an unpleasant and potentially limiting effect of intrathecal opiate administration [3].

Although numerous texts and publications have suggested various intrathecal injection cocktails [4], a commonly used combination is bupivacaine and fentanyl, with hyperbaric bupivacaine (0.75% in 8% dextrose) coming standard in many available epidural and combined spinal-epidural (CSE) kits.

Antihistamines and other agents have been used in an attempt to reduce the incidence of intrathecal opiate-induced pruritus with varying degrees of success [56]. The actual intrathecal injectate has also been suggested as a site for changing incidence of pruritus, with dextrose having been shown to decrease the incidence when added to a sufentanil solution [78]. Isobaric bupivacaine has not been shown to decrease this incidence during labor, [9] and specific evaluations of the effects of hyperbaric formulations have not been performed.

We wished to examine the incidence of pruritus after administration of a mixture of fentanyl and hyperbaric bupivacaine, the mixture most commonly used in our clinical practice, when compared to fentanyl in saline, fentanyl plus isobaric bupivacaine, and fentanyl plus dextrose. Our hypothesis was that the hyperbaric mixture (containing both local anesthetic plus dextrose) would be more effective than either the isobaric formulation or dextrose alone in reducing pruritus.

METHODS

100 ASA PS I or II parturients in stage I of labor requesting

neuroaxial analgesia for labor were asked to participate in this IRB approved study. All enrolled subjects completed the study, and all procedures were performed in a single major teaching institution over the course of 13mo. Cervical dilation at placement of block was ≥3 and ≤8cm. Both primiparous and multiparous subjects were included. Subjects with allergies to opiates (including pruritus to oral or intravenous agents), subjects taking anti-pruritic medications (including antihistamines, opioid antagonists and mixed agonist-antagonists), and subjects who had received intravenous opioids earlier during labor were excluded from study. Patients with non-singleton pregnancy, non-reassuring fetal heart rate tracing during the 30min prior to block, and EGA of <34wks were also excluded.

Consenting subjects were randomized (via computer) in a double-blinded manner to receive an intrathecal injection of the following: (1) fentanyl 25 g in 0.25 mL normal saline (Control group); (2) fentanyl 25 g plus isobaric bupivacaine (Astra Sensorcaine MPF CE 0.75%, sterile preservative-free) 1.9 mg (FIB group); (3) fentanyl 25 g plus hyperbaric bupivacaine (Astra Sensorcaine MPF Spinal 0.75%) 1.9 mg (FHB group); or (4) fentanyl 25 g plus 20 mg of sterile, preservative-free 8% dextrose (FD group). Injectate volumes were 0.75mL for the Control, FIB, and FHB groups, and 0.9mL for the FD group. The difference in volume was not felt to represent a risk to un-blinding given the type and size of the syringe (5mL) that came with our CSE kits. Diluent saline, when used, was obtained from the preservative free solution supplied with the CSE kit (Portex Combined Spinal Epidural Anesthesia Tray, Keene, New Hampshire). 1.9mg of bupivacaine was chosen based on ranges used in prior studies to achieve analgesia, and the dextrose quantity chosen in group FD was used to equal the 20mg present in the FHB formulation. All solutions were prepared at bedside by a research coordinator not involved with the assessment phase of the study, and anesthesia providers (faculty or residents) were blinded to solution composition. The epidural portion of the CSE was not used during the entirety of the study period, nor was a test-dose given until after data collection was complete. All procedures were performed with subjects in the sitting position, and subjects were placed in the supine position with left uterine displacement within 10 minutes of block placement. A bupivacaine-only group was not included because incidence of pruritus following intra-thecal bupivacaine is negligible [10].

Ten, 20, and 30-minutes after intrathecal injection (needle placement confirmed via free-flow of clear CSF), subjects were asked if they had pruritus, and if they did, to rate the intensity (specifically itching on arms, hands, face, or torso) using a 100 mm visual analog scale (using an unmarked 10-cm line labeled “no itching” on the left end representing zero and “worst itching imaginable” on the right end representing ten) [9]. Motor weakness was assessed via the modified Bromage score. Dermatomal level of pruritus was not assessed. Pain was assessed via a similar 100mm visual analog pain scale, and approximate spinal level was estimated using sensitivity to a cold alcohol swab. As the primary outcome measure of this study was incidence and severity of pruritus, analgesia duration (ie. duration of effect of the spinal component of CSE) was not assessed after the initial 30min assessment period.

Intergroup measurement data (e.g., age and weight) were compared using an analysis of variance (ANOVA). Intergroup visual analog scale ratings at each data collection interval are summarized as mean ± SEM and compared using a repeated measures-ANOVA. If F ratio was significant at the 0.05 level, Tukey’s HSD test was used to distinguish means. Categorical data (pruritus incidence) are summarized as either raw data or percentage and were compared using Pearson’s chi square or McNemar’s test as appropriate. Differences in level of block were compared using ANOVA and post hoc analysis with Scheffe’s test. Differences were considered significant when P was 0.05 or less. An original sample size of 144 (36 subjects per group) was chosen to detect a 30% difference in pruritus incidence with an value of 0.05 and value of 0.20 (power = 0.80). Intermediate analysis at 100 subjects revealed statistical significance, thus enrollment was terminated.

RESULTS

There were no significant intergroup differences at the 0.05 level in age (24 ±5 years), weight (82 ±17 kg), gravida (2.3 ±1.4), or gestational age (38.9 ±1.4 weeks); thus data were pooled for summary. The incidence of pruritus in group FHB was less at 10 ($p<0.002$ vs control), 20 ($p<0.002$ vs control and $p<0.03$ vs. FIB group), and 30 ($p<0.002$ vs control and $p<0.03$ vs. FIB group) minutes (Table 1).

[a]P = <.001 vs. Control; [b]P < .05 vs. FD.

Figure 1

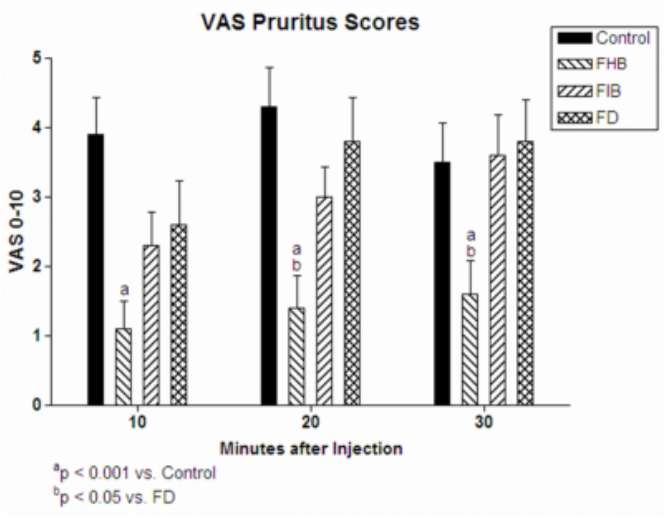
Table 1: Percent of subjects with pruritus following intrathecal injection of fentanyl with saline, hyperbaric local anesthetic, isobaric local anesthetic, and dextrose. Control: Fentanyl 25 Âµg + 0.25 mL normal saline. FHB: Fentanyl 25 Âµg + hyperbaric bupivacaine 1.9 mg. FIB: Fentanyl 25 Âµg + isobaric bupivacaine 1.9 mg. FD: Fentanyl 25 Âµg + dextrose 20 mg

Groups	N	Time after Injection		
		10min	20min	30min
Control	25	84%	84%	88%
FHB	27	26%[a]	41%[a,b]	41%[a,b]
FIB	25	60%	80%	88%
FD	23	57%	78%	91%

In those that complained of pruritus, VAS scores were lower in the FHB group at 10 ($p<0.001$ vs control), 20 ($p<0.001$ vs control), and 30 ($p<0.001$ vs control and $p<0.05$ vs FD group) minutes (Figure 1).

Figure 2

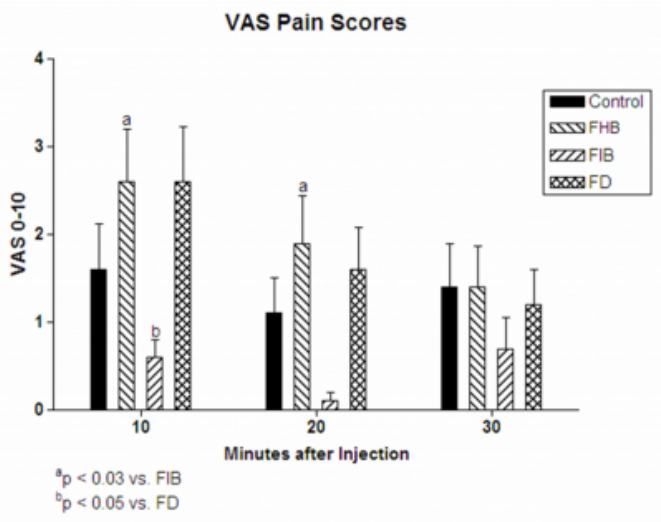
Figure 1: Pruritus scores on VAS (scale 0-10, with 10 being worst itching imaginable). Control: Fentanyl 25 Âµg + 0.25 mL normal saline. FHB: Fentanyl 25 Âµg + hyperbaric bupivacaine 1.9 mg. FIB: Fentanyl 25 Âµg + isobaric bupivacaine 1.9 mg. FD: Fentanyl 25 Âµg + dextrose 20 mg



VAS scores for pain were lower in the FIB group at 10 ($p<0.03$ vs control and $p<0.05$ vs FD group) and 20 ($p<0.03$ vs control) minutes (Figure 2).

Figure 3

Figure 2: Pain scores on VAS (scale 0-10, with 10 being worst pain imaginable). Control: Fentanyl 25 Âµg + 0.25 mL normal saline. FHB: Fentanyl 25 Âµg + hyperbaric bupivacaine 1.9 mg. FIB: Fentanyl 25 Âµg + isobaric bupivacaine 1.9 mg. FD: Fentanyl 25 Âµg + dextrose 20 mg.



Sensory block levels (as measured by subjective reduction in cold sensation) were: Control: T9 ± 5 levels; FD: T9 ± 6; FIB: T8 ± 4; FHB: L1 ± 3. FHB level was significantly lower than the other three groups ($p<0.001$ for Control, $p<0.001$ for FIB, $P=0.004$ for FD), and there were no other inter-group differences.

No subjects were dropped from the study, no complications from the procedure occurred (including post-dural puncture headache), and delivery outcomes were not measured. No subjects developed nausea or hypotension, and none developed motor weakness.

DISCUSSION

Baricity affects action and spread of intrathecally administered drugs. Consequently, level of sensory blockade is different for hypo-, iso-, and hyperbaric solutions of local anesthetics, and the actions of other drugs such as neostigmine show marked segmental differences when administered with and without dextrose [11]. Present findings suggest that increased baricity of local anesthetic reduces both the incidence and severity of pruritus associated with intrathecal fentanyl. That is, a combination of local anesthetic plus dextrose is better than either alone at

reducing the subjective sensation of itching above the level of analgesia. Pain, a secondary outcome, was lower in subjects receiving the isobaric mixture. This has been reported elsewhere [8] and likely is due to improved rostral spread of isobaric opiates as compared to a hyperbaric solution. Pain from stage 1 of labor is mediated by fibers arising from T10-L1, and interestingly subjects in both the Ferouz study and ours were blocked in the sitting position.

Mechanism of pruritus is less understood than pain, and seems to originate from both segmental spinal as well as supraspinal mechanisms [12]. At the spinal receptor level, itching appears to be modulated at mu-receptors (specifically in the dorsal horn of the spinal cord), and fentanyl is a relatively selective mu-receptor agonist. Spinal effects, however, cannot fully account for all side-effects of opiates, and epidurally administered fentanyl has been found to appear in cervical CSF within minutes of lumbar injection, demonstrating rapid cephalad spread [13]. Importantly, CSF levels in the brainstem and brain do not rise as quickly as facial itching occurs [14], and it has been suggested that facial itching is due to stimulation of the trigeminal nucleus, which descends as far caudally as C3 [15].

The relationship between pain (which is blocked below the level of injection) and pruritus (which can be generalized, or even isolated to the nose as is seen frequently in clinical practice) is complex and poorly understood. The relationship between pruritus and opiate, local anesthetic and dextrose is similarly complex, as revealed in our study results.

The presence of local anesthetics reduces the incidence of pruritus with intrathecally administered opiates [16]. Although the mechanism of this interaction is unclear, local anesthetics may be associated with a conformational change in spinal cord opiate receptors, such that mu-receptor binding is inhibited and delta and kappa receptor binding by opiates in increased [17]. Kappa receptor activation has been associated with a reduction in pruritus [18], and this favorable alteration in mu and kappa binding may contribute to reduction of pruritus with local anesthetics. Consistent with our findings, others have found that pruritus above the abdomen still occurs in patients receiving local anaesthetics in conjunction with intrathecal fentanyl [16]. How local anesthetics affect the supraspinally mediated effects of opiates on pruritus, and why we observed a pruritus-reducing affect with the hyperbaric formulation is unclear.

Discussed earlier, dextrose reduces pruritus associated with intrathecally administered opiates. However, dextrose alone did not result in a significant reduction of pruritus in this study (although there was a trend towards reduction versus the control group at 10 and 20min), but did when used in conjunction with bupivacaine suggesting that there is a benefit to both keeping the block “low” (that is, preventing rostral spread), and adding local anesthetic to interact with mu- and kappa-receptors as outlined above. Our patients were blocked in the sitting position and stayed upright for approximately ten minutes (while the epidural catheter was placed, secured, etc), allowing ample time for the hyperbaric solution to spread caudally (which was verified by a lower level of block in the FHB group). Although not eliminated, the incidence of pruritus was decreased in the FHB group versus the FIB group and the control group.. Patients reporting itching had a lower severity via VAS, but complained of symptoms above the level of the block (face, hands, arms, torso), again suggesting that pruritus is not a purely spinally mediated event.

In conclusion, baricity seems to influence pruritus via effects related to limitation of anesthetic spread, although our study did not find a significant reduction in incidence when dextrose was added to fentanyl alone. Local anesthetic also seems to reduce the incidence of pruritus, although we failed to observe a significant reduction when isobaric bupivacaine was added to fentanyl alone. When hyperbaric bupivacaine was added to intrathecal fentanyl, however, both the incidence and severity of pruritus were reduced. Although the mechanisms for this reduction are unclear, we hypothesize that multiple factors are involved including limitation of anesthetic spread and conformational change at the opiate receptor in the spinal cord.

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