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Lidocaine and Bupivacaine Mixtures for Epidural Blockade

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In a prospective double-blind clinical study, single-dose lumbar epidural blockade was instituted in 60 healthy patients undergoing lower abdominal surgery. Patients were randomly assigned to one of five groups. Each group received treatment with a different local anesthetic solution containing 1:200,000 epinephrine. Local anesthetic solutions used were 0.5 per cent bupivacaine HCl, 2 per cent lidocaine HCl, and lidocaine–bupivacaine mixtures in the ratios of 1:3, 1:1 or 3:1 by volume. Onset and complete spread of sensory blockade were similar in all five groups. Time to regression to two segments of partial and complete sensory blockade was positively correlated ($P < 0.05$) with increasing dose of bupivacaine in the solutions and ranged from 84 min (partial) and 70 min (complete) for lidocaine, to 128 min (partial) and 101 min (complete) for bupivacaine. Using skin temperature as a criterion of sympathetic blockade, all three mixtures demonstrated a duration of action intermediate between the two single drugs, lidocaine (124 ± 13 min) and bupivacaine (286 ±32 min). Onset of complete motor blockade was fastest and the degree of motor blockade was most profound with the mixture containing equal proportions of lidocaine and bupivacaine. Pharmacokinetics of individual drugs were unaltered in any of the mixutres. (Key words: Anesthetics, local: bupivacaine; lidocaine; mixtures. Anesthetic techniques: epidural. Pharmacokinetics.)

USED ALONE, bupivacaine has acquired a reputation for slow onset[1-3]. Hence, in a busy operating schedule, it would seem attractive to use an agent having the characteristics of fast onset while still retaining the desirable long-duration characteristics of bupivacaine. At first, it appeared that etidocaine would fulfill this requirement.[4] However, experience with etidocaine has revealed its propensity for producing prolonged motor blockade and this feature is not always desirable.[5,6] Consequently, there has been a resurgence of interest in mixtures of local anesthetic agents to combine the desirable properties of each component. Earlier animal studies[7] indicated that it may be possible to retain the favorable characteristics of each component of such mixtures, and *in vitro* studies are in agreement, provided that *p*H and concentration of the final solution are adjusted appropriately.[8]

Previous clinical studies of mixtures of local anesthetic agents have produced inconsistent findings. The advantage of shortening the latency of the long-acting local anesthetic agent bupivacaine by adding chloroprocaine[9] or carbonated lidocaine[10] has been demonstrated for brachial plexus blockade. Others have prolonged the duration of action of short-acting local anesthetics by adding tetracaine for peripheral nerve blockade.[11] However, the clinical advantages of mixing local anesthetics for epidural blockade have not been demonstrated clearly. Whereas, tetracaine prolonged the duration of analgesia from lidocaine, chloroprocaine, and mepivacaine,[11] analgesia from a mixture of bupivacaine and chloroprocaine did not last significantly longer than that from chloroprocaine alone.[12]

To date, there has been no controlled clinical study of the clinical effects and pharmacokinetics of mixtures of amide local anesthetics. The present study provides an objective clinical examination combined with a pharmacokinetic study of two commonly used local anaesthetics, lidocaine and bupivacaine, alone and mixed together.

Materials and Methods

STUDY PLAN

Using a double-blind method, clinical effects and pharmacokinetics were studied after epidural injection of either 2 per cent lidocaine HCl or 0.5 per cent bupivacaine HCl alone, or of any of three different mixtures of the two agents, all solutions containing 1:200,000 epinephrine. The subjects of the study were 60 healthy patients classified ASA I or II and undergoing lower abdominal surgery. After a detailed explanation of the protocol, ¶ informed written consent was obtained on the night before surgery. Twelve patients were allocated randomly into five groups, each group receiving a different local anesthetic solution. The composition of the local anesthetic solutions tested and the characteristics of the patients studied are shown in table 1.

PATIENT PREPARATION AND ASSESSMENT

Each patient was premedicated with 10 mg diazepam orally two hours before surgery. Prior to commencing the epidural block, an intravenous cannula was inserted and one liter of balanced saline solution was administered by the time surgery commenced. In the opposite arm, a

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TABLE 1. Composition of Local Anesthetic Solutions and Characteristics of Patients Assigned to Each Group

Group	4L*	3L:1B	2L:2B	1L:3B	4B
Local Anesthetic Solution					
2 per cent lidocaine HCl (ml)	20	15	10	5	0
0.5 per cent bupivacaine HCl (ml)	0	5	10	15	20
*p*H of mixture	4.0	3.9	3.8	3.7	3.6
Patient Characteristics†					
Age (years)	45 (15)	54 (15)‡	37 (11)	37 (9)	32 (10)
Weight (kg)	62 (12)	74 (10)‡	61 (9)	64 (14)	63 (9)
Height (cm)	165 (10)	172 (12)	167 (11)	162 (11)	164 (9)
Operation duration (min)	43 (3)	48 (3)	48 (3)	49 (2)	45 (3)

* All solutions contain 1:200,000 epinephrine.
† Mean (SD).
‡ Significantly different to other groups ($P < 0.05$).

central venous catheter was inserted so that by measurement, its tip was in the subclavian vein. This was used for sampling blood for pharmacokinetic purposes. Blood pressure was recorded by sphygmomanometry and pulse rate by palpation, prior to, and every 5 min following, the epidural injection. Mean arterial pressure (MAP) was derived from diastolic pressure plus 1/3 pulse pressure. Two thermistor probes were taped to the plantar surface of each great toe and connected to a two-channel telethermometer with chart recorder to monitor the progress of sympathetic blockade.

With the patient in either the right or left lateral position, an anesthesiologist administered the epidural blockade at the L1–2 interspace, using a single-dose technique. Local anesthetic solutions were mixed at the bedside from commercially available epinephrine-containing solutions (table 1). A standardized volume of the 20 ml local anesthetic solution was administered via the 18swg Tuohy needle at a rate of 1 ml/s and with the bevel of the needle facing caudally. The patient was then turned supine and a separate assessor, who was unaware of which drug was injected, commenced clinical observations of sensory and motor blockade.

Sensory Blockade

Sensory blockade at each dermatome was assessed every 2 min for 20 min and then every 5 min until surgery commenced at 40 min. Partial sensory blockade was defined as loss of pin prick sensation, and complete sensory blockade as loss of touch sensation. Latency of onset was defined as follows: initial—the time at which sensory blockade occurred at any one dermatome bilaterally; ±4 segments—the time at which 4 segments above and below the level of injection were blocked (as an index of readiness for surgery); complete—the time at which no further progression of blockade occurred; and S1—the time at which blockade occurred of the dermatome over the lateral aspect of the foot and little toe.

Duration of sensory blockade was recorded as follows: ±2 segment regression—time from complete spread to regression of 2 dermatomes; ±4 segment regression—time from onset of sensory blockade in 4 segments to regression of the same; and duration of each dermatome blocked from onset to offset.

Motor Blockade

Motor blockade in the lower limbs was assessed every 5 min as above by testing power of a specific joint movement of both lower limbs which were regarded as equivalent to the following myotomes: L2—hip flexion; L3—knee extension; L4—ankle dorsiflexion; L5—big toe dorsiflexion; and S1—ankle plantar flexion.

This was regarded as the most practical, albeit indirect, assessment of accompanying abdominal muscle relaxation. Time to onset of partial motor blockade was defined as time to any reduction in power, complete motor blockade as absent power at a myotome, and intensity of motor blockade was recorded as myotome score, which was the number of myotomes blocked from 0 to maximal 10 (*i.e.*, 5 myotomes in each lower limb).

Forty-five minutes after epidural blockade, light general anesthesia was induced with 1 mg/kg iv methohexitone and maintained with 4:2 l/min nitrous oxide/oxygen and 0.5 per cent halothane, with patients breathing spontaneously through a Mapleson A circuit.

Postoperatively, clinical evaluation of sensory and motor profiles were continued in the recovery room at 15-min intervals for a further period of four hours or until return of sensory and motor functions, whichever occurred earlier.

PHARMACOKINETIC STUDIES

Blood samples for pharmacokinetic studies were obtained prior to and at 5 min intervals for 45 min, after the epidural blockade. Lidocaine and bupivacaine blood concentrations were determined with the gas chromatographic technique of Mather and Tucker,[13] using a nitrogen selective detector and mepivacaine as the internal standard. From these data, maximum blood concentra-

tions (C_{max}) and the times at which C_{max} occurred (T_{max}) were determined by inspection. The areas under the blood concentration time curves from 0 to 45 min (AUC) were determined by application of the trapezoidal rule using a digital computer. Because different amounts of agents were injected between groups, comparisons of C_{max} and AUC were adjusted for mass of each component injected.

Statistical Analysis

Data analysis was performed on a digital computer (Digital Equipment Corporation DEC-10®) using the Statistical Package for the Social Sciences[14] and nonparametric methods. Specifically, Kruskal-Wallis analysis of variance was used to examine inter- and intragroup variability and the Spearman correlation test was used to examine variables as a function of the concentrations of components. A probability of $P < 0.05$ was regarded as statistically significant.

Results for the variables have been reported as mean and standard deviation to facilitate calculated comparisons between groups.

Results

Patient Variables

There were no significant differences in the mean height of patients or the duration of surgery among the five groups (table 1). In spite of random allocation, both the mean age and weight of Group 3L:1B were significantly greater than the other groups. Therefore, age and weight were used as covariates in the analysis of data but there was no change in the statistical outcome when these parameters were excluded as covariates.

Sensory Blockade

There were no significant differences among the five groups for time to onset of partial and complete sensory blockade (fig. 1, table 2) or for number of dermatomes blocked at 40 min after injection. The duration of partial sensory blockade of segments T11–S5 was significantly longer for Group 4B, as was the duration of complete sensory blockade of segments T11–L5 and S3–S5. The duration of both partial and complete sensory blockade correlated with the fractional dose of bupivacaine in the solution (table 3).

Motor Blockade

Among the five groups, there was no significant difference in latency of partial motor blockade. However the latency of complete motor blockade was significantly longer in Group 1L:3B (table 4). Mean myotome score for complete motor blockade was greatest with Group 2L:2B but least with Group 1L:3B, during the period from 15 to 35 min after administration of the epidural blockade (fig. 2). Group 1L:3B consistently had the greatest mean myotome score for partial motor blockade at all time intervals from 15 min to 4 h postoperatively, although statistical significance ($P < 0.05$) was only obtained in half of these time intervals.

Sympathetic Blockade

The times of onset and the magnitude of the rise in the temperature of the great toe were similar in all five groups (table 5). However, the duration of the maximum rise in temperature was significantly longer in Group 4B, shortest in Group 4L, and intermediate in the three mixtures.

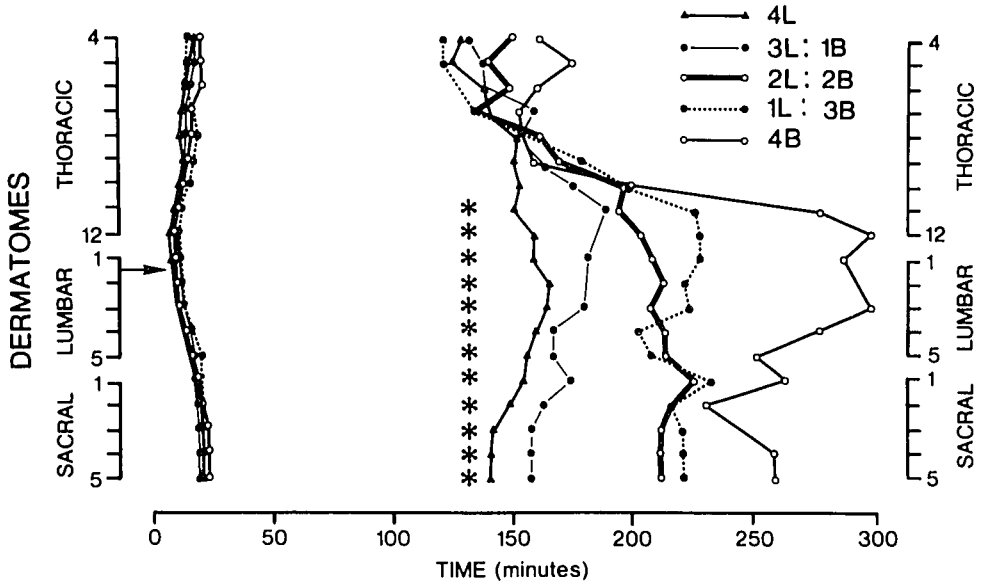

FIG. 1. Mean time-segment diagram for partial sensory blockade at each dermatome level. Data points plotted are mean values. (—) = site of injection of local anesthetics. *Denotes significant difference among groups ($P < 0.05$). A similar time-segment diagram for complete sensory blockade was obtained.

TABLE 2. Onset of Bilateral Sensory Blockade

Group	4L	3L:1B	2L:2B	1L:3B	4B	*P**
Partial Sensory Block‡						
Initial onset (min)	6 (3)	7 (4)	6 (3)	7 (2)	5 (2)	NS†
±4 segments spread (min)	13 (8)	12 (4)	15 (8)	16 (7)	12 (5)	NS†
Complete spread (min)	26 (9)	23 (7)	30 (10)	27 (11)	27 (8)	NS†
S1 block onset (min)	16 (9)	14 (7)	14 (11)	15 (7)	14 (10)	NS†
Complete Sensory Block‡						
Initial onset (min)	12 (6)	9 (5)	10 (6)	14 (6)	16 (11)	NS†
±4 segment spread (min)	25 (12)	14 (5)	26 (14)	33 (12)	26 (17)	NS†
Complete spread (min)	35 (9)	32 (8)	36 (9)	37 (10)	39 (8)	NS†
S1 block onset (min)	30 (14)	24 (4)	24 (18)	37 (6)	30 (14)	NS†
Number of patients with complete S1 blockade	3	6	4	3	3	

* Probability of significant difference among groups (Kruskal-Wallis test).

† No significant difference among the groups ($P > 0.05$).

‡ Mean (SD).

HEMODYNAMICS

In each group, mean arterial pressure (MAP) was reduced significantly following epidural blockade, the maximum decrease being greatest for group 3L:1B (table 5). However, the lowest MAP after the block was not significantly different from that following the induction of general anesthesia. Heart rate did not differ significantly among the five groups following the epidural blockade but decreased 15 per cent following induction of anesthesia.

PHARMACOKINETICS

When the individual values of C_{max} were adjusted for each 100 mg of agent injected, there were no significant differences between the groups. However T_{max} and AUC (per 100 mg) were weakly inversely correlated with the fraction of bupivacaine in the mixtures (Spearmans r −0.37 [$P < 0.02$] and −0.24 [$P < 0.02$], respectively, table 6).

Discussion

Two important findings have emerged from this study. First, it was found that epidural injection of mixtures of lidocaine and bupivacaine resulted in no substantial advantage over either agent alone. Second, maximum blood concentrations associated with the various mixtures of lidocaine and bupivacaine were the same as if the components had been injected individually.

The finding that time to onset of sensory blockade did not differ among the local anesthetic mixtures was in agreement with an analogous study of epidural anesthesia using chloroprocaine–bupivacaine mixtures.[12] In the present study, the number of spinal segments with sensory block at 40 min postinjection did not differ among the groups. Delay in onset of complete blockade of the large S1 root[15] was similar in all groups. Although partial sensory block of S1 was obtained in all patients, only a few patients in each group had complete sensory and motor blockade of S1. Thus, when safe doses of local anesthetic were injected into the epidural space via the needle, the onset of sensory blockade was as rapid for bupivacaine as for lidocaine. This suggests that bulk flow and rapid transfer of amide local anesthetics into spinal fluid, perhaps via arachnoid granulations in dural cuff regions, is the major determinant of onset of action.[16] Alternatively, local ischemia exerted by epinephrine has an overwhelming influence and nullifies the individual characteristics of the agents.[16] However, when smaller

TABLE 3. Duration of Sensory Blockade

Group	4L	3L:1B	2L:2B	1L:3B	4B	*r**
2 Segment Regression†						
Partial (min)	84 (45)	99 (27)	98 (31)	108 (33)	138 (68)	0.38‡
Complete (min)	76 (30)	73 (29)	89 (35)	77 (33)	113 (51)	0.22‡
±4 Segment Regression†						
Partial (min)	132 (64)	140 (21)	151 (67)	147 (57)	168 (44)	0.22‡
Complete (min)	100 (55)	81 (26)	100 (46)	79 (19)	135 (48)	0.17‡

* r Spearman nonparametric correlation coefficient for duration with increasing dose of bupivacaine.

† Mean (SD).

‡ $P < 0.05$.

TABLE 4. Times to Onset of Bilateral Motor Blockade

Group	4L	3L:1B	2L:2B	1L:3B	4B	P*
Partial Motor Block†						
Initial onset (min)	8 (3)	13 (7)	10 (3)	16 (10)	14 (10)	NS‡
Complete spread (min)	27 (14)	25 (7)	27 (10)	28 (14)	27 (14)	NS‡
S1 onset (min)	25 (14)	25 (14)	19 (10)	34 (24)	28 (17)	NS‡
Number of patients with partial S1 blockade	4	5	7	4	4	
Complete Motor Block†						
Initial onset (min)	16 (7)	18 (7)	15 (7)	28 (14)	19 (3)	0.01
Complete spread (min)	35 (10)	26 (10)	24 (14)	36 (14)	29 (14)	NS‡
S1 onset (min)	40	35 (14)	24 (14)	—	45	NS‡
Number of patients with complete S1 blockade	1	2	4	0	1	

* Probability of significant difference among groups (Kruskal-Wallis test).

† Mean (SD).

‡ No significant difference among the groups ($P > 0.05$).

doses are injected epidurally, differences between agents have been detected by comparing the time of onset of blockade of the S1 outflow.[17,18]

It would not have been surprising if the duration of sensory blockade had been positively correlated with the dose of bupivacaine in the local anesthetic mixture. However, the correlation was so weak so that the only group with a distinct prolongation of sensory blockade was that where bupivacaine alone was used. These findings support those of Moore *et al.*[11] who reported increased duration of analgesia when tetracaine crystals were added to lidocaine solution to make a mixture of approximately 1:3.

Degree of motor blockade sufficient for abdominal surgery can be achieved by epinephrine-containing solutions of 2 per cent lidocaine, 1.5 percent etidocaine, or 0.75 per cent bupivacaine. However, persistence of motor blockade into the postoperative period, particularly after surgery of short duration, is undesirable. Thus, mixtures of 2 per cent lidocaine and 0.5 per cent bupivacaine theoretically could retrain the high degree of motor blockade of lidocaine for the duration of surgery and the longer analgesic property of bupivacaine for postoperative analgesia. In this study, the mixture containing equal proportions by volume of 2 per cent lidocaine and 0.5 per cent bupivacaine resulted in a greater number of myotomes with complete motor blockade between 15 and 40 min after injection, as well as the highest frequency of S1 motor blockade. Therefore, this mixture would appear to be useful for a single-dose epidural blockade where motor paralysis is required for the operative procedure followed by some residual postoperative analgesia.

Duration of blockade of sympathetic vasoconstrictor fibers was similar for all three mixtures but lidocaine alone was of significantly shorter duration than bupivacaine alone. Blood pressure and heart rate decreased following epidural blockade in all five groups, presumably reflecting sympathetic blockade. Subsequent induction of light general anesthesia resulted in no further change in blood pressure and this is in keeping with previous studies of epidural blockade and light general anesthesia.[19] However, pulse rate was decreased significantly after general anesthesia. This may have been due to the negative chronotropic effect of halothane, in addition to epidural sympathetic blockade.

In a previous pharmacokinetic study of a mixture of ester and amide local anesthetics chloroprocaine and bupivacaine, Raj *et al.* reported that the T_{max} values of the components were separated widely but for a mixture of the amides, lidocaine, and bupivacaine, similar values of T_{max} resulted.[20] Recent blood concentration data obtained with a specific assay for chloroprocaine[21] have invalidated the conclusion regarding the amide-ester mixture. However, the current study agrees with the

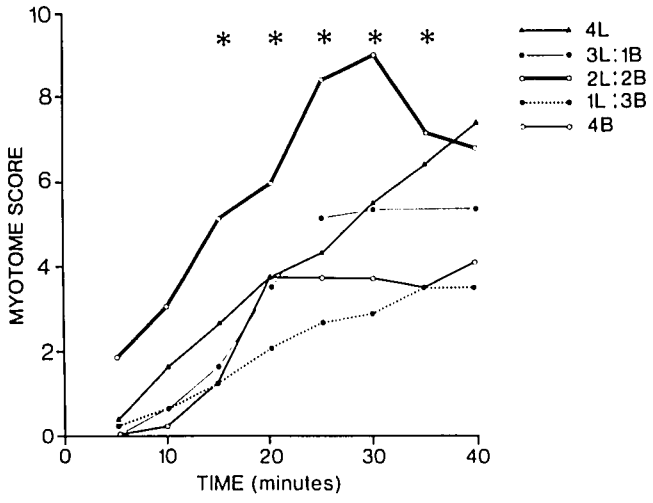

FIG. 2. Mean time-myotome score for total number of myotomes with complete motor blockade at each time interval after administration of epidural blockade (maximum possible number = 10 myotomes, *i.e.*, five for each right and left side). *Denotes significant difference among groups ($P < 0.05$).

TABLE 5. Sympathetic Blockade Indicated by the Skin Temperature at the Great Toe and Decrease in Mean Arterial Pressure (MAP) after Administration of Epidural Blockade

Group	4L	3L:1B	2L:2B	1L:3B	4B	P*
Skin temperature						
Maximum change in temperature (°C)‡	7 (0.7)	7 (0.4)	9 (0.5)	7 (1.6)	8 (0.6)	NS†
Time to initial rise (min)‡	10 (3)	8 (2)	9 (2)	7 (2)	7 (1)	NS†
Time to maximum rise (min)‡	31 (6)	25 (4)	24 (5)	21 (5)	23 (4)	NS†
Duration of maximum rise (min)‡	124 (13)	136 (20)	166 (26)	182 (27)	286 (32)	0.001
Mean Arterial Pressure						
Maximum decrease between 0–40 min (mmHg)‡	20 (4)	30 (4)	10 (2)	15 (4)	10 (4)	0.01
After induction of general anesthesia‡	15 (3)	10 (4)	15 (3)	10 (6)	10 (2)	NS†

* Probability of significant difference among the groups (Kruskal-Wallis test).

† No significant difference among the groups ($P > 0.05$).

‡ Mean (SD).

finding of similar values of T_{max} for the amide mixture components. Under these conditions toxicity would be expected to be additive, and this is supported by studies of direct intravenous infusions in monkeys.[22]

While the blood concentrations found in this study were in the range considered to be without toxicity,[16] it should be remembered that the relative toxicity of bupivacaine is approximately four times that of lidocaine.[16,22] By expressing the C_{max} values from table 6 as lidocaine equivalents (1 mg/l bupivacaine = 4 mg/l lidocaine), a comparison between the toxic potentials of the different solutions administered epidurally may be obtained. Thus, for solutions 4L and 4B, respectively, the toxic potentials are 3.2 and 2.4 mg/l lidocaine equivalents. Similarly, the toxic potentials for solutions 3L:1B, 2L:2B, and 1L:3B are, respectively, 2.1, 2.4, and 2.2 mg/l lidocaine equivalents, *i.e.*, the presence of bupivacaine does not increase the toxicity. In fact, based on intravenous data in healthy adults,[16] the presence of bupivacaine still would not increase the toxic potential even though all solutions would produce intense toxicity if rapidly injected intravenously.

In conclusion, there was little evidence of any advantage of mixing lidocaine with bupivacaine when maximum clinical doses are injected via the needle for epidural anesthesia. If an epidural catheter is inserted, individual drugs can be chosen to obtain optimal motor and sensory blockade for surgery and then sensory block without motor blockade postoperatively. Only when single-dose techniques are used does the 1:1 mixture of lidocaine: bupivacaine appear to have some merit in achieving rapid onset of motor blockade with persistence of analgesia postoperatively, although the gains are small.

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TABLE 6. Pharmacokinetic Analysis of Vascular Absorption of Lidocaine and Bupivacaine

Group	4L	3L:1B	2L:2B	1L:3B	4B	r*
C_{max}† ($mg \cdot l^{-1} \cdot 100\ mg^{-1}$)‡						
Lidocaine	0.8 (0.5)	0.5 (0.3)	0.6 (0.2)	0.7 (0.3)	—	NS§
Bupivacaine	—	0.6 (0.5)	0.6 (0.2)	0.5 (0.2)	0.6 (0.2)	NS§
T_{max} (min)‡						
Lidocaine	17 (5)	20 (8)	25 (6)	17 (9)	—	NS§
Bupivacaine	—	22 (8)	18 (9)	15 (6)	14 (6)	−0.37¶
AUC† ($mg \cdot l^{-1}\ min \cdot 100\ mg^{-1}$)‡						
Lidocaine	21 (8)	16 (7)	19 (7)	21 (9)	—	NS§
Bupivacaine	—	19 (5)	18 (5)	16 (6)	17 (6)	−0.24¶

C_{max} = maximum blood concentration achieved. T_{max} = time at which maximum blood concentration was achieved. AUC = area under concentration-time curve 0–45 min.

* Spearman nonparametric correlation coefficient for effect with increasing dose of bupivacaine.

† Note that these values are adjusted per 100 mg of agent injected.

‡ Mean (SD).

§ No significant difference among the groups.

¶ $P < 0.02$.

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