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## Dose-Response Characteristics of Spinal Bupivacaine in Volunteers

### Clinical Implications for Ambulatory Anesthesia

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**Background:** Small doses of bupivacaine may be a reasonable choice for spinal anesthesia for patients having ambulatory surgery. However, few dose-response data are available to guide the selection of reasonable doses of bupivacaine for different ambulatory procedures.

**Methods:** Eight volunteers per group were randomized to receive 3.75, 7.5, or 11.25 mg of 0.75% bupivacaine with 8.25% dextrose in a double-blind manner. Sensory block was assessed with pinprick, transcutaneous electrical stimulation equivalent to surgical incision at the ankle, knee, pubis, and umbilicus, and with duration of tolerance to pneumatic thigh tourniquet. Motor block at the quadriceps and gastrocnemius muscles was assessed with isometric force dynamometry. Times until recovery from spinal anesthesia were recorded. Dose-response relationships were determined by linear regressions. Mean (95% confidence intervals) for durations of sensory and motor block per milligram of bupivacaine administered were calculated from linear regressions.

**Results:** Significant dose-response relationships ( $P < 0.006$ ) were determined for sensory block, motor block, and time until recovery (R from 0.6 to 0.9). Within the range of doses studied, each additional milligram of bupivacaine was associated with an increase in duration of tolerance to transcutaneous electrical stimulation of 10 (7 to 13) min, an increase in tolerance to tourniquet of 7 (2 to 11) min, an increase in duration of motor block of 8 (5 to 12) min, and an increase in time until recovery of 21 (17 to 25) min.

**Conclusions:** These dose-response data may guide the selection of reasonable doses of bupivacaine for various outpatient procedures, although individual responses vary. (Key words:

Anesthesia: ambulatory. Anesthetic techniques: spinal. Anesthetics, local: bupivacaine. Pain: tourniquet, tetanic stimulation.)

INTEREST has recently increased in using small doses of spinal bupivacaine as an alternative to lidocaine for outpatient surgery.<sup>1-4</sup> Lidocaine has enjoyed great popularity as a spinal anesthetic for brief procedures,<sup>5</sup> but concerns have arisen regarding potential neurotoxicity.<sup>1,3,6-8</sup> Spinal anesthesia with 5%, 2%, and 1.5% lidocaine have all been reported to produce transient neurologic complaints in humans.<sup>1,3,5,9-11</sup> In contrast, prospective studies comparing spinal bupivacaine with lidocaine have found lower incidences of transient neurologic complaints after use of bupivacaine (0.6% vs. 28% on average).<sup>1,3,12,13</sup> These findings have prompted recent editorials questioning the use of hyperbaric 5% lidocaine for spinal anesthesia<sup>4,5</sup> and recommending the consideration of spinal bupivacaine as a substitute.<sup>4</sup> Information regarding dose-response characteristics of small doses of bupivacaine for spinal anesthesia would be useful for selecting appropriate doses for ambulatory surgery. Unfortunately, most previous dose-response studies involving spinal bupivacaine have examined relatively large doses (7.5 to 20 mg) and have not quantitatively examined anesthetic recovery profiles.<sup>14-16</sup> Thus few data exist from which to guide selection of doses of spinal bupivacaine that provide adequate anesthesia with minimal recovery time for ambulatory surgery. This study was designed to determine dose-response characteristics of spinal bupivacaine in human volunteers from which clinical doses could be extrapolated for various ambulatory surgical procedures.

### Methods

After institutional review board approval and informed consent were acquired, eight volunteers per

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group were randomized to receive either 3.75, 7.5, or 11.25 mg of 0.75% bupivacaine with 8.25% dextrose in a double-blind manner. Randomization was stratified to include four men and four women in each group, and all participants were categorized as American Society of Anesthesiologists physical status 1. Participants fasted for 6 hours and voided immediately before each study. Lactated Ringer's solution was administered as a bolus of 6 ml/kg<sup>-1</sup> for 15 min before subarachnoid block, followed by 8 ml · kg<sup>-1</sup> · hr<sup>-1</sup> for the first hour, then maintenance infusion at a rate of 2 ml · kg<sup>-1</sup> · hr<sup>-1</sup>. With the volunteer in the left lateral decubitus position, lumbar puncture was performed at the L2-3 interspace with a 25-gauge Whitacre spinal needle through a 20-gauge introducer with the orifice of the spinal needle turned cephalad. Cerebrospinal fluid (0.2 ml) was aspirated, bupivacaine injected at a rate of approximately 0.25 ml · sec<sup>-1</sup>, and an additional 0.2 ml of cerebrospinal fluid was aspirated and reinjected after injection of bupivacaine. After injection, participants were immediately placed supine and they remained level for the rest of the study. All participants were monitored using an oscillometric blood pressure cuff (model 90603A; Spacelabs Medical, Redmond, WA) and pulse oximetry (Biox 3700; Ohmeda Inc., Liberty Corner, NJ). Blood pressures (from blood pressure cuff) and heart rates (from pulse oximeter) were recorded every 5 min while the rest of the spinal anesthetic was administered. Volunteers were questioned 24 and 48 hours after each study period for symptoms of transient radicular irritation (back pain radiating down a lower extremity with resolution within 72 hr).<sup>9</sup>

Tolerance to transcutaneous electrical stimulation (TES) equivalent to surgical incision was assessed as previously described.<sup>11</sup> Leads for TES were placed at the umbilicus, pubis, medial knee, and lateral ankle. Five seconds of 50-Hz tetanus at 60 mA with a commercially available nerve stimulator (model NS252; Fisher & Paykel, Auckland, New Zealand) was considered equivalent to surgical incision.<sup>17,18</sup> Tolerance to electrical stimulation was assessed at baseline, 4 min after injection of spinal solution, and every 10 min thereafter by initially testing with 10 mA and then increasing in 10-mA increments to a maximum of 60 mA for 5 sec. Each TES location was tested in a systematic order moving from distal to proximal sites. In addition, dermatomal levels to pinprick (18-G needle) were measured at baseline and every 5 min after injection of spinal solution until recovery of pinprick at S2.

Fifteen minutes after injection of bupivacaine, the

left leg was exsanguinated by gravity, and a 7-cm orthopedic pneumatic tourniquet was inflated around the left mid-thigh to 300 mmHg. The volunteers were instructed that the tourniquet would be deflated when discomfort became intense enough that they would request supplemental anesthesia. A cutoff time of 2 hr after inflation was used.

A commercially available isometric force dynamometer (Micro FET; Hoggan Health Industries, Draper, UT) was used to assess 5-sec isometric maximal force contraction of the right quadriceps and gastrocnemius, as previously reported.<sup>11</sup> Measurements were performed at baseline and every 10 min after injection until return to at least 90% of baseline. Measurements were performed in triplicate and averaged for each measurement period.

Discharge criteria were defined as recovery of sensation to pinprick at dermatome S2, ability to walk without assistance, and ability to void. Participants tried to fulfill all criteria immediately after recovery of sensation to pinprick to S2 and every 10 min thereafter.

#### Statistical Analysis

Dose-response relationships were determined with linear regression. For bilateral measurements, averaged values were used. Mean and 95% confidence intervals of predicted durations of sensory block, motor block, and duration until achievement of discharge criteria per milligram increment of spinal bupivacaine were calculated from the mean and 95% confidence intervals of the slope of the regression line. Baseline heart rate and systolic blood pressure were defined as measurements obtained in the supine position immediately before positioning for anesthesia. Maximal measured depression in heart rate and systolic blood pressure was defined as the difference between baseline hemodynamics and the lowest measured values in the first 60 min after injection of spinal anesthetic. Significance was defined as  $P < 0.05$ .

## Results

Spinal anesthesia (aspiration of cerebrospinal fluid before and after injection) was successful in all participants. Their demographics were similar in the three groups (table 1). Durations of sensory and motor block increased with increasing dose of bupivacaine (figs. 1 to 5 and table 2). Significant dose-response relationships ( $R$  from 0.6 to 0.9,  $P < 0.006$ ) were determined

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**Table 1. Subject Demographics**

	Dose of Bupivacaine (mg)		
	3.75	7.5	11.25
Age (yr)	35 ± 7	35 ± 7	34 ± 5
Height (cm)	152 ± 8	152 ± 6	153 ± 8
Weight (kg)	67 ± 10	67 ± 12	65 ± 11
Baseline heart rate (beats/min)	71 ± 11	69 ± 15	70 ± 13
Baseline systolic blood pressure (mmHg)	116 ± 11	108 ± 6	116 ± 6

Values are mean ± SD.

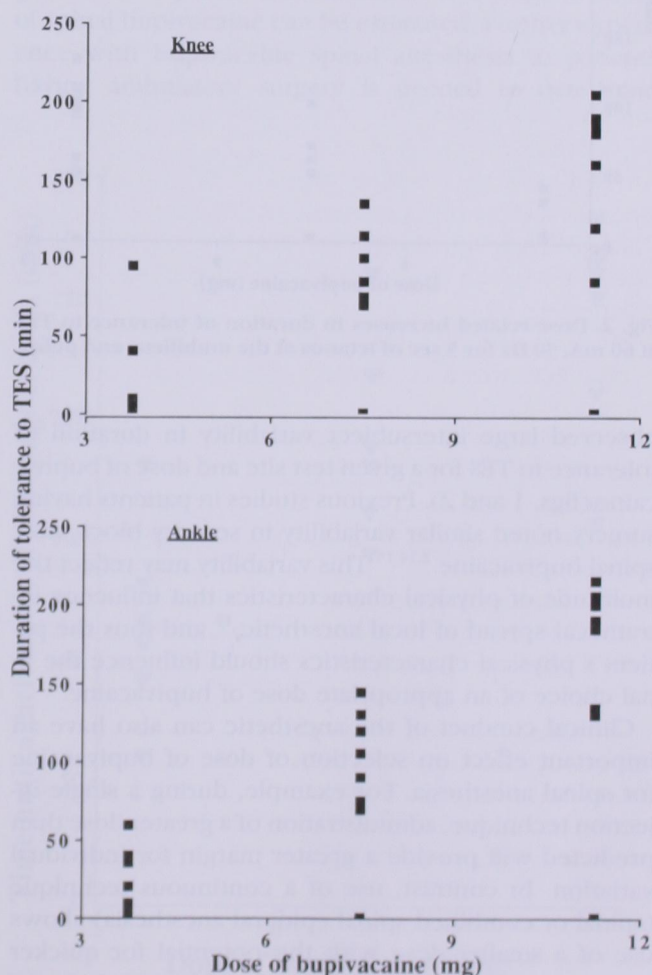
for bupivacaine and tolerance to electrical stimulation, tolerance of tourniquet, motor block, and time until achievement of discharge criteria (table 3). Within the dose range studied, each additional milligram of bupivacaine was associated with a mean increase in duration of tolerance to TES ranging from 5 min at the umbilicus to 15 min at the ankle, an increase in tolerance to tourniquet of 7 min, an increase in duration of motor block of 6 to 10 min, and an increase in time until achievement of discharge criteria of 21 min (table 3). Dose of bupivacaine did not correlate with maximal hemodynamic depression measured in the first 60 min (fig. 6). One volunteer reported back pain radiating down both legs after receiving 11.25 mg of bupivacaine; the pain resolved within 48 hours.

## Discussion

Hyperbaric spinal bupivacaine produced dose-dependent sensory block, tolerance to tourniquet pain, motor block, and time until full recovery from anesthesia. All of these measurements have clinical implications. Increasing doses of spinal bupivacaine produced increasing cephalad spread and increased the duration of sensory block to pinprick. Previous dose-response studies using single-injection spinal anesthesia have noted similar peak dermatomal levels of sensory block to pinprick (from T9 to T4) within doses of hyperbaric bupivacaine ranging from 7.5 to 12 mg.<sup>14-16</sup> Our observations of increasing durations of sensory block to pinprick are also consistent with previous reports of durations until recovery of pinprick at dermatome S2 of 150 to 240 min for doses ranging from 7.5 to 15 mg.<sup>14,15</sup> However, sensory block to pinprick provides uncertain information about depth of anesthesia and subsequent tolerance of surgical incision. Transcutaneous electri-

cal stimulation has been shown to provide a stimulus equivalent to surgical incision in studies of minimum alveolar concentration of volatile anesthetics.<sup>17,18</sup> Thus duration of tolerance to TES provides a reasonable model for predicting duration of surgical depth of spinal anesthesia at multiple test sites.

Duration of tolerance to TES displayed a significant dose-response relationship at each site tested. These data can guide clinical selection of a dose of bupivacaine for a desired duration of surgical anesthesia for various surgical sites (table 3). Our dose-response relationships only indicate estimated durations of tolerance to an electrical model of surgical stimulation, and thus an individual dose of bupivacaine should be further refined based on clinical judgment. For example, we



**Fig. 1.** Dose-related increases in duration of tolerance to transcutaneous electrical stimulation (TES) at 60 mA, 50 Hz for 5 sec of tetanus at the knee and ankle.

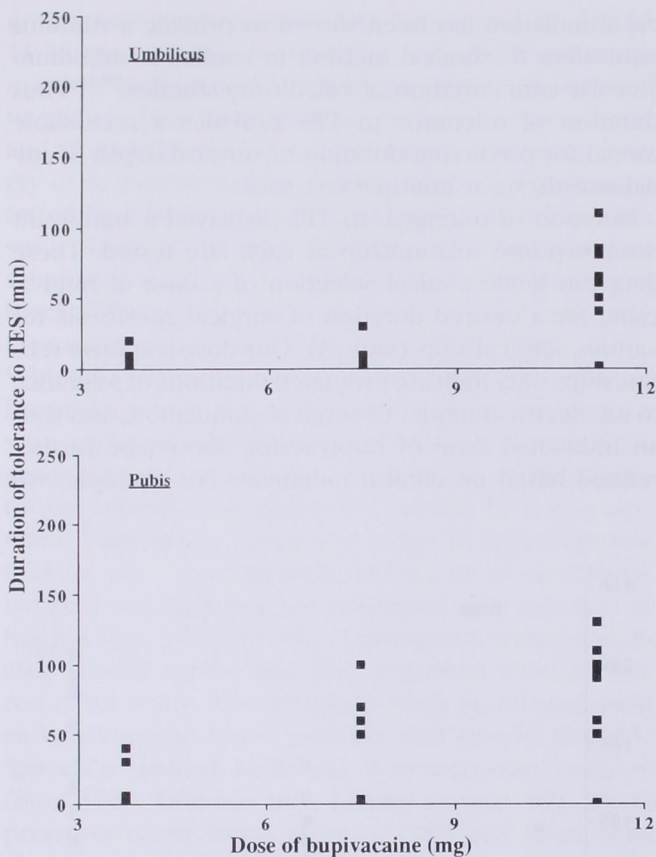


Fig. 2. Dose-related increases in duration of tolerance to TES at 60 mA, 50 Hz for 5 sec of tetanus at the umbilicus and pubis.

observed large intersubject variability in duration of tolerance to TES for a given test site and dose of bupivacaine (figs. 1 and 2). Previous studies in patients having surgery noted similar variability in sensory block after spinal bupivacaine.<sup>2,14,15</sup> This variability may reflect the multitude of physical characteristics that influence intrathecal spread of local anesthetic,<sup>19</sup> and thus the patient's physical characteristics should influence the final choice of an appropriate dose of bupivacaine.

Clinical conduct of the anesthetic can also have an important effect on selection of dose of bupivacaine for spinal anesthesia. For example, during a single injection technique, administration of a greater dose than predicted will provide a greater margin for individual variation. In contrast, use of a continuous technique (spinal or combined spinal epidural anesthesia) allows use of a smaller dose with the potential for quicker recovery from spinal anesthesia. In addition, choice of intravenously administered adjuncts can affect spinal anesthesia. A previous study found increased cephalad

extension of sensory analgesia from spinal anesthesia after administration of fentanyl.<sup>20</sup> Therefore, we emphasize that our study only provides an estimate of appropriate doses of spinal bupivacaine, and other clinical factors should also guide in selection of an individual dose of bupivacaine.

Pneumatic tourniquets are frequently used for lower-extremity procedures. Tourniquet pain is a poorly understood phenomenon<sup>21</sup> that may compromise an otherwise satisfactory spinal anesthetic. Bupivacaine may be especially useful in procedures requiring lower-extremity tourniquets, because previous studies suggest that spinal bupivacaine is particularly efficacious in preventing tourniquet pain.<sup>22</sup> We observed a significant dose-response relationship between spinal bupivacaine and duration of tolerance to tourniquet pain that can help the anesthesiologist select an adequate dose.

Motor block of lower extremities is often desirable for surgical procedures.<sup>23</sup> Selection of a dose of spinal bupivacaine to provide adequate motor block has been problematic because of the poor motor blocking characteristics of spinal bupivacaine.<sup>24,25</sup> We used isometric force dynamometry and frequent measurements to sensitively measure motor block of the quadriceps and gastrocnemius muscles for a range of doses of bupivacaine appropriate for outpatient anesthesia. Motor

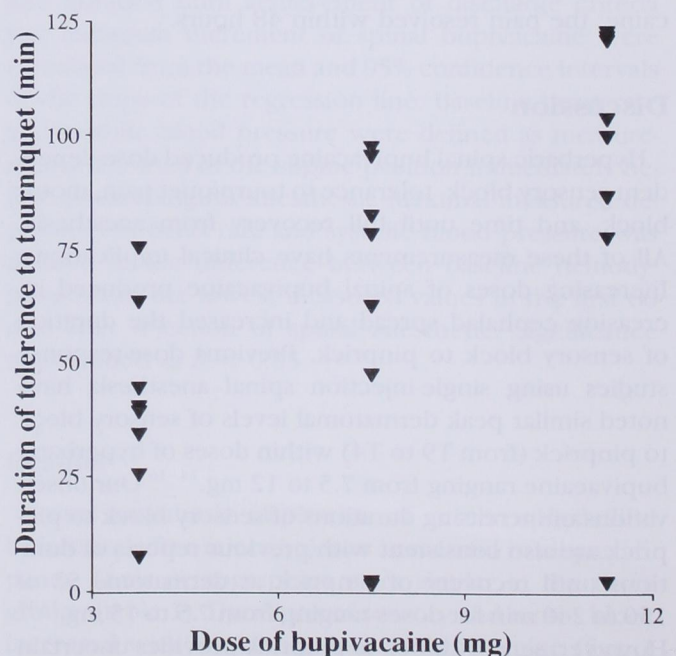


Fig. 3. Dose-related increases in duration of tolerance to pneumatic thigh tourniquet.

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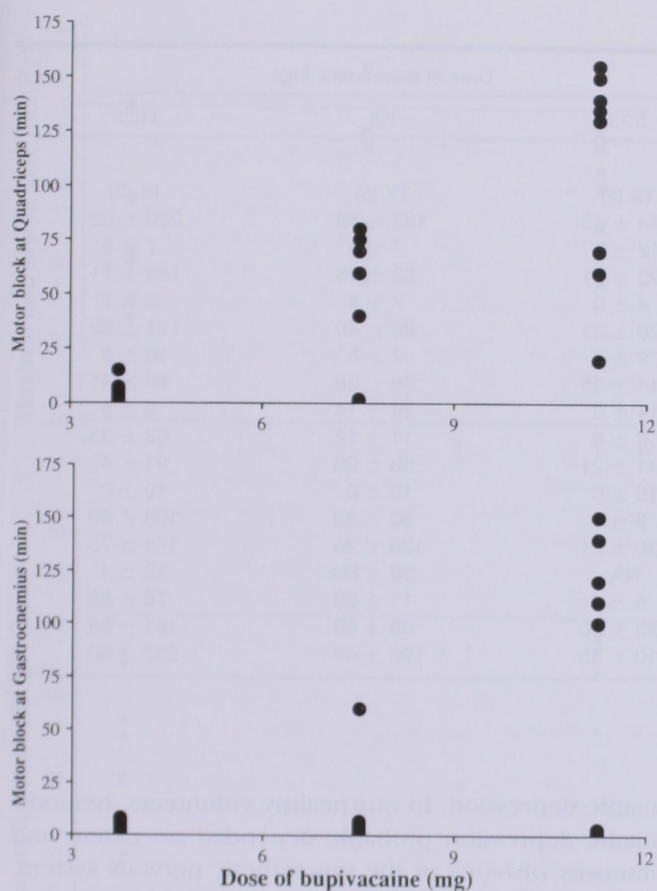


Fig. 4. Dose-related increases in duration of complete motor block at the quadriceps and gastrocnemius muscles as assessed with isometric force dynamometry.

block, especially at the gastrocnemius, was often incomplete and of brief duration for the doses studied (fig. 4 and table 2). These findings correlate with those of previous studies examining doses of bupivacaine ranging from 7.5 to 15 mg that reported durations of complete motor block ranging from 84 to 120 min.<sup>14-16</sup> We speculate that the poor motor-blocking characteristics of spinal bupivacaine may be due to preferential block of sensory fibers.<sup>22</sup> In addition, the least amount of motor block was seen in the gastrocnemius muscle (innervated by S1-S2), yet the longest durations of sensory block occurred in the same sacral distribution. This discrepancy may be explained by the anatomic relationships of the motor and sensory nerve bundles of the sacral roots. Based on fresh cadaveric dissections, the motor bundle of the S1 nerve root lies more anteromedially than the sensory roots from the conus medullaris to vertebral disc level S1.<sup>26</sup> Because

we used a hyperbaric solution in supine patients, it is possible that the more ventral motor bundles of S1 were in contact with the least amount of local anesthetic and thus developed the least degree of conduction block.

The ability of patients' rapid recovery from outpatient anesthesia to improve use of postanesthesia care unit resources and decrease total perioperative costs is controversial.<sup>27,28</sup> Nonetheless, reasonable doses of bupivacaine for outpatient spinal anesthesia should provide the minimal amount of time required for complete recovery from anesthesia. We measured time until achievement of commonly used discharge criteria (recovery of sensation to pinprick at dermatome S2, ability to ambulate without assistance, and ability to void).<sup>2</sup> From these data, average time required for complete recovery after administration of a range of doses of spinal bupivacaine can be estimated. Further experience with bupivacaine spinal anesthesia in patients having ambulatory surgery is needed to determine

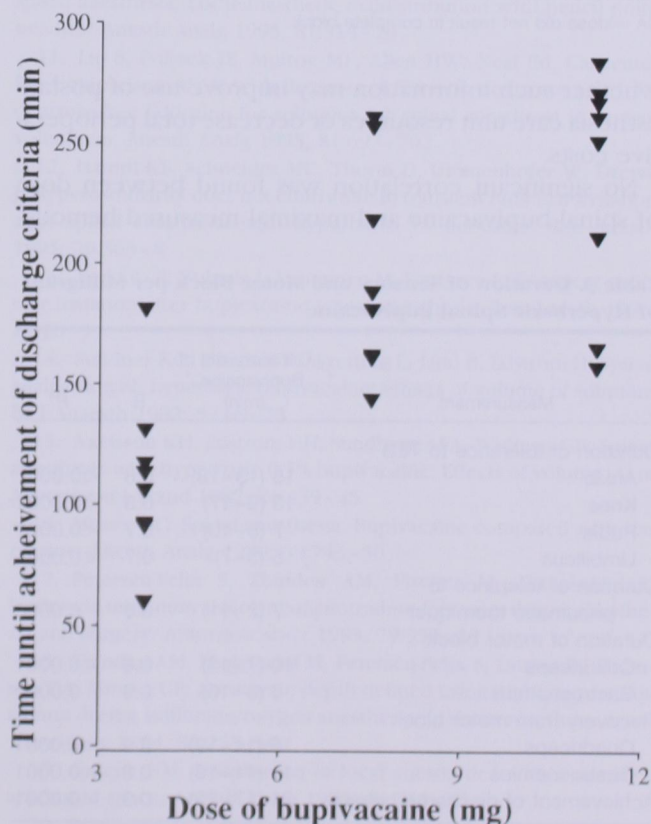


Fig. 5. Dose-related increases in duration until achievement of discharge criteria (regression of sensory block to pinprick to S2, ability to walk, ability to urinate).

**Table 2. Spinal Anesthesia Characteristics**

	Dose of Bupivacaine (mg)		
	3.75	7.5	11.25
Peak dermatomal block to pinprick [median (interquartile range)]	T9 (5)	T7 (5)	T4 (3)
Time until recovery of pinprick at S2 (min)	74 ± 43	133 ± 59	220 ± 52
Onset of tolerance to TES at ankle (min)	12 ± 9	7 ± 5	7 ± 3
Duration of tolerance to TES at ankle (min)	22 ± 21	92 ± 45	158 ± 71
Onset of tolerance to TES at knee	4 ± 0	7 ± 4	5 ± 2
Duration of tolerance to TES at knee	20 ± 31	82 ± 40	111 ± 62
Onset of tolerance to TES at pubis	9 ± 7	7 ± 5	10 ± 8
Duration of tolerance to TES at pubis	11 ± 15	36 ± 39	80 ± 41
Onset of tolerance to TES at umbilicus	14 ± 0	24 ± 14	8 ± 6
Duration of tolerance to TES umbilicus	6 ± 6	11 ± 12	62 ± 33
Duration of tolerance to pneumatic tourniquet	41 ± 21	58 ± 39	91 ± 40
Onset of motor block at quadriceps	10 ± 0	10 ± 0	10 ± 0
Duration of motor block at quadriceps	5 ± 4	50 ± 32	108 ± 50
Time until 90% recovery at quadriceps	30 ± 31	120 ± 20	174 ± 75
Onset of motor block at gastrocnemius	NA	30 ± NA	12 ± 4
Duration of motor block at gastrocnemius	5 ± 3	11 ± 20	78 ± 65
Time until 90% recovery at gastrocnemius	23 ± 20	68 ± 50	161 ± 55
Duration until achievement of discharge criteria	110 ± 35	196 ± 44	232 ± 50

Values are mean ± SD.

NA = dose did not result in complete block.

whether such information may improve use of postanesthesia care unit resources or decrease total perioperative costs.

No significant correlation was found between dose of spinal bupivacaine and maximal measured hemody-

**Table 3. Duration of Sensory and Motor Block per Milligram of Hyperbaric Spinal Bupivacaine**

Measurement	Duration · mg of Bupivacaine <sup>-1</sup> (min)	R	P*
Duration of tolerance to TES			
Ankle	15 (13–18)	0.8	<0.0001
Knee	13 (9–17)	0.8	<0.0001
Pubis	7 (5–10)	0.7	<0.0001
Umbilicus	5 (3–7)	0.7	<0.0001
Duration of tolerance to pneumatic tourniquet	7 (2–11)	0.6	0.0006
Duration of motor block			
Quadriceps	10 (7–13)	0.8	<0.0001
Gastrocnemius	6 (3–10)	0.6	0.0002
Recovery from motor block			
Quadriceps	16 (14–19)	0.9	<0.0001
Gastrocnemius	14 (11–18)	0.8	<0.0001
Achievement of discharge criteria	21 (17–25)	0.9	<0.0001

Values are mean (95% confidence interval). Values were derived from linear regression.

\* Significance of linear regression.

amic depression. In our healthy volunteers, hemodynamic depression probably depended on extent and intensity of block of the sympathetic nervous system. Both extent and intensity of sympathetic block after spinal anesthesia are controversial. Different techniques for measuring sympathetic function (cold, thermography, laser Doppler flowmetry, and skin conductance responses) display wide discrepancies in supposed extent of sympathetic block after spinal anesthesia.<sup>29–32</sup> Although spinal anesthesia has traditionally been thought to produce dense sympathetic block, recent studies indicate that high thoracic levels of spinal anesthesia in healthy volunteers result in incomplete sympathetic block (measured by cold pressor test) and correspondingly little effect on hemodynamics.<sup>31</sup> Thus the lack of correlation between dose of spinal bupivacaine and magnitude of hemodynamic depression may be explained by both variable extent and intensity of sympathetic block after spinal anesthesia.

In conclusion, we determined dose-response relationships between hyperbaric spinal bupivacaine and sensory block, motor block, and time until full recovery from spinal anesthesia. With the realization that individual responses to spinal anesthesia from small doses of bupivacaine are highly variable, these data may provide a guide for selection of doses of bupivacaine for various

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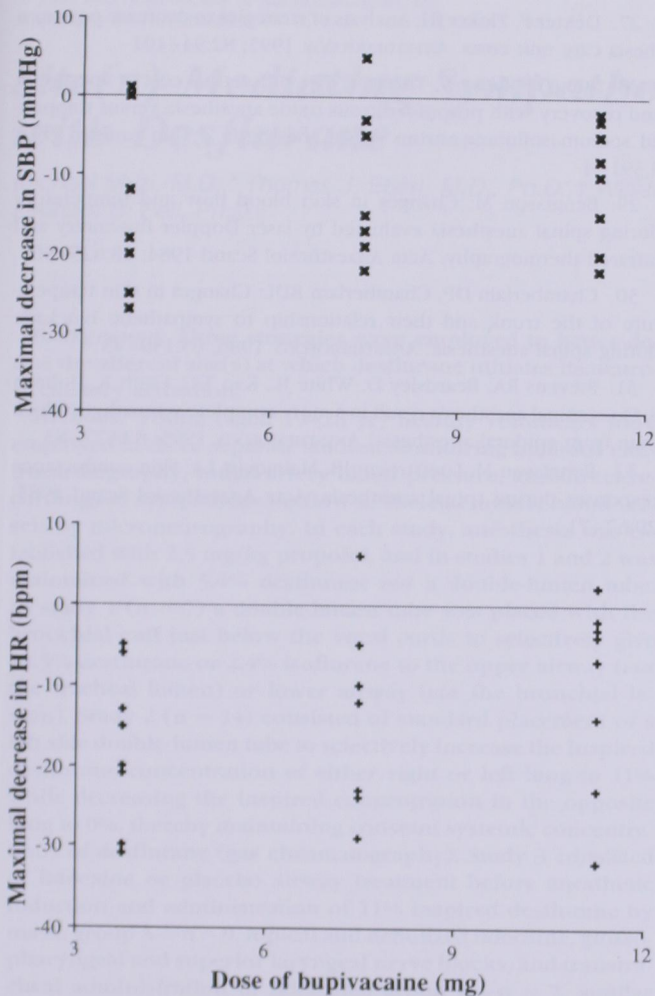


Fig. 6. Scattergrams showing lack of correlation ( $R$  from 0.2 to 0.3;  $P > 0.2$ ) between maximal measured hemodynamic depression and dose of spinal bupivacaine.

outpatient procedures. Further experience with low doses of spinal bupivacaine in patients having surgery are needed to confirm and refine optimal doses of spinal bupivacaine for ambulatory surgery.

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