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Regulation of Proprioceptive Memory by Subarachnoid Regional Anesthesia

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Background: **Patient perception of limb position during regional anesthesia is frequently incorrect. The existing model ascribes this misperception, or phantom sensation, as a reversion to a fixed, slightly flexed, body schema. A model was developed to evaluate the influence of limb position changes on the incidence of incorrect or phantom sensations during regional anesthesia.**

Methods: **Forty American Society of Anesthesiologists physical status I–III adult patients undergoing genitourinary procedures under subarachnoid anesthesia were assigned to a lidocaine or bupivacaine treatment group and randomly assigned to one of four time groups (1, 4, 7, and 10 min). After blockade, patients were placed supine and blinded to limb positioning manipulations. One leg was flexed and the contralateral leg extended, with leg positions subsequently reversed at the assigned time point. At 10 min, patients were asked to identify the position of each leg. Percentage of incorrect response was analyzed using a logistic regression model with two independent variables: treatment and time. A supplemental study was undertaken to evaluate the observed difference in incorrect perceptions relative to flexed first versus extended limb first sequencing.**

Results: **The inability to perceive a change in limb position under regional anesthesia is dependent on the time after the block that the position change is initiated in relation to the onset characteristics of the local anesthetic. A phantom sensation of an extended leg position clearly exists. The flexed-first limb has a significantly higher incidence of incorrect or phantom perceptions.**

Conclusion: **Proprioceptive memory involves a dynamic neuroplastic imprinting process that is influenced by limb or joint position prior to onset of regional anesthesia. This contrasts with previously held beliefs of a purely fixed body schema. (Key words: Phantom sensation; spinal anesthesia; spinal memory.)**

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PATIENT perception of limb position during regional anesthesia is frequently incorrect. Patients often perceive their arm or leg as bent or flexed when it is actually straight. Prior investigations have attributed this "phantom sensation" during regional block to the existence of a universal, fixed body schema derived from partially flexed, "position-of-rest" posture patterns in the central nervous system.[1] Phantom sensation may be more than an operating room curiosity.

Currently there is no good *in vivo* human evidence of spinal memory. However, it is known that repetitive stimulation of small diameter primary afferent fibers produces a reduction in threshold stimulus requirements and a prolonged increase in the excitability (wind-up) of dorsal horn wide-dynamic range interneurons.[2] It is postulated that nociceptive input may modify the synaptic connections involving these secondary interneurons, resulting in a central sensitization or imprinting of the painful stimulus in the spinal cord.[3] Pathologic pain may result from a stimulus-induced neuroplasticity.

Our objective was to reexamine the controversy of rigid *versus* plastic influences on phantom sensations under regional anesthesia. We proposed that positional or proprioceptive memory is a potentially useful model of spinal memory. If a mechanism exists for memory imprinting of proprioceptive information within the spinal cord, interruption of this proprioceptive information by local anesthetics should prevent or attenuate new position sense from being learned or imprinted into memory. A clinical model of proprioceptive memory imprinting will allow us to better understand proprioceptive memory imprinting processes and could be of practical utility in gaining insight into possible correlates with pathophysiologic aspects of spinal memory imprinting in chronic pain states.

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Methods

Study Protocol

The Research Subject Review Board of the University of Rochester Medical Center approved this study, and informed consent was obtained from all patients. All American Society of Anesthesiologists physical status I–III adult patients presenting for elective genitourinary procedures of less than 2-hr duration and agreeable to subarachnoid anesthesia were prospectively considered for recruitment to the study. Exclusion criteria included patients with lower extremity injury, neurologic deficit, or documented peripheral polyneuropathy consistent with a proprioception deficit. Patients unable to flex either knee at least 90 degrees were excluded. Patients in whom the subarachnoid block failed to achieve a bilateral T10 sensory level to pinprick within 10 min or provide adequate anesthesia for surgery were excluded.

Patients were placed in the sitting position with their legs resting comfortably on a stool and given a single-dose subarachnoid injection using standard techniques. Study participants with procedures scheduled for 1 h or less were placed in group I and received plain lidocaine (1.5 ml of 5% lidocaine in 7.5% dextrose). Study participants with procedures scheduled for longer than 1 h were placed in group II and received plain bupivacaine (1.5 ml of 0.75% bupivacaine in 7.5% dextrose). Patients in each group were then randomized to one of four time groups, at 1, 4, 7, and 10 min.

Preoperative medication was limited to a maximum of 2 mg of intravenous midazolam. After administration of the subarachnoid block, patients were immediately placed in the supine position and an opaque screen (a white linen bed sheet clipped to adjacent IV poles) was attached in front of the patients so they could not see their legs. Patients' arms were flexed at the elbow and placed on their chests. The leg flexed first was assigned as the ipsilateral limb. For logistic reasons, the study assigned the dominant leg (as reported by patient hand dominance) to the flexed-first ipsilateral limb. The ipsilateral leg was flexed 90 degrees or greater at the knee, and the contralateral, nondominant leg was completely extended. This position was maintained for 1, 4, 7, or 10 min, depending on the patient's assigned time group. At the designated time point, the original patient leg positions were simultaneously switched by repositioning the flexed knee to extended and the extended knee to flexed. Patients were maintained in this position until the completion of questioning.

Dermatomal level of sensory deficit to pinprick was assessed to determine the extent of blockade. Sensory testing to pinprick was confined to the torso and undertaken by the operating room anesthesiology team. Sensory testing occurred at least at time of position change and at 10 min after injection for each group—therefore, at least once at 10 min for the 10-min time group. Testing was used both for block level assessment and as a distraction to the patient while limbs were repositioned to minimize any movement cues. After the 10-min sensory level assessment, patients were asked to state their home phone number as a cursory mental status check. Patients were then read a scripted question that asked whether they perceived each knee as either bent or straight. Patients were told there was no "in-between" answer; the response of the patient regarding perception of limb position was limited to bent or straight. An independent research nurse assistant recorded participant responses as a binary variable of correct or incorrect. Final assessment of sensory level and scripted questioning took less than 1 min to complete.

A supplemental study was undertaken to evaluate the influence of dominance on the incidence of incorrect or phantom perceptions between the originally flexed ipsilateral and originally extended contralateral limbs. A supplementary group consisting of the next five enrolled patients was matched to the five participants in the time and treatment subgroup of the primary study with the greatest difference in incidence of incorrect perceptions between the ipsilateral and contralateral limbs, the lidocaine 4-min group. Study protocol was maintained, except limb assignments relative to dominance were reversed. The originally flexed ipsilateral limb was now assigned to the nondominant leg, and the contralateral originally extended limb was assigned to the dominant leg.

Statistical Methods

Statistical analysis required measuring data by proportions or number of observations in two categories: incorrect and correct. Power analysis determined that a sample size of n = 5 would allow detection of a 75% difference in proportions for a given variable set, *i.e.*, a particular treatment at a particular time point between groups I and II ($\alpha = 0.05$, power = 0.8, Sigmastat, SPSS, Chicago, IL).

The relation among the dependent variable, incidence of incorrect perception, and the independent variables of time and treatment were determined by logistic regression analysis. The incidence of incorrect perception (phantom sensation) in each leg was the dependent

Table 1. Subject Demographic Variables

	Lidocaine Group		Bupivacaine Group	
Variables	Mean ± SD	Range	Mean ± SD	Range
Age (yr)	51 ± 19	19–89	53 ± 15	27–82
Gender	13 men, 7 women		13 men, 7 women	
Weight (kg)	87 ± 14	65.3–118	97 ± 24	58–162
Height (cm)	171 ± 11	155–198	169 ± 10	163–196
ASA status	I 6		I 3	
	II 13		II 14	
	III 1		III 3	

ASA = American Society of Anesthesiologists.

response variable. Let p_j be the probability that the response of subject j was incorrect. Logistic regression[4] models the dependency of p_j on the independent explanatory variables treatment (TRT; two level factor: 0 = bupivacaine and 1 = lidocaine) and time from the block to change of the leg position (TIME; four level factor: 1, 4, 7, and 10) through the relation:

$$\log(\rho j/1 - \rho j) = \alpha + \beta^{*}\mathrm{TRT}j + \gamma^{*}\mathrm{TIME}j \quad (1)$$

where α, β, and γ are parameters relating to unknown, treatment, and time, respectively. Parameter estimation of this logistic regression model using the maximum likelihood method was accomplished using LogXact (Cytel Software, Cambridge, MA). The statistical significance and testing of the hypothesis that the estimated parameters are significantly different from 0 was based on the conditional scores test.

Testing that a subject's incidence of incorrect perception on the ipsilateral leg equals the same subject's incidence on the contralateral leg was performed by the McNemar test of a 2-×-2 contingency table. Testing to compare the distribution of incorrect or phantom observations while controlling for either dominance or limb position was undertaken by Fisher exact testing of 2-×-2 contingency tables.

Results

Forty-one American Society of Anesthesiologists physical status I–III adult patients undergoing elective genitourinary surgical procedures under subarachnoid block were enrolled. One patient was dropped from the study due to inadequate surgical anesthesia from the subarachnoid block. Data are presented for 40 patients, 20 patients in each treatment group, five patients randomized to each of the four time points. There was no difference in subject demographics between the two treatment groups (table 1). All patients had a sensory level of T10 or higher bilaterally when questioned about leg position 10 min after injection. No patient received more than 2 mg of midazolam for preoperative medication, and all patients correctly reported their home phone number when asked prior to leg position questioning.

The results are presented in figures 1 and 2, which are plots of incidence of incorrect answers (in percentage) *versus* time after administration of the subarachnoid block for lidocaine (crosses) and bupivacaine (circles) for the initially flexed ipsilateral and initially extended contralateral legs, respectively. The lines are the best logistic regression models fit for the two treatment groups. The inability to perceive a change in leg position is dependent on the time after the spinal block that the position change is initiated relative to the onset time of the local anesthetic used. This occurs for both the ipsilateral initially flexed ($P = 0.024$) and contralateral initially extended ($P = 0.023$) legs. With the ipsilateral leg, 60% of patients in the lidocaine group incorrectly identified limb position at 1 min after the initiation of the subarachnoid block. Essentially all lidocaine subjects were unable to identify the correct, repositioned, straight ipsilateral limb position at time points of more than 4 min. This suggests that lidocaine can block most proprioceptive information within that time period, and any subsequent limb position change 4 min after onset will not be appreciated. A flexed extremity after the block is fixed was perceived as such even after subsequent repositioning during the block. This observation is consistent with classic phantom sensation experience under regional anesthesia. This time-related block of proprioception also occurs with bupivacaine, but with a slower onset consistent with bupivacaine's slower onset time *versus* that of lidocaine. At the 10-min time point, 20% of bupivacaine subjects can correctly perceive the

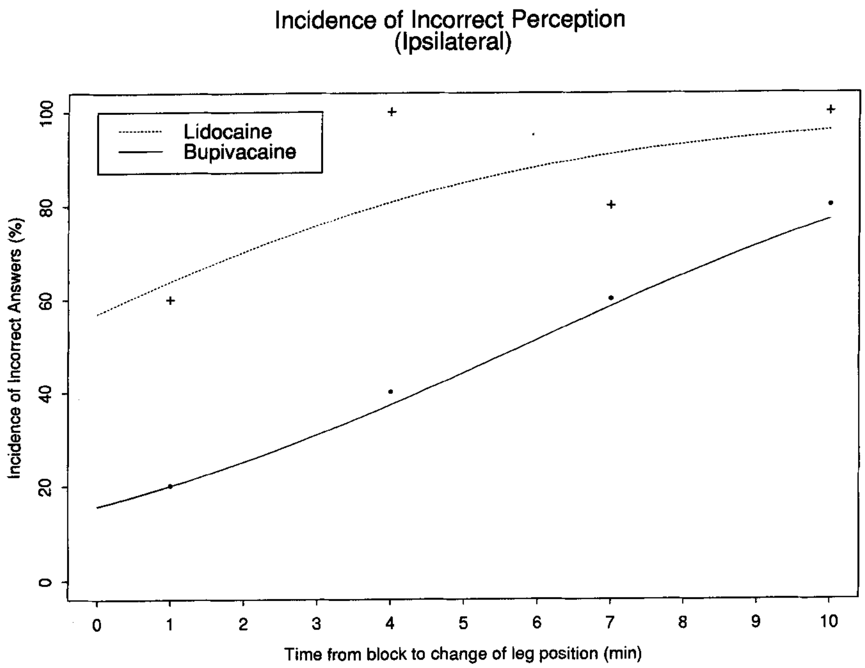

Fig. 1. Incidence of incorrect ipsilateral leg perception. Percentage of incorrect answers (*i.e.*, leg is bent) plotted against the time at which the initially bent leg was straightened. Crosses indicate the lidocaine group and circles indicate the bupivacaine group. The lines are the best-fitting logistic regression models.

recently repositioned ipsilateral limb position as now straight. A logistic regression analysis of the ipsilateral leg data shows that the difference between lidocaine and bupivacaine treatments is significant (P = 0.029).

As the contralateral leg was maintained in its original straight position for longer periods of time, the subsequent repositioning into the flexed position was not perceived, and the percent of incorrect answers eventually increased (fig. 2). Logistic regression analysis of the data confirms that the time factor is significant for the contralateral leg, as it was for the ipsilateral leg (P = 0.023). With increasing time after the block, the percent-

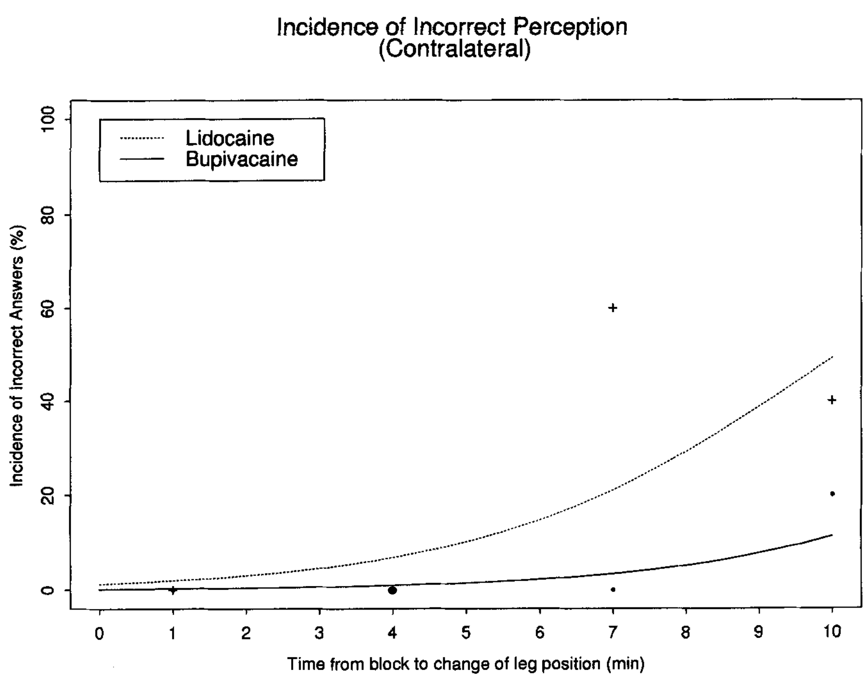

Fig. 2. Incidence of incorrect contralateral leg perception. Same as figure 1 except using the contralateral leg. Here the leg was initially straight and bent at the indicated time, therefore the incorrect answer is "leg is straight."

Table 2. A 2-×-2 Contingency Table of Ipsilateral and Contralateral Leg Perception

		Contralateral Leg	
		Correct Perception	Incorrect Perception
Ipsilateral leg	Correct perception	12	1
	Incorrect perception	22	5

age of incorrect answers after limb repositioning increased. A straight extremity during fixation of the block was perceived as such even after subsequent repositioning during the block. This data indicates that the straight leg position can be imprinted on proprioceptive memory. Incorrect perception of leg position was again delayed with bupivacaine in the contralateral leg and only appeared to trend toward significant difference from lidocaine with increasing time ($P = 0.151$).

The McNemar statistic for a 2-×-2 contingency table (table 2), testing proportions of all assessments is 19.14 ($P = 0.0001$). This strongly confirms the observation that the ipsilateral originally flexed and dominant limb has a significantly higher incidence of incorrect answers compared with the contralateral originally extended nondominant limb. This occurs with both lidocaine and bupivacaine local anesthetics.

The supplemental study group was matched to the 4-min time and lidocaine treatment subgroup of the primary study to evaluate the influence of dominance *versus* limb position on the difference between the ipsilateral and contralateral legs. The original 4-min lidocaine time and treatment subgroup expressed a 100% incidence of incorrect or phantom limb perceptions for the ipsilateral originally flexed, or dominant, limb compared with a 0% incidence for the contralateral originally extended, or nondominant, limb (figs. 1 and 2). The supplemental 4-min lidocaine patient population demonstrated no significant demographic differences compared with the original 4-min lidocaine population. In the supplemental 4-min lidocaine subgroup, a complementary 100% incidence of incorrect or phantom perception was observed in the originally flexed but now nondominant limb, whereas a 0% incidence of incorrect limb perception in the originally extended but now dominant limb was observed. Fisher exact analysis of a 2-×-2 contingency set comparing dominance and nondominance while keeping limb position sequencing constant shows no statistically significant difference ($P = 1.0$). A 2-×-2 contingency set analysis comparing limb position sequencing while controlling for dominance shows the flexed first leg position has a statistically greater incidence of incorrect or phantom perceptions compared with the extended first leg ($P = 0.0079$).

Discussion

The neural origin underlying phantom sensations associated with regional anesthesia was reported by Bromage and Melzack[1] as a fixed, slightly flexed, universal "body schema" that is nearly identical in all patients following block of afferent stimulation. This model is not consistent with recent concepts of neuroplasticity, nor with earlier observations suggesting that phantom sensations during regional anesthesia might be dependent on limb position prior to block onset.[5] If limb proprioception following deafferentation is based on a neuroplastic imprinting, or memory, the position of the limb prior to onset of block should be retained regardless of what new positions the limb is placed in throughout the duration of the block.

In the ipsilateral leg, the use of bupivacaine, which is slower in onset *versus* lidocaine, revealed the gradual influence of time on the ability to perceive position changes. A majority of patients whose ipsilateral limb was repositioned from flexed to straight at 4 min or less had insufficient bupivacaine block fixation to interfere with their proprioceptive perceptions. These patients correctly perceived the limb position change and reported their limb as straight when questioned at 10 min. The straight limb position was the last position perceived by the central nervous system before fixation of the block occurred in the subsequent time period.

In the contralateral limb, patients whose extremity was positioned straight for the duration of block fixation and subsequently moved into the flexed position, increasingly perceived their extremity also as straight, especially with the quicker onset of lidocaine. When perceived and actual limb position coincide with the expected position, we should not assume that a phantom could not exist in that position. It can be hypothesized that such perceptions of straight, or normal, may have led to a bias that may have precluded detection of straight extremity phantoms by earlier investigators. Our observations support the dynamic, neuroplastic concept that the last position perceived by the central nervous system before fixation of regional anesthesia block becomes the imprinted, proprioceptive memory that can alter any existing fixed, universal "body schema."[1]

The contralateral leg was used to reverse the order of positioning so leg position would be changed from straight to bent, with each patient serving as his or her own control. We expected to mirror the results of the ipsilateral leg. The noticeable rightward shift or delay in the incidence of incorrect answers *versus* time for the contralateral leg compared with the ipsilateral leg was not expected (figs. 1 and 2). The ipsilateral originally flexed leg appears more likely to have a local anesthetic-induced "phantom" or incorrect perception of the subsequent straight position. One can speculate that this difference occurs because of the existence of an underlying universal foundation of proprioceptive memory imprinting of the flexed position, as proposed by Bromage and Melzack.[1] However, as noted previously, a majority of subjects that received bupivacaine and had the ipsilateral limb repositioned to straight within 4 min correctly perceived their ipsilateral limb as straight when questioned at 10 min.

Supplemental evaluation of the confounding influence of limb position *versus* limb dominance in accounting for the observed difference in incidence of incorrect or phantom perceptions between the ipsilateral and contralateral limbs show that this difference is dependent on initial limb positioning. The limb first positioned in the flexed position has a higher incidence of phantom perception. It appears that the flexed limb either imprints its position more intensely or is more susceptible to local anesthetic blockade and therefore not as capable of registering subsequent limb position changes.

Skoglund[6] reported that the greatest numbers of joint receptor sensory endings are active when the knee is at maximal extension. More recent reports suggest that maximum afferent activity may occur in flexion in some animals and in extension in others.[7] It has been suggested that joint receptors probably play no more than a supportive or duplicative role to muscle and cutaneous sensors,[8] and in humans, cutaneous afferents are used by the nervous system to prevent ambiguity in the perception of joint angle.[9] Pressure on the soles of subjects' feet[10] while in the bent position or cutaneous stimulation from the examiners hand holding the leg in the bent position may act as sensory cues and contribute to increased afferent stimulation and imprinting of position. A position change from straight to bent would penetrate through a partial local anesthetic block, decreasing or delaying the incidence of incorrect perception at any given time point relative to the onset of local anesthetic blockade. The first flexed joint and associated sensory cues may transmit more afferent information and definitive position imprinting so that it is less responsive to subsequent, less intense, extended position stimulus in the presence of a developing local anesthetic block. The higher local anesthetic affinity for inactivated Na^+ channels that have been stimulated (phasic block) *versus* resting (tonic block) channels[11,12] may complement and magnify any difference in joint position afferent imprinting on proprioceptive memory.

Although we propose that the neuroplastic changes underlying proprioceptive memory occur within the spinal cord, the actual memory loci could be spinal, supraspinal, or both. Using the current understanding of central sensitization and long-term potentiation, afferent input must be transmitted across a synapse for "memory" to be established.[2,13,14] Intrathecal administration of local anesthetics should block the afferent action potentials originating in peripheral nerves from reaching synapses within the dorsal horn of the spinal cord, thereby preventing the formation of a memory or imprinting at spinal or supraspinal levels.

The phantom phenomenon, including nonpainful phantom sensation, is seen in 60-80% of patients following amputation.[15,16] Phantom sensation often includes altered or incorrect proprioception of length, mass, position, or movement of the deafferented limb. Phantom limb position after local anesthetic deafferentation and the clinically significant postamputation phantom sensation may be hypothesized as sharing fundamentally similar mechanisms. If partial deafferentation leads to disinhibition of secondary spinal cord neurons, addition of adjuvant drugs known to potentiate spinal inhibition (*e.g.*, baclofen, benzodiazepines) at the time of local anesthetic administration should restore inhibition and attenuate the development of phantom sensation.

The development of phantom sensation after local anesthetic subarachnoid block corresponds to the time course of limb repositioning relative to the onset of sensory blockade development. A phantom sensation of extended leg position clearly exists, indicating that flexible, dynamic neuroplastic processes influence proprioceptive memory imprinting. Limb position prior to the onset of local anesthetic blockade may have a more prominent role than previously appreciated in influencing the incidence of phantom limb perception and may explain the flexed phantom limb perception commonly observed with regional anesthesia. Future research could use this phantom limb model to quantify and possibly correlate the influence of intrathecal adjuvants on proprioceptive memory and extrapolate the results to pain perception and possibly long-term painful imprinted memory in the central nervous system.

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