Peripheral Nerve Injury After Local Anesthetic Injection

Scott J. Farber, MD, Maryam Saheb-Al-Zamani, MD, MS, Lawrence Zieske, Osvaldo Laurido-Soto, Amit Bery, Daniel Hunter, RA, Philip Johnson, PhD, and Susan E. Mackinnon, MD

BACKGROUND: A well-known complication of peripheral nerve block is peripheral nerve injury, whether from the needle or toxicity of the medication used. In this study, we sought to determine the extent of damage that results from intrafascicular injection of various commonly used local anesthetics (LAs).

METHODS: Sixteen Lewis rats received an intrafascicular injection of saline (control) or 1 of 3 LAs (bupivacaine, lidocaine, or ropivacaine) into the sciatic nerve (n = 4). At a 2-week end point, the sciatic nerves were harvested for histomorphometric and electron microscopic analysis.

RESULTS: Animals that received intrafascicular LA injections showed increased severity of injury as compared with control. In particular, there was a significant loss of large-diameter fibers as indicated by decreased counts (P < 0.01 for all LAs) and area (P < 0.01 for all LAs) of remaining fibers in severely injured versus noninjured areas of the nerve. There was a layering of severity of injury with most severely injured areas closest to and noninjured areas furthest from the injection site. Bupivacaine caused more damage to large fibers than the other 2 LAs. In all groups, fascicular transection injury from the needle was observed. Electron microscopy confirmed nerve injury.

CONCLUSIONS: Frequently used LAs at traditional concentrations are toxic to and can injure the peripheral nerve. Any combination of motor and/or sensory sequelae may result due to the varying fascicular topography of a nerve. (Anesth Analg 2013;117:00–00)

Neurotoxicity after the use of local anesthetics (LAs) for peripheral nerve block has been recognized for decades.1–4 Many experimental studies have documented that the intraneural injection of drugs, including LAs, is neurotoxic.2,3,5–15 Similarly, loss of sensation, motor function, pain, and causalgia have been reported as a result of intraneural injection of LAs.1,16–22 More recently, some studies have claimed that the inadvertent intraneural injection of LAs does not always result in lasting neurological injury or functional impairment.23–27 In addition, some anesthesiology textbooks and technical manuals, in addition to mini-
in a manner previously described. First, they were all harvested sciatic nerves from the Lewis rats were processed

Light Microscopy and Histomorphometry

The right hindquarters of the animals were shaved and sterilized with povidone iodine solution. The sciatic nerve was exposed via a gluteal muscle-splitting incision. An area 5 mm proximal to the takeoff of the tibial nerve from the sciatic nerve trifurcation was used as a reproducible injection site. The intrafascicular injections were performed with an insulin syringe fitted with a 29-gauge × 1/2" needle (Terumo Medical Co., Elkton, MD) and aimed deep into the fascicles and distally using constant finger pressure. Intrafascicular injections are administered directly into the nerve fascicles, and placement was confirmed under the microscope by an obscured needle bevel. Caution was taken not to impart a “through and through” injury of the nerve with the needle. A symmetric fusiform ballooning of the nerve after injection confirmed that our intrafascicular injections were properly placed. To minimize the issue of injury imparted by the needle, the same method of injection was used for every animal and was performed by the same operator. The injury site was marked with a single 10-0 nylon microsuture. Muscle and skin were reapproximated with 6-0 Vicryl (Ethicon Corporation, Somerville, NJ) and 4-0 nylon, respectively. Anesthesia was then reversed with 0.2 mg/kg subcutaneous injection of atipamezole HCl (Pfizer Animal Health, Exton, PA). At the 2-week end point, animals were reanesthetized and the incision site was reopened. Neurolysis was performed to expose the sciatic and tibial nerves. The nerves were sharply excised, ensuring that a 10 mm section both proximal and distal to the injection site was removed en bloc. The nerve was promptly placed in 3% glutaraldehyde at 4°C. They were then postfixed with 1% osmium tetroxide, dehydrated in graded concentrations of ethanol, and embedded in Araldite 502 (Polysciences, Inc., Warrington, PA). Cross-sections, 1-µm thick, from the injured region of the nerve were stained with toluidine blue.

Electron Microscopy

Samples embedded in Araldite 502 (Polysciences Inc.) were cut into sections with an ultramicrotome, stained with uranyl acetate and lead citrate, and evaluated with a Jeol 1200EX electron microscope (Jeol USA Inc., Peabody, MA) for qualitative assessment of myelination, perineurial competence, extent of fibrosis, and cellular damage. EM was performed by a nonblinded operator.

Statistical Analysis

Statistical analysis was performed with Statistica version 7 (StatSoft, Tulsa, OK). Sample size was determined by power calculation. Four animals were used per group to achieve a power of 0.80 and to detect a decrease in fiber density of more than 30% or 6000 fibers per mm² with a standard deviation of about 2000 fibers per mm². Four animals per group were all that was necessary to show the significant histological damage as determined by the experienced blinded observer (DH).

All groups and injury parameters were independently compared using analysis of variance. Any statistically significant differences in sample means were further evaluated by Dunnett test, and the corrected \( P \) value was reported. Given the small sample size and consequently the inability to test for normality and equal variance, a stringent \( P \) value <0.01 was considered to be statistically significant in all comparisons. After treating the animal as a fixed effect, there was no effect of the animal on any dependent variables (minimum \( P > 0.378 \)).

Determination of Injury and Toxicity

A characteristic LA injection injury caused neuronal damage from needle trauma, increased intraneural pressure with injection, and toxicity intrinsic to a given drug. The combination of these factors can result in variable degrees of neuronal injury and was classified as intermediate or severe (Table 1). Intermediate nerve injury was defined by a focal area of partial loss of large myelinated fibers with endoneurial expansion secondary to edema. Severe nerve injury was defined as a focal area of total loss of large myelinated fibers along with extensive fibrosis (Fig. 2).
Increasing toxicity of a drug is reflected in increased severity of injury as well as a more expansive region of injury. Severity of injury was determined by degree of loss of myelinated fibers and fibrosis within the injected nerve as described earlier.

**RESULTS**

**Histomorphometry and Light Microscopy**

**Injection Injury**

All histomorphometric results are summarized in Table 2. The noninjured zone of saline-injected nerves was used as a negative control. The insult from administration of an anesthetic by injection resulted in a significant decrease in the number of nerve fibers in the zone of intermediate injury (bupivacaine $P < 0.0001$, lidocaine $P < 0.0001$, ropivacaine $P < 0.0001$, and saline $P < 0.0001$) and smaller fiber percent per nerve (bupivacaine $P < 0.0001$, lidocaine $P < 0.0001$, ropivacaine $P < 0.0001$, and saline $P < 0.0001$) in comparison with the control noninjured zone in saline-injected nerves. In particular, there was a loss of large--diameter fibers as exhibited by a decrease in fiber area of the remaining nerves (bupivacaine $P < 0.0001$, lidocaine $P < 0.0001$, ropivacaine $P < 0.0001$, and saline $P < 0.0001$) compared with noninjured fibers in the control zone. The area of intermediate injury was smaller than the noninjured area (bupivacaine $P < 0.0001$, lidocaine $P < 0.0001$, ropivacaine $P < 0.0001$, and saline $P < 0.0001$), which explains the lack of difference in fiber density within the zone of intermediate injury relative to fiber density in uninjured control areas (bupivacaine $P = 0.0700$, lidocaine $P = 0.1493$, ropivacaine $P = 0.0019$, and saline $P = 0.6106$).

Cross-sections of whole nerves were analyzed, and a comparison of intermediate injured zones among groups injected with bupivacaine, lidocaine, ropivacaine, and saline revealed that a comparable number of axons were

<table>
<thead>
<tr>
<th>Degree of injury</th>
<th>Histologic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate</td>
<td>Focal areas of partial loss of large myelinated fibers with endoneurial expansion secondary to edema</td>
</tr>
<tr>
<td>Severe</td>
<td>Focal areas of total loss of large myelinated fibers along with extensive fibrosis and collagen disarray</td>
</tr>
</tbody>
</table>

**Table 1. Description of Nerve Injection Injuries**

**Figure 2.** Light microscopy at 2 weeks postinjection (100×): Demonstration of the 4 injectate groups. S = severe injury area; I = intermediate injury area; N = normal area. Black arrow indicates direction of needle track. The interfascicular injection of saline produced little nerve fiber damage. By contrast, the interfascicular injection of the local anesthetic agents caused variable damage relating to the injection site with the most significant axonal injury closest to the injection site.
affected as measured by mean total fiber count, size of remaining fibers, fiber density, area of injury, and percent nerve ($P > 0.01$ for all group comparisons across all measures, Tables 3 and 4). Needle track injury was observed in all groups, resulting in a sixth-degree injury, or one that includes Sunderland first-through fifth-degree injuries, further detailed in the Discussion section.

The degree of injury decreased with increasing distance from site of injection, with the zone of severe injury (if present) surrounded by zones of intermediate and no injury, in succession (Fig. 3). As the concentration of the LA decreased as it dispersed, a progressive decline in damage away from the injection site was seen. Administration of saline resulted in intermediate damage to nerves, indicating a baseline level of injury associated with injecting any agent into a nerve.

**Drug Toxicity**

In the negative control group, administration of 50 µL saline resulted in no severe injury to nerve fibers. This is in contrast to bupivacaine, lidocaine, and ropivacaine, where nearly all of the injected nerves showed areas of severe injury, defined by total loss of large myelinated fibers and extensive fibrosis. Regardless of the drug used, there was a significant decrease in number of fibers (bupivacaine $P < 0.0001$, lidocaine $P < 0.0001$, ropivacaine $P < 0.0001$) and percent nerve in severely injured nerve zones as compared with noninjured control zones (bupivacaine $P = 0.0003$, lidocaine $P < 0.0001$, and ropivacaine $P < 0.0001$) and decrease in fiber area (bupivacaine $P = 0.0002$, lidocaine $P = 0.0002$, and ropivacaine $P = 0.0002$) denoting a drop-off of large-diameter fibers. There was also a trend toward smaller fiber density in lidocaine-injected ($P = 0.0110$) and ropivacaine-injected ($P = 0.0102$) groups relative to bupivacaine-injected nerves ($P = 0.3433$). No differences were observed between the drug-injected nerves across any measurements of severely injured areas (Fig. 4). No zone of severe injury was observed in saline-injected nerves as defined by the variables outlined earlier.

Axon–myelin ratios, previously described, were measured in all groups. The normal ratio is approximately 0.6, with a higher ratio indicating a decreased amount of myelin surrounding the axon. In the bupivacaine, lidocaine, and ropivacaine groups, the intermediate injury zones had an axon–myelin ratio of 0.68, 0.66, and 0.77, respectively. The severely injured zones had axon–myelin ratios of 0.76, 0.81, and 0.83, respectively. As indicated by the increasing ratios, there was a decrease in myelin thickness as injury progressed from the intermediate zone to the severe zone in all 3 experimental groups.

**Electron Microscopy**

Cross-sections of the nerve were analyzed via EM and revealed that the extent and location of fascicular injury varied widely among the LA groups. In the saline group, no injury was observed apart from the occasional injury caused by the needle. Figure 5 represents an EM of an uninjured section of nerve in the saline group with normal-appearing myelinated

### Table 2. Summary of Histomorphometric Analysis of Nerves Following Injection Injuries

<table>
<thead>
<tr>
<th>Zone of injury</th>
<th>Injected drug</th>
<th>No. of nerves with injury</th>
<th>Mean total nerve fibers per nerve</th>
<th>Mean fiber area (fibers/mm²)</th>
<th>Mean nerve fiber density (fibers/µm²)</th>
<th>Mean percent area of fibers per nerves (%)</th>
<th>Mean total area of injury (µm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>Bupivacaine</td>
<td>4</td>
<td>254 ± 229</td>
<td>11.23 ± 4.03</td>
<td>12,104 ± 10,246</td>
<td>16.06 ± 17.10</td>
<td>27,261 ± 27,815</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Bupivacaine</td>
<td>4</td>
<td>803 ± 485</td>
<td>14.59 ± 2.51</td>
<td>12,477 ± 3658</td>
<td>18.70 ± 7.77</td>
<td>74,226 ± 64,321</td>
</tr>
<tr>
<td>None</td>
<td>Bupivacaine</td>
<td>4</td>
<td>678 ± 1830</td>
<td>28.98 ± 0.86</td>
<td>20,750 ± 2701</td>
<td>60.01 ± 6.79</td>
<td>329,127 ± 86,330</td>
</tr>
<tr>
<td>Severe</td>
<td>Lidocaine</td>
<td>3</td>
<td>48 ± 20</td>
<td>6.33 ± 0.93</td>
<td>2306 ± 226</td>
<td>1.95 ± 1.75</td>
<td>29,733 ± 16,767</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Lidocaine</td>
<td>4</td>
<td>1049 ± 668</td>
<td>13.66 ± 2.55</td>
<td>13,465 ± 2188</td>
<td>18.69 ± 5.05</td>
<td>76,712 ± 42,247</td>
</tr>
<tr>
<td>None</td>
<td>Lidocaine</td>
<td>4</td>
<td>733 ± 927</td>
<td>33.52 ± 1.70</td>
<td>16,842 ± 1416</td>
<td>56.35 ± 3.63</td>
<td>434,947 ± 30,769</td>
</tr>
<tr>
<td>Severe</td>
<td>Ropivacaine</td>
<td>4</td>
<td>127 ± 139</td>
<td>11.62 ± 3.24</td>
<td>332 ± 3314</td>
<td>4.14 ± 0.95</td>
<td>55,127 ± 51,551</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Ropivacaine</td>
<td>4</td>
<td>482 ± 368</td>
<td>19.66 ± 3.20</td>
<td>8039 ± 4334</td>
<td>16.01 ± 8.70</td>
<td>57,390 ± 16,233</td>
</tr>
<tr>
<td>None</td>
<td>Ropivacaine</td>
<td>4</td>
<td>8535 ± 568</td>
<td>45.44 ± 4.35</td>
<td>14,010 ± 1135</td>
<td>63.38 ± 3.81</td>
<td>614,641 ± 90,389</td>
</tr>
<tr>
<td>Severe</td>
<td>Saline</td>
<td>0</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Saline</td>
<td>2</td>
<td>214 ± 120.33</td>
<td>13.10 ± 4.26</td>
<td>15,107 ± 3217</td>
<td>19.29 ± 3.40</td>
<td>13,748 ± 5857</td>
</tr>
<tr>
<td>None</td>
<td>Saline</td>
<td>4</td>
<td>8400 ± 1144</td>
<td>31.02 ± 1.35</td>
<td>18,390 ± 2434</td>
<td>56.96 ± 7.06</td>
<td>456,812 ± 11,736</td>
</tr>
</tbody>
</table>

Values represent mean ± SD.

Intermediate nerve injury is defined by a focal area of partial loss of large myelinated fibers with endoneurial expansion secondary to edema. Severe nerve injury is defined as a focal area of total loss of large myelinated fibers along with extensive fibrosis and collagen disarray.

*Significantly different ($P < 0.01$) from zone of no injury in saline-injected nerves (negative control).

### Table 3. Statistical Comparisons of Nerve Parameters Between Injected Drugs in Severe Zones of Injuries

<table>
<thead>
<tr>
<th>Severe zone of injury from injectate</th>
<th>Comparison with severe zone of injury of injectate</th>
<th>No. of nerves with injury</th>
<th>Mean total nerve fibers per nerve</th>
<th>Mean fiber area (fibers/mm²)</th>
<th>Mean nerve fiber density (fibers/µm²)</th>
<th>Mean percent area of fibers per nerves (%)</th>
<th>Mean total area of injury (µm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine (n = 4)</td>
<td></td>
<td>4</td>
<td>254 ± 229</td>
<td>11.23 ± 4.03</td>
<td>12,104 ± 10,246</td>
<td>16.06 ± 17.10</td>
<td>27,261 ± 27,815</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Bupivacaine</td>
<td>3</td>
<td>975 ± 0.007</td>
<td>0.2034</td>
<td>0.2281</td>
<td>0.3298</td>
<td>0.9185</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>Bupivacaine</td>
<td>4</td>
<td>9997 ± 0.007</td>
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and unmyelinated fibers. In the intermediate zone of injury, normal Wallerian degeneration was seen alongside smaller, uninjured fibers (Fig. 6). EM demonstrated decreased axon–myelin ratios along with some axons that maintained normal axon–myelin ratios. In the severe zone, EM revealed near complete loss of myelin along with increased fibrosis indicated by an increase in fibroblasts (Fig. 7). There was also increased collagen disorganization evident in this zone.

Injury was also evident in the perineurium surrounding this zone, evident by perineurial thickening. In addition, edema and fibrosis were evident on EM throughout the endoneurium in all of our experimental groups.

**DISCUSSION**

Peripheral nerve block with LA is a common practice in providing pain control for a wide range of surgical procedures.
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and pain syndromes. Inadvertent intrafascicular injection of an LA can generate a variety of nerve injuries, some of which may result in long-term disability. All anesthetics used in this study produced some degree of damage to the nerve when injected intrafascicularly, as evidenced by demyelination and Wallerian degeneration. The most severe injury occurred closest to the site of injection, and the extent of injury tapered off as distance from the injection site increased. This led to mixing of the injuries, evident in all LA groups on histological analysis as seen in Figure 4. Although there were minor differences in the extent of injury caused by the 3 LAs, there was an overall reduction of fiber quantity and fiber area in both the intermediate and severe injury zones. EM confirmed the severe injury zones by demonstrating absence of nerve fibers associated with severe fibrosis and collagen disarray. Intermediate injury was seen in all LA groups as areas of Wallerian degeneration alongside normal myelinated fibers. All 3 LAs used in this study—ropivacaine, lidocaine, and bupivacaine—caused considerable histological abnormalities when injected intrafascicularly.

Nerve injury from peripheral nerve blockade is well described; however, case reports of incidence, duration, and extent of sequelae are varied. Nerve injection injury is considered to be multifactorial in nature. Factors such as needle type and size, site of insertion, angle of insertion, pressure achieved during injection, type, and dose of medication injected (toxicity) affect degree of nerve injury according to various studies. All of these variables account for the disparity in the incidence of nerve injury with anesthetic injection reported in the literature.

The effect of intrafascicular and extrafascicular injection of numerous drugs in common use has been extensively studied.
studied by our laboratory.\textsuperscript{2,3,5–7,9,10,12,38} In general, most drugs caused nerve injury when injected intrafascicularly, and, in contrast, extrafascicular injections produced little to no damage. A few exceptions, dexamethasone, botulinum toxin, and bovine collagen, demonstrated little to no axonal damage after intrafascicular injection.\textsuperscript{7,9,38} LAs have been shown to have a direct toxic effect on the nerve. Several studies have demonstrated that LAs can lead to fragmentation of DNA and disrupt the membrane potential in mitochondria, resulting in the uncoupling of oxidative phosphorylation. This in turn releases cytochrome c and activates caspase, which may result in apoptosis.\textsuperscript{41,42} The activation of pro-apoptotic enzymes in neuronal cells such as p38 mitogen-activated protein kinase and Jun N-terminal kinase have been shown to be initiated by lidocaine, bupivacaine, and ropivacaine.\textsuperscript{41,43} Generation of reactive oxygen species in Schwann cells by bupivacaine results in apoptosis.\textsuperscript{54} LAs have been shown to cause rapid necrosis of human neuronal cells. In addition, there is a direct correlation between concentration of the LA and time of exposure to the nerve with Schwann cell death.\textsuperscript{42,45} Rat, porcine, and canine sciatic nerves with exposure to LAs demonstrate infiltration of the nerve with macrophages and associated myelin damage.\textsuperscript{45} In addition to inducing apoptotic pathways and signals, LAs have been shown to constrict vasculature and decrease the blood flow to the nerves.\textsuperscript{6–48} There are a number of previous studies that have demonstrated differing levels of toxicity among various LAs.\textsuperscript{52,45,49} The observed toxicity from these previous studies is consistent with our study demonstrating that all 3 LAs produced neural damage.

In addition to toxicity of the medication used, the intraneural pressures achieved during accidental injection of drug into the nerve have been shown to be damaging. Hadzic et al.\textsuperscript{18} found that when using the same injectate volumes, intrafascicular injections resulted in higher pressures and were associated with lasting motor deficits and histological damage. More recently, Orebaugh et al.\textsuperscript{50} reported that all intrafascicular injections at the level of the brachial plexus root in fresh human cadavers result in high injection pressure. The saline control in this study demonstrated some areas of intermediate damage, comparable with that of the 3 anesthetic groups. Although we did not measure intraneural pressure, this may reinforce the idea that intermediate level injury can be largely attributed to the trauma of increased intraneural pressure on injection. However, the role of drug toxicity in producing intermediate level injury cannot be completely discounted as only 2 of the 4 nerves in the saline group showed intermediate injury whereas all 4 nerves in the bupivacaine, lidocaine, and ropivacaine groups showed intermediate injury.

In this study, intrafascicular injection resulted in varying grades of injury to the nerve as indicated by histomorphometry. Traditionally, peripheral nerve injury has been classified into 5 different degrees, as described by Sunderland.\textsuperscript{51} A first-degree injury, or neurapraxia, involves segmental demyelination. Second-degree injury, or axonotmesis, involves injury to both the axon and the myelin; however, the endoneurial tissue is not damaged. Third-degree injury involves an injury to the axon, myelin, and endoneurium and leaves the perineurium intact. A fourth-degree injury involves injury to the axon, myelin, and endoneurium, and perineurium; the fascicle is scarred with only the epineurium being intact. Fifth-degree injuries occur when the fascicle or entire nerve has been transected. Sixth-degree injury was first described by Mackinnon et al.\textsuperscript{52,53} and involves a combination of first- through fifth-degree injuries. Fourth- through sixth-degree injuries require operative resection and repair. These types of injuries have been demonstrated by Sala-Blanch et al.\textsuperscript{38} where complete transection of fascicles (fifth- or sixth-degree injury) was observed. Our results demonstrate that all 3 LA groups demonstrated sixth-degree injury, as the nerves exhibited signs of first- to fifth-degree injuries. Saline-injected nerves (control) demonstrated areas of third-degree injury, with occasional axonal transection, or fifth-degree injury.

In summary, peripheral nerve injury from LA injection into the nerve occurs and remains a real clinical danger. The sequelae from such an injury may be long lasting and require surgical intervention. Intentional intraneural injection, as recommended by some clinicians to hasten the onset of the block, is not recommended.

DISCLOSURES

Name: Scott J. Farber, MD.
Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
Attestation: Scott J. Farber has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
Name: Maryam Saheb-Al-Zamani, MD, MS.
Contribution: This author helped analyze the data and write the manuscript.
Attestation: Maryam Saheb-Al-Zamani has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
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Contribution: This author designed the study and analyze the data.
Attestation: Lawrence Zieske has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
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Contribution: This author helped design the study and analyze the data.
Attestation: Osvaldo Laurido-Soto has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
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Contribution: This author helped design the study and analyze the data.
Attestation: Daniel Hunter has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Phillip Johnson, PhD.
Contribution: This author helped design and conduct the study and write the manuscript.
Attestation: Phillip Johnson has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Susan Mackinnon, MD.
Contribution: This author helped design the study and write the manuscript.
Attestation: Susan Mackinnon has seen the original study data and approved the final manuscript.

This manuscript was handled by: Terese T. Horlocker, MD.

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