

## Appendix B

**Table A. Prospective studies reporting neurological dysfunction.**

| Study                            | Type of study | Guidance method* | Blocks                                   | Short-term assessment | Long-term assessment | Method of assessment                                                                                                          | Key findings                                                                                                                                                                                                                                                                                                                                                |
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| Liu et al. <sup>14</sup>         | Cohort study  | US               | Supraclavicular (135)/Interscalene (122) | 1 wk and 6 wks        | Not mentioned        | <ul style="list-style-type: none"> <li>Standardized questionnaire</li> </ul>                                                  | <ul style="list-style-type: none"> <li>Unintentional intraneural injections are common following supraclavicular or interscalene blocks (17%) and may not necessarily result in neurological complications (0%).</li> </ul>                                                                                                                                 |
| Hara et al. <sup>12</sup>        | Cohort study  | US + NS          | Subgluteal sciatic (282)                 | 4 wks                 | Not mentioned        | <ul style="list-style-type: none"> <li>Surgical team follow-up (neurological examination)</li> </ul>                          | <ul style="list-style-type: none"> <li>Unintentional intraneural injections are common following subgluteal sciatic nerve blocks (17%) and may not necessarily result in neurological complications (0%).</li> <li>Intraneural injections have a fast block onset compared to extraneural injections with no effect on the duration of blockade.</li> </ul> |
| Ruiz et al. <sup>104</sup>       | RCT           | US + NS          | Femoral                                  | 24 hrs                | Not mentioned        | <ul style="list-style-type: none"> <li>Onset or persistence of sensory-motor symptoms</li> </ul>                              | <ul style="list-style-type: none"> <li>Needle-nerve contact and apparent intraneural injections can be more common with an out-of plane approach (64%) compared to in-plane approach (9%) for femoral nerve block.</li> <li>No differences between the groups regarding incidence of paresthesia or nerve injury.</li> </ul>                                |
| Robards et al. <sup>103</sup>    | Cohort study  | US + NS          | Sciatic                                  | 24-48 hrs             | Not mentioned        | <ul style="list-style-type: none"> <li>Presence of any sensory-motor symptoms in the distribution of sciatic nerve</li> </ul> | <ul style="list-style-type: none"> <li>Deliberate intraneural injection during popliteal sciatic nerve block with injection pressures &lt;20 psi does not result in immediate neurological dysfunction.</li> <li>Motor response was absent in 16.7% with current up to 1.5 mA even when needle was intraneural on US.</li> </ul>                            |
| Sala-Blanch et al. <sup>16</sup> | Cohort study  | NS               | Sciatic                                  | 1 wk                  | Not mentioned        | <ul style="list-style-type: none"> <li>Neurological examination</li> </ul>                                                    | <ul style="list-style-type: none"> <li>Intraneural (subepineurial) injection during nerve stimulation-guided popliteal sciatic nerve block may occur commonly (up to 66%) without imminent neurological injury.</li> </ul>                                                                                                                                  |

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|                                 |              |    |                 |                        |                        |                                                                                                        | <ul style="list-style-type: none"> <li>• Intraneural injections may have a faster block onset.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Sauter et al. <sup>107</sup>    | Cohort study | US | Radial, Ulnar   | NS study, no injection | NS study, no injection | -                                                                                                      | <ul style="list-style-type: none"> <li>• High current thresholds [1.7 (0.4-4.5) mA radial and 1.0 (0.4-2.0) mA ulnar] and short nerve-to-needle distances were often needed to obtain motor responses.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                            |
| Gadsden et al. <sup>55</sup>    | Cohort study | US | Interscalene    | 2 wks                  | Not mentioned          | <ul style="list-style-type: none"> <li>• Surgical team follow-up (neurological examination)</li> </ul> | <ul style="list-style-type: none"> <li>• All extraneural injections had opening injection pressure &lt;15 psi.</li> <li>• Limiting injection pressure to 15 psi prevented injection upon needle-nerve contact in all but one instance.</li> <li>• Monitoring of opening injection pressure may be helpful in detecting needle-nerve contact.</li> </ul>                                                                                                                                                                                                                                                                      |
| Bigeleisen et al. <sup>37</sup> | Cohort study | US | Supraclavicular | 3 wks                  | 6 mos                  | <ul style="list-style-type: none"> <li>• Surgical team follow-up (neurological examination)</li> </ul> | <ul style="list-style-type: none"> <li>• US was able to detect the location of the needle tip clearly in 69% of cases.</li> <li>• Stimulation currents of <math>\leq 0.2</math> mA detect intraneural position of the needle reliably.</li> <li>• Stimulation thresholds <math>&gt;0.2</math> and <math>\leq 0.5</math> mA could not rule out intraneural needle tip placement.</li> <li>• 10% of patients had temporary neurological symptoms mostly unrelated to nerve blocks.</li> <li>• Diabetic patients require higher stimulation thresholds both outside and inside the nerve to elicit a motor response.</li> </ul> |
| Morau et al. <sup>15</sup>      | Cohort study | NS | Sciatic         | 1 wk                   | Not mentioned          | <ul style="list-style-type: none"> <li>• Surgical team follow-up (neurological examination)</li> </ul> | <ul style="list-style-type: none"> <li>• Intraneural spread of local anesthetic was common following NS-guided popliteal sciatic block (39% had a nerve surface area increase of 15%).</li> <li>• Patients with intraneural injections had faster block onset and better success rate.</li> </ul>                                                                                                                                                                                                                                                                                                                            |
| Bigeleisen et al. <sup>36</sup> | Cohort study | US | Axillary        | 3 wks                  | 6 mos                  | <ul style="list-style-type: none"> <li>• Qualitative sensory and motor testing</li> </ul>              | <ul style="list-style-type: none"> <li>• Deliberate intraneural injection during axillary brachial plexus block did not result in long term neurological dysfunction.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Dufour et al. <sup>51</sup>     | Cohort study | NS | Median          | 1 mo                   | Not mentioned          | <ul style="list-style-type: none"> <li>• Surgical team follow-up</li> </ul>                            | <ul style="list-style-type: none"> <li>• NS-guided median nerve block has ~43% incidence of intraneural injection.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

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|                                   |              |             |                 |                  |               | (neurological examination)                                                                                                | <ul style="list-style-type: none"> <li>In the absence of intraneural injection, presence of circumferential local anesthetic spread seemed predictive of successful sensory block in ~75% of cases.</li> </ul>                                                                                                                                                                     |
| Sala-Blanch et al. <sup>105</sup> | Cohort study | NS          | Sciatic         | 1 wk and 1 mo    | Not mentioned | <ul style="list-style-type: none"> <li>Neurologic examination + electrodiagnostic tests</li> </ul>                        | <ul style="list-style-type: none"> <li>None of the patients exhibited clinical or electrophysiological evidence of neurological injury after deliberate intraneural injection.</li> <li>16/17 (94%) patients had US criteria of intraneural injection after deliberate NS-guided intraneural injection.</li> <li>Average increase in post-injection nerve area was 45%.</li> </ul> |
| Tran et al. <sup>123</sup>        | RCT          | US          | Sciatic         | 1 wk             | Not mentioned | <ul style="list-style-type: none"> <li>Presence of persistent paresthesia/motor deficit by home contact</li> </ul>        | <ul style="list-style-type: none"> <li>A single subepineural injection resulted in better success rates, faster onset time, and fewer needle passes than targeted injections around tibial and common peroneal nerve.</li> <li>None of the 45 patients followed up at one wk showed sensory or motor deficit.</li> </ul>                                                           |
| Choyce et al. <sup>47</sup>       | Cohort study | Paresthesia | Axillary        | 2 wks            | Not mentioned | <ul style="list-style-type: none"> <li>Neurologic questionnaire (by telephone interview)</li> </ul>                       | <ul style="list-style-type: none"> <li>After paresthesia, 77% of needle placements produced motor activity <math>\leq 0.5</math> mA (median 0.17 mA; range 0.03-3.3 mA).</li> </ul>                                                                                                                                                                                                |
| Kaiser et al. <sup>69</sup>       | RCT          | NS          | Sciatic         | Not mentioned    | Not mentioned | <ul style="list-style-type: none"> <li>Not mentioned</li> </ul>                                                           | <ul style="list-style-type: none"> <li>Complete paralysis was achieved in all patients only with low current (0.1 mA).</li> </ul>                                                                                                                                                                                                                                                  |
| Keschner et al. <sup>76</sup>     | Cohort study | NS          | Infraclavicular | 24 hrs           | Not mentioned | <ul style="list-style-type: none"> <li>Telephone interview/ standardized questionnaire</li> </ul>                         | <ul style="list-style-type: none"> <li>Block success rate of 94% with stimulating current <math>&lt; 0.3</math> mA, with no neurological complications noted on first postoperative visit.</li> </ul>                                                                                                                                                                              |
| Seidel et al. <sup>108</sup>      | RCT          | US vs. NS   | Sciatic         | 24 hrs and 6 wks | Not mentioned | <ul style="list-style-type: none"> <li>Short term by the investigators</li> <li>Long term by the surgical team</li> </ul> | <ul style="list-style-type: none"> <li>Success rate was significantly higher in the US group (94.9% vs. 61.9%, <math>p &lt; 0.001</math>). Paresthesia was more common in US group (51.7%) vs. NS group (23.7%).</li> <li>Paresthesias indicated an intraneural needle position with an odds ratio of 27.4 (specificity 98.8%, sensitivity 45.9%).</li> </ul>                      |

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| Barrington et al. <sup>2</sup>  | Prospective multicenter study                   | US+/-NS | Interscalene (889); Periclavicular (499), Axillary (1251), Distal upper limb (211), Trunk (711), Femoral (2463), Lumbar plexus (691), Sciatic (1285), Distal lower limb (83) | 7-10 days and 6 wks                                                            | Not mentioned                                                                         | <ul style="list-style-type: none"> <li>Short term: standardized questionnaire</li> <li>Long term: referral to neurologist</li> </ul>                                                 | <ul style="list-style-type: none"> <li>Incidence attributable to nerve block is 0.04%.</li> <li>2/3 blocks with nerve injury related to PNB were done using NS alone; other used US+NS (not significant).</li> </ul>                                                                                                                                                                                                                                                                         |
| Fredrickson et al. <sup>3</sup> | Prospective database study                      | US      | Interscalene (659), Supraclavicular (32), Infraclavicular (122), Femoral (99), Sciatic (98)                                                                                  | 10 days                                                                        | >3 mos                                                                                | <ul style="list-style-type: none"> <li>Short term: telephone interview on day 10-21</li> <li>Long term: neurology referral (incl. EMG if symptoms persisted beyond 3 mos)</li> </ul> | <ul style="list-style-type: none"> <li>Most common causes of postoperative neurological dysfunction are unrelated to PNB.</li> <li>Elicitation of paresthesia was associated with an increased odds ratio for development of new neurological symptoms.</li> </ul>                                                                                                                                                                                                                           |
| Auroy et al. <sup>1</sup>       | Prospective multi-center adverse event database | -       | Various (21,278)                                                                                                                                                             | Non -specific: all neurological symptoms presented within 48 postoperative hrs | Non-specific: All neurological symptoms persisting beyond 3 mos were deemed permanent | <ul style="list-style-type: none"> <li>Standardized questionnaire</li> </ul>                                                                                                         | <ul style="list-style-type: none"> <li>Lidocaine spinals associated with more complications than bupivacaine spinals.</li> <li>9/12 complications that occurred after PNB used NS.</li> </ul>                                                                                                                                                                                                                                                                                                |
| Borgeat et al. <sup>26</sup>    | Cohort study                                    | NS      | Interscalene (520)                                                                                                                                                           | day 10: acute; 10 days-1 mo: subacute                                          | >9 mos: long term (evaluated at 3, 6, and 9 mos)                                      | <ul style="list-style-type: none"> <li>Short term: standardized questionnaire;</li> <li>Long term: neurology referral (incl. EMG)</li> </ul>                                         | <ul style="list-style-type: none"> <li>Up to 14% and 7.9% of patients have neurological symptoms not related to shoulder surgery at 10 days and 1 mo respectively.</li> <li>All symptoms appeared within 23 days after the block; 10% developed symptoms between days 10-23, but most resolved spontaneously.</li> <li>Long-term neurological dysfunction due to interscalene block is rare (0.4%); treatable causes (e.g., sulcus ulnaris syndrome) need to be identified early.</li> </ul> |
| Candido et                      | Cohort                                          | NS      | Interscalene (693)                                                                                                                                                           | 24 and 48 h, 2                                                                 | Nonspecific:                                                                          | <ul style="list-style-type: none"> <li>Short term:</li> </ul>                                                                                                                        | <ul style="list-style-type: none"> <li>Incidence of neurologic sequelae in</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                        |

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| al. <sup>27</sup>              | study                                          |    |                                                                                                                                                  | and 4 wks                                   | surgical team follow-up and referral                  | Telephone interview via standardized questionnaire <ul style="list-style-type: none"> <li>Long term: neurology referral (incl. EMG) by the surgical team</li> </ul> | brachial plexus distribution after interscalene block was 3.3% and 0.1% at 1 and 3 mo. <ul style="list-style-type: none"> <li>Pain/paresthesia at the block site are independent predictors of neurological sequelae.</li> </ul>                                                                                                                                             |
| Borgeat et al. <sup>42</sup>   | Cohort study                                   | NS | Interscalene catheter (700)                                                                                                                      | day 10: acute; 10 days-1 mo: subacute       | >6 mos: long term (evaluated at 3 and 6 mos with EMG) | <ul style="list-style-type: none"> <li>Short term: standardized questionnaire</li> <li>Long term: neurology referral (incl. EMG at 1, 3, and 6 mos)</li> </ul>      | <ul style="list-style-type: none"> <li>Minor neurologic complications of 2.4%, 0.3%, and 0% at 1, 3, and 6 mos., respectively using lateral modified approach for interscalene block.</li> <li>Two patients had a severe and prolonged sensory-motor deficit involving the middle and lower trunks; these patients needed 19 and 28 wks to recover, respectively.</li> </ul> |
| Capdevila et al. <sup>44</sup> | Prospective multicenter study                  | NS | Continuous PNB: Interscalene (256), Axillary (126), Lumbar plexus (20), Femoral (683), Fascia iliaca (94), Sciatic (32), Popliteal sciatic (167) | 6-12 postoperative hrs; 2 wks, 6 wks by EMG | 3 mos by EMG                                          | <ul style="list-style-type: none"> <li>Suspected neurological complication was assessed by ultrasound (for hematoma) and subsequently by EMG</li> </ul>             | <ul style="list-style-type: none"> <li>Incidence of short-term neurological dysfunction following continuous PNB is ~0.21% for femoral nerve block.</li> <li>Minor symptoms such as dysesthesia range between 1.5-3%.</li> <li>High risk for neurological dysfunction include intensive care unit stay, patient age &lt;40 yrs, and bupivacaine infusion.</li> </ul>         |
| Ecoffey et al. <sup>52</sup>   | Prospective web based survey                   | US | Axillary                                                                                                                                         | Deficit at home interview (7-10 days)       | Not mentioned                                         | <ul style="list-style-type: none"> <li>Standardized questionnaire</li> </ul>                                                                                        | <ul style="list-style-type: none"> <li>After US-guided axillary block, overall incidence of postoperative neurologic symptoms was 0.37/10,000.</li> <li>Most were mild in nature and unrelated to the block.</li> </ul>                                                                                                                                                      |
| Auoy et al. <sup>31</sup>      | Prospective multicenter adverse event database | -  | Spinals (70.58%)<br>Epidurals (17.64%)<br>PNB (11.76%)                                                                                           | Not mentioned                               | Not mentioned                                         | <ul style="list-style-type: none"> <li>Standardized questionnaire</li> </ul>                                                                                        | <ul style="list-style-type: none"> <li>4 neurological injuries total; incidence of 1.9/10,000 blocks.</li> </ul>                                                                                                                                                                                                                                                             |
| Klein et al. <sup>78</sup>     | Cohort study                                   | NS | Interscalene (733), Supraclavicular                                                                                                              | 1 wk (24 hr and 7 day interview)            | Not mentioned                                         | <ul style="list-style-type: none"> <li>Standardized questionnaire</li> </ul>                                                                                        | <ul style="list-style-type: none"> <li>Incidence of short term neurological dysfunction was 0.17%</li> </ul>                                                                                                                                                                                                                                                                 |

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|                                |              |                    | (193),<br>Axillary (193),<br>Lumbar plexus (338),<br>Femoral (263),<br>Sciatic (662)                                                                                      |                                                                      |                                                 |                                                                                                                                                                                              | <ul style="list-style-type: none"> <li>Neurological injury occurs infrequently with the use of long-acting LA.</li> </ul>                                                                                                                                                                                                    |
| Watts et al. <sup>135</sup>    | Cohort study | US                 | Femoral (261),<br>Interscalene (242),<br>Lumbar plexus (218),<br>Sciatic (187),<br>Axillary (74),<br>Supraclavicular (15),<br>Infraclavicular (27),<br>Paravertebral (24) | 1 wk                                                                 | Not mentioned                                   | <ul style="list-style-type: none"> <li>Short term: symptoms of paresthesia, dysesthesia, motor weakness on 7-10th day</li> <li>Long term: neurology referral (incl. EMG)</li> </ul>          | <ul style="list-style-type: none"> <li>13/1065 (1.22%) had short term dysfunction and 2/1065 (0.22%) had long term injury (&gt;6 mos)</li> <li>30% blocks performed on awake patients; 25.6% under sedation, and 44.4% under GA.</li> <li>Catheters used in 7/13 blocks associated with neurological dysfunction.</li> </ul> |
| Compere et al. <sup>49</sup>   | Cohort study | NS                 | Popliteal sciatic catheter (400)                                                                                                                                          | Symptoms persisting >48 hrs after block discontinuation; 4 wks (EMG) | EMG in symptomatic patients at 3, 6, and 12 mos | <ul style="list-style-type: none"> <li>Short term: symptoms of paresthesia, dysesthesia, motor weakness at 48 hours post block</li> <li>Long term: neurology referral (incl. EMG)</li> </ul> | <ul style="list-style-type: none"> <li>2/400 (0.05%) had long term neurological dysfunction.</li> <li>One complication resolved at 18 mos, and the other persisted; paresthesia was noted during block placement in the latter patient.</li> </ul>                                                                           |
| Neuberger et al. <sup>96</sup> | Cohort study | NS                 | Continuous PNB: Axillary (936), Interscalene (473), Infraclavicular (125), Lumbar plexus (74), Femoral (900), Sciatic (964)                                               | <6 wks                                                               | Not mentioned                                   | <ul style="list-style-type: none"> <li>Short-term failure of sensation: &lt;6 wks</li> <li>Severe nerve damage: significant loss of function needing neurological consultation</li> </ul>    | <ul style="list-style-type: none"> <li>0.3% at &lt;6 wks; 6 patients (0.2%) had symptoms lasting &gt;6 wks</li> <li>Neurological complications following PNB catheters are rare.</li> </ul>                                                                                                                                  |
| Selander et al. <sup>110</sup> | Cohort study | NS vs. paresthesia | Axillary (33)                                                                                                                                                             | Few wks                                                              | 1 yr                                            | <ul style="list-style-type: none"> <li>Short term: symptoms of nerve dysfunction</li> <li>Long term: neurology</li> </ul>                                                                    | <ul style="list-style-type: none"> <li>Difficult to avoid paresthesia in the artery group.</li> <li>All 10 patients with complications reported painful paresthesia during block procedure.</li> </ul>                                                                                                                       |

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|                                 |              |                      |                        |                  |               | consultation for prolonged symptoms (incl. EMG)                                                                                                                                                               | <ul style="list-style-type: none"> <li>1.9% (8 in paresthesia-guidance group and 2 in artery-guidance group).</li> <li>3/533 (0.56%) (1.03% in paresthesia group) had symptoms lasting &gt;1 yr.</li> </ul>                                                                                                                                    |
| Bardou et al. <sup>32</sup>     | Cohort study | Electrical impedance | Various PNB (140)      | Not measured     | Not measured  | -                                                                                                                                                                                                             | <ul style="list-style-type: none"> <li>A &gt;4.3% increase in electrical impedance may indicate accidental nerve puncture during peripheral nerve block.</li> </ul>                                                                                                                                                                            |
| Liu et al. <sup>88</sup>        | RCT          | US vs. NS            | Interscalene (230)     | 1 wk and 4-6 wks | Not mentioned | <ul style="list-style-type: none"> <li><b>Neurological questionnaire via telephone for short term; surgeon visit for long term.</b></li> <li><b>Further follow-up until resolution of symptoms</b></li> </ul> | <ul style="list-style-type: none"> <li><b>At 1 wk follow-up: 11% for NS and 8% for US.</b></li> <li><b>At 6 wks: 7% for NS and 6% for US.</b></li> <li><b>Use of US did not significantly reduce the incidence or severity of postoperative neurological symptoms after interscalene block for outpatient shoulder arthroscopy.</b></li> </ul> |
| Cuvillon et al. <sup>50</sup>   | Cohort study | NS                   | Femoral catheter (208) | 24-48 hrs; 6 wks | Not mentioned | <ul style="list-style-type: none"> <li>Paresthesia, motor, or sensory deficits were followed up individually after 6 wks</li> </ul>                                                                           | <ul style="list-style-type: none"> <li><b>48 hr infusion through femoral catheter resulted in femoral nerve dysfunction of 0.48%.</b></li> </ul>                                                                                                                                                                                               |
| Bigeleisen et al. <sup>99</sup> | Cohort study | US                   | Axillary (20)          | 3 wks            | 6 mos         | <ul style="list-style-type: none"> <li>Qualitative sensory and motor testing</li> </ul>                                                                                                                       | <ul style="list-style-type: none"> <li>4/20 cases had long-lasting neurological dysfunction lasting 3-12 mos.</li> </ul>                                                                                                                                                                                                                       |

\* US, ultrasound; NS, nerve stimulation

**Table B: Retrospective studies evaluating neurological outcomes in relation to peripheral nerve blockade.**

| Study                       | Follow-up period | Number of PNB or claims (CC) | Incidence of temporary nerve injury (<6 mo.)                                                                                                                                                                           | Incidence of long-term injury (>6 mo.)                                                        | Key findings                                                                                                                                                                                                                                                                                                                                                                                    |
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| Kroll et al. <sup>82</sup>  | N/A              | CC (1541)                    | <ul style="list-style-type: none"> <li>Most claims were for disabling injury</li> </ul>                                                                                                                                | -                                                                                             | <ul style="list-style-type: none"> <li>GA (61%) was more commonly associated with nerve damage claims compared to RA (36%).</li> <li>GA was involved in a majority of ulnar nerve injuries (85%).</li> </ul>                                                                                                                                                                                    |
| Cheney et al. <sup>46</sup> | N/A              | CC (4813)                    | -                                                                                                                                                                                                                      | -                                                                                             | <ul style="list-style-type: none"> <li>RA was more frequently associated with nerve damage claims compared to GA.</li> <li>Ulnar nerve injury occurred predominantly in men (75%).</li> <li>Increase in spinal cord complications compared to previous analysis.</li> </ul>                                                                                                                     |
| Lee et al. <sup>83</sup>    | N/A              | CC (189)                     | -                                                                                                                                                                                                                      | -                                                                                             | <ul style="list-style-type: none"> <li>51% of claims were for nerve damage.</li> <li>68% of claims were for temporary or non-disabling injury.</li> <li>32% of claims were associated with permanent and/or disabling injuries.</li> <li>6/8 spinal cord injury claims related to interscalene blocks with cervical spinal cord damage; 4 of these 6 blocks were performed under GA.</li> </ul> |
| Lee et al. <sup>84</sup>    | N/A              | CC (1005)                    | <ul style="list-style-type: none"> <li>51% of claims were for nerve damage.</li> <li>68% were for temporary or non-disabling injury.</li> <li>32% were associated with permanent and/or disabling injuries.</li> </ul> | 6/8 spinal cord injury claims related to interscalene block and 4/6 blocks performed under GA | <ul style="list-style-type: none"> <li>Majority of claims (72%) associated with temporary or non-disabling injuries.</li> <li>1/4 of claims involved disabling injuries.</li> <li>Majority of claims were associated with outpatient procedures (66%).</li> </ul>                                                                                                                               |

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| Jacob et al. <sup>67</sup>    | N/A                       | Knee arthroplasty (3883) | -                                                                                                                            | -     | <ul style="list-style-type: none"> <li>Nerve injury following TKA was not associated with PNB (odds ratio 0.97) or type of anesthesia (odds ratio 1.1 [neuraxial vs. general]) but with prolonged tourniquet time.</li> <li>Patients with nerve injury who underwent PNB were less likely to have complete neurologic recovery.</li> </ul>                                                      |
| Welch et al. <sup>136</sup>   | N/A                       | Surgical patients (6685) | -                                                                                                                            | -     | <ul style="list-style-type: none"> <li>0.3% incidence of iatrogenic injuries.</li> <li>Significant association of iatrogenic injuries with certain types of surgery, GA, and epidural anesthesia but a similar association was not found with PNB.</li> </ul>                                                                                                                                   |
| Jacob et al. <sup>66</sup>    |                           | Hip arthroplasty (2444)  | -                                                                                                                            | -     | <ul style="list-style-type: none"> <li>Nerve injury following hip arthroplasty was not associated with type of anesthesia or PNB.</li> <li>The risk for nerve injury was associated with younger age, female gender, longer operations, and posterior surgical approach.</li> </ul>                                                                                                             |
| Sviggum et al. <sup>119</sup> | N/A                       | Interscalene (1138)      | -                                                                                                                            | -     | <ul style="list-style-type: none"> <li>Use of interscalene block does not increase the risk of nerve injury in patients undergoing total shoulder arthroplasty.</li> <li>Use of interscalene block was associated with significantly lower odds for nerve injury (0.44; 95% CI = 0.22-0.86).</li> <li>Incidence of nerve injury after elective total shoulder arthroplasty was ~2.2%</li> </ul> |
| Hebl et al. <sup>61</sup>     | 2, 3, and 6 wks post-op   | Axillary (100)           | <ul style="list-style-type: none"> <li>6/100 receiving axillary block and 4/100 receiving GA* at 2-3 wk follow-up</li> </ul> | -     | <ul style="list-style-type: none"> <li>Regional anesthesia does not seem to worsen neurologic outcome in patients with pre-existing ulnar neuropathy who undergo ulnar nerve transposition.</li> </ul>                                                                                                                                                                                          |
| Orebaugh et al. <sup>4</sup>  | 24 hrs or until the block | Various PNB (5436)       | -                                                                                                                            | 0.09% | <ul style="list-style-type: none"> <li>3 EMG-confirmed cases of nerve injury with landmark-NS technique vs. no long-term injury with US technique.</li> </ul>                                                                                                                                                                                                                                   |

|                               |              |                      |                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                            |
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|                               | resolved     |                      |                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                           | <ul style="list-style-type: none"> <li>No statistically significant difference between the two groups in frequency of neurologic injury.</li> </ul>                                                                                                        |
| Sites et al. <sup>6</sup>     | 5 days-6 mo. | Various PNB (12,668) | <ul style="list-style-type: none"> <li>Femoral 0.09% [95% CI = 0.02-0.23]</li> <li>Interscalene 0.35% [95% CI = 0.14-0.73]</li> <li>Supraclavicular 0.20% [95% CI = 0.04-0.58]</li> <li>Popliteal 0.40% [95% CI = 0.11-1.04]</li> <li>Femoral (continuous) 0.1% [95% CI = 0.11-1.04]</li> <li>Interscalene (continuous) 1.2% [95% CI = 0.27-3.76]</li> <li>Axillary 2.3 [95% CI = 0.06-12.57]</li> </ul> | <ul style="list-style-type: none"> <li>Femoral 0.02% [95% CI = 0-1.2]</li> <li>Interscalene 0.25% [95% CI = 0.08-0.58]</li> <li>Supraclavicular 0% [95% CI = 0-0.24]</li> <li>Popliteal 0.31% [95% CI = 0.06-0.89]</li> <li>Femoral (continuous) 0.1% [95% CI = 0.11-1.04]</li> <li>Interscalene (continuous) 0.87% [95% CI = 0.10-3.11]</li> <li>Axillary 0% [95% CI = 0-8.4]</li> </ul> | <ul style="list-style-type: none"> <li>Overall incidence of short-term (lasting up to 5 days) symptoms following PNB was 0.18%.</li> <li>Symptoms lasting &gt;6 mo. was 0.09%.</li> </ul>                                                                  |
| Orebaugh et al. <sup>5</sup>  | 1 year       | Various PNB (9069)   | 4/9069 at 6-12 mo.                                                                                                                                                                                                                                                                                                                                                                                       | 1/9069 at >12 mo.                                                                                                                                                                                                                                                                                                                                                                         | <ul style="list-style-type: none"> <li>Nerve injuries lasting 6-12 mos were more frequent with NS-guided blocks compared to US-guided blocks.</li> <li>Long term nerve injuries (&gt;12 mos) were no different between NS- or US-guided blocks.</li> </ul> |
| Szypula et al. <sup>121</sup> | N/A          | CC (366)             |                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                           | <ul style="list-style-type: none"> <li>Claims related to PNB constituted 3% of the total closed claims and 13% of all regional anaesthesia claims.</li> <li>Epidural (72%), spinal (15%) and</li> </ul>                                                    |

|                               |                             |                        |                                                                                                |                                                                                  |                                                                                                                                                                                                                                    |
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|                               |                             |                        |                                                                                                |                                                                                  | <p>combined spinal/epidural (2%) constituted most of the claims and were mostly related to obstetrics.</p> <ul style="list-style-type: none"> <li>Non-obstetric claims had worse outcomes compared to obstetric claims.</li> </ul> |
| Bogdanov et al. <sup>40</sup> | 4-8 wks                     | Interscalene (548)     | -                                                                                              | -                                                                                | <ul style="list-style-type: none"> <li>Modification of Winnie's technique allows interscalene block to be performed safely on anesthetized patients.</li> </ul>                                                                    |
| Lenters et al. <sup>85</sup>  | N/A                         | Interscalene (3172)    | 27/3172, 11 of which had recovery of normal function at a mean of 202 days (range 10-760 days) | Persistent deficits present in 14/3172 at a mean of 176 days (range 17-416 days) | <ul style="list-style-type: none"> <li>Interscalene block is associated with a 0.73% incidence of neurological dysfunction and 0.16% incidence of chronic neuropathy.</li> </ul>                                                   |
| Weigel et al. <sup>138</sup>  | 3 <sup>rd</sup> mo. post-op | Continuous PNBs (1398) | 12 (0.9%) had transient neurological deficits                                                  | One permanent neurological injury noted after femoral nerve block                | <ul style="list-style-type: none"> <li>Major complications after continuous PNB are rare, but minor transient adverse effects are not uncommon after continuous PNB.</li> </ul>                                                    |
| Weber et al. <sup>143</sup>   | N/A                         | Various PNB (218)      | 2/218 (0.91%)                                                                                  | -                                                                                | <ul style="list-style-type: none"> <li>Two patients had temporary neurologic injuries that persisted at six wks.</li> <li>One patient had long term nerve damage (&gt;1 yr).</li> </ul>                                            |
| Hajek et al. <sup>60</sup>    | N/A                         | Continuous PNBs (157)  | -                                                                                              | 1.26%                                                                            | <ul style="list-style-type: none"> <li>Higher prevalence of neurological dysfunction and long term neuropathy compared to other studies with 72-hr continuous PNB.</li> </ul>                                                      |
| Nye et al. <sup>97</sup>      | surgery clinic follow-up    | Lumbar plexus (213)    | 6.6%                                                                                           | 1.9%                                                                             | <ul style="list-style-type: none"> <li>High incidence of temporary (6.6%) neurological dysfunction following 72-hr lumbar plexus catheters.</li> </ul>                                                                             |
| Sharma et al. <sup>112</sup>  | 2, 6, 12 wks and 1 yr       | Femoral (709)          | 0.66%                                                                                          | 0.13%                                                                            | <ul style="list-style-type: none"> <li>Overall rate of femoral neuropathy/neuritis was 0.59%.</li> <li>In all but one patient, neurologic deficits resolved within 1 yr of total knee arthroplasty.</li> </ul>                     |
| Swenson et al. <sup>120</sup> | N/A                         | Various PNB (620)      | 2/620 (0.3%)                                                                                   | -                                                                                | <ul style="list-style-type: none"> <li>In both patients reporting neurological</li> </ul>                                                                                                                                          |

|                                |     |                 |       |   |                                                                                                                                                                                                  |
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|                                |     |                 |       |   | dysfunction, complications resolved within 6 wks.                                                                                                                                                |
| Horlocker et al. <sup>63</sup> | N/A | Axillary (1614) | 11.3% | - | <ul style="list-style-type: none"> <li>• Only 7 of 62 (11.3%) nerve injuries were related to the anesthetic technique.</li> <li>• No association of PNB with worsening of neuropathy.</li> </ul> |

\* GA, general anesthesia

**Table C. Summary of findings from laboratory studies.**

| Study                             | Guidance method* | Number of insertions/ attempts | Block type               | Key findings                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----------------------------------|------------------|--------------------------------|--------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sala-Blanch et al. <sup>106</sup> | direct vision    | 10                             | Sciatic                  | <ul style="list-style-type: none"> <li>Intraneural needles likely traverse connective tissue rather than fascicular tissue.</li> <li>30° bevel needles did not result in fascicular injury; incidence of fascicular injury after insertion of 15° bevel needles was ~3%.</li> </ul>                                                                                                                                                                           |
| Moayeri et al. <sup>92</sup>      | US               | 36                             | Supraclavicular, sciatic | <ul style="list-style-type: none"> <li>Intraneural injection can be detected on US by injecting a small amount of injectate.</li> <li>The ultrasonographic criterion ‘increase in cross-sectional surface area together with change in echogenicity’ identified intraneural injection with 94% precision.</li> <li>Cross-sectional surface area increased 8-9% in both brachial plexus and sciatic nerve.</li> </ul>                                          |
| Moayeri et al. <sup>93</sup>      | N/A              | 4                              | N/A                      | <ul style="list-style-type: none"> <li>The area of the connective tissue compartment surrounding the brachial plexus increased proximally to distally, while the neural component remained the same.</li> <li>Ratio of connective to neural tissue increases progressively from proximal to distal part of brachial plexus.</li> </ul>                                                                                                                        |
| Moayeri et al. <sup>94</sup>      | N/A              | 5                              | Sciatic                  | <ul style="list-style-type: none"> <li>Ratio of neural to non-neural tissue in sciatic nerve changes significantly from 2:1 (midgluteal and subgluteal) to 1:1 (midfemoral and popliteal).</li> </ul>                                                                                                                                                                                                                                                         |
| Krediet et al. <sup>80</sup>      | US               | 18 intraneural, 14 extraneural | Sciatic                  | <ul style="list-style-type: none"> <li>Random assessment of 500 video clips of injection of 0.5 mL injectate (211 intraneural, 268 extraneural, 21 undetermined), mean sensitivity of experts and novices in detecting intraneural injections were 84% and 65%, respectively.</li> <li>Assessments by both groups were highly specific (98%) for intraneural injections.</li> <li>Among novices, 20-50% of all intraneural injections were missed.</li> </ul> |
| Orebaugh et al. <sup>98</sup>     | US               | 10                             | Interscalene             | <ul style="list-style-type: none"> <li>With US-guided needle tip placement in the interscalene region, frequency of intra-epineurial injection was relatively high (50%).</li> <li>In cases with intra-epineurial needle placement, there was no evidence of fascicular injection or axonal damage.</li> </ul>                                                                                                                                                |
| Sunderland and                    | N/A              | 40                             | Sciatic                  | <ul style="list-style-type: none"> <li>No exchange of bundles between the two popliteal divisions of the</li> </ul>                                                                                                                                                                                                                                                                                                                                           |

|                              |     |     |                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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| Ray <sup>118</sup>           |     |     |                       | sciatic trunk. <ul style="list-style-type: none"> <li>• Direct relationship found between number of fascicles and thickness of nerves (cross sectional area).</li> <li>• Branching of fascicles varied greatly among nerves at any given level.</li> </ul>                                                                                                                                                                                                                                                             |
| Theron et al. <sup>122</sup> | N/A | N/A | N/A                   | <ul style="list-style-type: none"> <li>• Syringe feel cannot help anesthesiologists determine reliably whether needle tip is placed intraneurally irrespective of operator experience.</li> <li>• 30% of subjects correctly identified the nerve.</li> <li>• 30% of self-identified experienced regional anesthesiologists correctly identified the nerve.</li> </ul>                                                                                                                                                  |
| Tsui et al. <sup>125</sup>   | N/A | N/A | N/A                   | <ul style="list-style-type: none"> <li>• When tested on nine different needle-syringe combinations, CAIT effectively maintained injection pressures below 1034 mmHg in an in vitro system.</li> </ul>                                                                                                                                                                                                                                                                                                                  |
| Claudio et al. <sup>48</sup> | N/A | N/A | N/A                   | <ul style="list-style-type: none"> <li>• Anesthesiologists vary widely in perception of “normal” pressure and speed during simulated PNB injection.</li> <li>• Pressures varied as much as 20X among needles of the same gauge/length.</li> <li>• Pressure &gt;20 psi was generated 70% of the time; &gt;25 psi, 50% of the time; &gt;30 psi, 10% of the time.</li> </ul>                                                                                                                                              |
| Tsui et al. <sup>126</sup>   | N/A | N/A | N/A                   | <ul style="list-style-type: none"> <li>• No anesthesiologist generated pressures &gt;1034 mmHg using CAIT.</li> <li>• 29/30 subjects generated pressures &gt;1034 mmHg at some point when using ‘syringe feel’ method.</li> <li>• Mean pressure using CAIT was lower (<math>636 \pm 71</math> vs. <math>1378 \pm 194</math> mmHg, <math>p = 0.03</math>); ‘syringe feel’ method resulted in higher peak pressures (<math>1875 \pm 206</math> vs. <math>715 \pm 104</math> mmHg, <math>p &lt; 0.001</math>).</li> </ul> |
| Sunderland <sup>117</sup>    | N/A | 37  | Median, radial, ulnar | <ul style="list-style-type: none"> <li>• Fascicular pattern changed along the entire length of each nerve.</li> <li>• The longest section of any nerve with a constant pattern was 15 mm.</li> <li>• Size and number of fascicles were inversely related at any one level.</li> <li>• There was no constant or characteristic fascicular pattern for any nerve.</li> </ul>                                                                                                                                             |

\* US, ultrasound

**Table D: Animal studies investigating neurological injury**

| Study                            | Animal model | Number of blocks/ attempts | Block type      | Key findings                                                                                                                                                                                                                                                                                                                                                                                      |
|----------------------------------|--------------|----------------------------|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Hadzic et al. <sup>59</sup>      | Dog          | 14                         | Sciatic         | <ul style="list-style-type: none"> <li>Perineural injections required low injection pressure (&lt;4 psi) while 4/7 intraneural injections required high injection pressure (&gt;25 psi).</li> <li>High injection pressures resulted in severe persistent motor deficits throughout the study period (7 days) and histological changes of nerve injury.</li> </ul>                                 |
| Selander et al. <sup>111</sup>   | Rabbit       | 20                         | Sciatic         | <ul style="list-style-type: none"> <li>Intrafascicular injection required higher injection pressures (&gt;600 mmHg) and showed a rapid longitudinal spread within the fascicle.</li> <li>Rupture of the perineurium occurred at pressures between 125-900 mmHg.</li> </ul>                                                                                                                        |
| Selander et al. <sup>22</sup>    | Rabbit       | 30                         | Sciatic         | <ul style="list-style-type: none"> <li>Nerve fascicles slid or rolled away easily from the needle tip, especially with short-bevel needles.</li> <li>The most severe fascicular injuries occurred more frequently with long-bevel (14°) than with short-bevel (45°) needles.</li> </ul>                                                                                                           |
| Macias et al. <sup>91</sup>      | Rat          | 12                         | Sciatic         | <ul style="list-style-type: none"> <li>The nerve trunk rotated and slipped at the time of contact with the needle more frequently with a short bevel than with a long bevel.</li> <li>Four animals in the short bevel group showed a decrease in movement and flexion tendency.</li> </ul>                                                                                                        |
| Steinfeldt et al. <sup>113</sup> | Pig          | 40                         | Brachial plexus | <ul style="list-style-type: none"> <li>Nerve damage (hematoma and myelin damage) and injury scores were greater with larger needle diameter after intentional nerve perforation.</li> </ul>                                                                                                                                                                                                       |
| Maryuama et al. <sup>90</sup>    | Rabbit       | 90                         | Sciatic         | <ul style="list-style-type: none"> <li>All needles caused axonotmesis and interruption of myelin sheath. The mean number of transected axons was significantly less for tapered needle than for the beveled needle.</li> <li>The number of damaged axons was reduced significantly by inserting the bevelled needle parallel to the nerve fibers.</li> </ul>                                      |
| Steinfeldt et al. <sup>114</sup> | Pig          | 58                         | Brachial plexus | <ul style="list-style-type: none"> <li>No significant difference with regard to incidence of intraneural hematoma or myelin damage after both needle injuries.</li> <li>Myelin damage was 40% with both Sprotte and Tuohy needles, and hematoma was 55% with the Sprotte needle compared to 60% with the Tuohy needle.</li> </ul>                                                                 |
| Rice et al. <sup>101</sup>       | Rat          | 63                         | Sciatic         | <ul style="list-style-type: none"> <li>After deliberate intrafascicular needle insertion, short-bevel needles caused more axonal damage and neuronal edema compared to long-bevel needles.</li> <li>The structural (axonal degeneration and neuronal edema) and functional changes after short-bevel needle insertion persist for a long time and result in disorganized regeneration.</li> </ul> |
| Kapur et al. <sup>75</sup>       | Dog          | 30                         | Sciatic         | <ul style="list-style-type: none"> <li>High injection pressures during intraneural injection may be indicative of intrafascicular injection and usually result in functional and histological changes indicative of nerve injury.</li> <li>Intraneural injections with low pressure resulted in significantly longer duration of</li> </ul>                                                       |

|                                |                      |     |         |                                                                                                                                                                                                                                                                                                                                                                                                                            |
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|                                |                      |     |         | sensory motor blockade.                                                                                                                                                                                                                                                                                                                                                                                                    |
| Gentili et al. <sup>56</sup>   | Rat                  | 140 | Sciatic | <ul style="list-style-type: none"> <li>Nerve damage seems to be highest with 1% tetracaine and 2% procaine. Damage seems to recover with time and was minimal by 9-12 days.</li> <li>Damage by lidocaine with or without epinephrine was mild and least with bupivacaine and mepivacaine without epinephrine.</li> </ul>                                                                                                   |
| Yang et al. <sup>142</sup>     | Rat                  | 16  | Sciatic | <ul style="list-style-type: none"> <li>Local anesthetics cause Schwann cell death in vitro in a time- and concentration-dependent manner.</li> <li>Prolonged exposure of nerves in vivo to continuous infusions of bupivacaine causes damage to myelin as well as infiltration and activation of macrophages</li> </ul>                                                                                                    |
| Lupu et al. <sup>89</sup>      | Pig                  | 20  | Median  | <ul style="list-style-type: none"> <li>Nerve expansion seen on ultrasound during intraneural injection of a clinically relevant volume of local anesthetic results in histological evidence of nerve injury but does not necessarily translate into functional neuropathy.</li> </ul>                                                                                                                                      |
| Iohom et al. <sup>65</sup>     | Rat                  | 52  | Sciatic | <ul style="list-style-type: none"> <li>Intraneural injection of ropivacaine at concentrations routinely used in clinical practice had no deleterious effect on sciatic nerve motor function.</li> </ul>                                                                                                                                                                                                                    |
| Myers et al. <sup>95</sup>     | Rat                  | 48  | Sciatic | <ul style="list-style-type: none"> <li>Epinephrine reduces nerve blood flow (NBF) significantly; this effect is more pronounced after addition of lidocaine. The reduced NBF is not reversed with washout in local anesthetic groups.</li> </ul>                                                                                                                                                                           |
| Bouaziz et al. <sup>43</sup>   | Rat                  | 48  | Sciatic | <ul style="list-style-type: none"> <li>All local anesthetics studied decrease NBF.</li> <li>The greatest decrease was noted with ropivacaine followed by levobupivacaine (0.75%) and then by the rest.</li> <li>Addition of epinephrine did not result in further decrease in NBF.</li> <li>Although significant, the reduction in NBF did not result in subsequent histopathological changes of neurotoxicity.</li> </ul> |
| Partridge et al. <sup>38</sup> | Rat                  | 90  | Sciatic | <ul style="list-style-type: none"> <li>Epinephrine + lidocaine causes dose-dependent reduction in NBF which continues after washout.</li> <li>Bupivacaine causes dose-dependent improvements in NBF and is reversed by washout.</li> <li>Tetracaine results in no significant change in NBF</li> </ul>                                                                                                                     |
| Whitlock et al. <sup>137</sup> | Rat                  | 54  | Sciatic | <ul style="list-style-type: none"> <li>Ropivacaine is capable of inducing demyelination and Wallerian degeneration when administered directly into or placed onto an exposed nerve, but the extent of injury is always less than that of phenol, and nerve regeneration is near normal at 2 weeks.</li> </ul>                                                                                                              |
| Williams et al. <sup>141</sup> | Cultured rat neurons | n/a | n/a     | <ul style="list-style-type: none"> <li>Ropivacaine (2.5 mg/mL) is more neurotoxic than high concentrations of preservative-free adjuvants, clonidine, buprenorphine, dexamethasone, and midazolam.</li> <li>Midazolam increased the neurotoxic potential of ropivacaine.</li> </ul>                                                                                                                                        |
| Tüfek et al. <sup>128</sup>    | Rat                  | 40  | Sciatic | <ul style="list-style-type: none"> <li>Total antioxidant status of sciatic nerve was almost equal between sham, saline, dexmedetomidine and bupivacaine + dexmedetomidine groups but was significantly lower in the bupivacaine group.</li> </ul>                                                                                                                                                                          |

|                                |                                |     |                          |                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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|                                |                                |     |                          | <ul style="list-style-type: none"> <li>No difference in total oxidant status between the sham, saline, and dexmedetomidine groups but significant increase in the bupivacaine group.</li> </ul>                                                                                                                                                                                                                                               |
| Chan et al. <sup>45</sup>      | Pig                            | 28  | Brachial plexus          | <ul style="list-style-type: none"> <li>Threshold current was variable [0.43 mA (range: 0.12–1.8 mA)] with the threshold being 0.5 mA in 45% and 1 mA in 5%.</li> <li>Intrafascicular injection occurred in 2/24 injections.</li> </ul>                                                                                                                                                                                                        |
| Tsai et al. <sup>124</sup>     | Pig                            | 40  | Sciatic                  | <ul style="list-style-type: none"> <li>Type I motor response was obtainable only when needles were positioned 0.1 cm from the nerve or closer.</li> <li>Distance : current : frequency was 0.1 cm : <math>0.92 \pm 0.33</math> mA : 70%.</li> <li>On epineurium = <math>0.39 \pm 0.33</math> mA : 95%; Intraneural = <math>0.56 \pm 0.54</math> mA : 100%.</li> </ul>                                                                         |
| Altermatt et al. <sup>29</sup> | Pig                            | 24  | Brachial plexus, femoral | <ul style="list-style-type: none"> <li>The diameter increased by more than 50% compared with pre-intervention images.</li> <li>The current required to elicit a motor response was variable (0.2-3.3 mA).</li> <li>Minimum current threshold was <math>\leq 0.5</math> mA in 75% of cases and <math>&gt; 1.0</math> mA in 17% of cases.</li> </ul>                                                                                            |
| Wiesmann et al. <sup>139</sup> | Pig                            | 50  | Brachial plexus          | <ul style="list-style-type: none"> <li>Nerve contact and intraneural needle placement showed similar threshold current intensities (<math>\leq 0.2</math> mA), irrespective of the pulse duration.</li> <li>No significant difference between needle-nerve contact and intraneural needle tip positions.</li> <li>Control nerve stimulation required significantly higher threshold current, regardless of applied pulse duration.</li> </ul> |
| Vuckovic et al. <sup>133</sup> | Rat                            | 24  | Median                   | <ul style="list-style-type: none"> <li>All injections were characterized by an initial rise in pressure, which was followed by a similar but lower pressure. The majority of intraneural injections showed higher injection pressure (<math>86.552 \pm 13.262</math> kPa in comparison to <math>25.128 \pm 3.49</math> kPa for paraneural injection).</li> </ul>                                                                              |
| Vuckovic et al. <sup>132</sup> | Rats & stillborn human fetuses | 48  | Median                   | <ul style="list-style-type: none"> <li>All perineural injections resulted in pressure <math>\leq 27.92</math> kPa, while the majority of intraneural injections had injection pressure <math>\geq 69.8</math> kPa.</li> </ul>                                                                                                                                                                                                                 |
| Rigaud et al. <sup>102</sup>   | Dog                            | 24  | Sciatic                  | <ul style="list-style-type: none"> <li>Ink distribution patterns were not different between low and high stimulation threshold groups.</li> <li>One intraneural injection occurred in the high threshold group.</li> <li>Average stimulation threshold in the hyperglycemic group was the same as in the low threshold normoglycemic group, but ink distribution patterns were all intraneural in the hyperglycemic animals.</li> </ul>       |
| Kroin et al. <sup>81</sup>     | Rat                            | n/a | Sciatic                  | <ul style="list-style-type: none"> <li>All of the local anesthetic solutions produced a longer mean duration of sensory nerve block in diabetic rats versus non-diabetic rats.</li> <li>None of the sciatic nerves examined in the percutaneous injection study showed <math>&gt; 3\%</math> nerve fiber degeneration overall.</li> </ul>                                                                                                     |
| Belda et al. <sup>34</sup>     | Piglet                         | 12  | Sciatic                  | <ul style="list-style-type: none"> <li>Cross sectional area and relative echogenicity values were different immediately after</li> </ul>                                                                                                                                                                                                                                                                                                      |

|                                  |        |     |                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|----------------------------------|--------|-----|--------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                  |        |     |                          | <p>12the injections and returned to pre-puncture values within four days.</p> <ul style="list-style-type: none"> <li>• Injections did not exceed &gt;20 psi or result in motor deficits</li> <li>• Histology showed intact perineurium and signs of inflammation immediately and on days one and two post-injection.</li> </ul>                                                                                                                                                                                                                                                                                                                                                          |
| Voelckel et al. <sup>131</sup>   | Pig    | 20  | Sciatic                  | <ul style="list-style-type: none"> <li>• Motor response to currents &gt;0.5 mA ensures extraneural injections while low current (&lt;0.2 mA) is specific for intraneural injections.</li> <li>• The mean <math>\pm</math> SD current required to obtain a motor response was <math>0.4 \pm 0.05</math> mA in the standard current group and <math>0.15 \pm 0.04</math> mA in the low current group.</li> <li>• Standard current group showed no signs of inflammation. In 5/10 low current group animals, inflammation was found sub-, peri-, and intraneurally.</li> <li>• One sciatic nerve specimen of the low current group revealed disruption of perineurium and axons.</li> </ul> |
| Steinfeldt et al. <sup>116</sup> | Pig    | 42  | Sciatic                  | <ul style="list-style-type: none"> <li>• Myelin damage following perineural hematoma was seen in 15% of cases.</li> <li>• Both blood and albumin around the nerve result in aseptic inflammation of the nerves and severe structural nerve injury/ inflammation.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                              |
| Steinfeldt et al. <sup>115</sup> | Pig    | 50  | Brachial plexus          | <ul style="list-style-type: none"> <li>• Small (24 G) pencil-point needles do not seem to be superior to short-bevel needles of the same gauge with respect to damage from nerve perforation.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Vassiliou et al. <sup>130</sup>  | Pig    | 611 | Brachial plexus, sciatic | <ul style="list-style-type: none"> <li>• Dual guidance showed greater accuracy of needle tip placement in proximity to the nerve (98.5%) and fewer intraneural needle placements (0.5%).</li> <li>• Significant differences in close needle placement: US+NS (98.5%); NS group (90.1%), and US group (81.6%).</li> <li>• Fewer intraneural needle placements in the US+NS group (0.5%) compared with the US group (4%). Intraneural needle placement was 2.5% in NS group.</li> <li>• Puncture-related hematomas more frequent with NS (10.8%) compared with US (2.5%) or dual guidance (1.5%).</li> </ul>                                                                               |
| Farber et al. <sup>53</sup>      | Rat    | 16  | Sciatic                  | <ul style="list-style-type: none"> <li>• Animals that received intrafascicular injections showed increased severity of injury compared to control animals.</li> <li>• A layering of severity of injury was found with most severely injured areas closest to and uninjured areas furthest from the injection site.</li> <li>• Bupivacaine caused more damage to large fibers than the other local anesthetics.</li> </ul>                                                                                                                                                                                                                                                                |
| Hirasawa et al. <sup>62</sup>    | Rabbit | 50  | Sciatic                  | <ul style="list-style-type: none"> <li>• Least disturbance/damage from tapered needle.</li> <li>• Followed in increasing order of damage by short bevel/parallel insertion, long bevel/parallel insertion, short bevel/perpendicular insertion, long bevel/perpendicular insertion.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                           |
| Kalichman et al. <sup>70</sup>   | Rat    | 20  | Sciatic                  | <ul style="list-style-type: none"> <li>• Streptozocin-induced diabetic rats had lower motor nerve conduction velocity compared to normal rats.</li> <li>• Extraneurally placed LA caused neural edema, which was more pronounced with lidocaine 4% than saline or lidocaine 2% in diabetic rats.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                              |

|                                |        |       |         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|--------------------------------|--------|-------|---------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                |        |       |         | <ul style="list-style-type: none"> <li>• Nerve fibre injury scores were greater in diabetic rats compared to control groups.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Kalichman et al. <sup>71</sup> | Rat    | ?     | Sciatic | <ul style="list-style-type: none"> <li>• Procaine (10%) but not saline, 80% ethanol, or 80% glycerol induced statistically significant decreases in nerve blood flow.</li> <li>• Procaine and cocaine were associated with dose-dependent decreases in nerve blood flow, but cocaine was more potent.</li> <li>• At 48 h, injury scores were elevated significantly for 80% ethanol and 10% procaine; nerve injury from procaine and cocaine was dose-dependent.</li> </ul>                                                                                                             |
| Kalichman et al. <sup>72</sup> | Rat    | 60    | Sciatic | <ul style="list-style-type: none"> <li>• Etidocaine, lidocaine, chlorprocaine, and procaine caused concentration-dependent nerve injury.</li> <li>• The highest concentration of LA caused endoneurial edema, especially in larger fascicles.</li> </ul>                                                                                                                                                                                                                                                                                                                                |
| Kalichman et al. <sup>73</sup> | Rat    | 83    | Sciatic | <ul style="list-style-type: none"> <li>• Nerve fiber injury and disturbances of endoneurial microenvironment occur after 48 hours exposure to various LAs.</li> <li>• Degree and extent of nerve injury varied among the LAs.</li> <li>• Edema and nerve injury were typically greatest subjacent to the site of LA injection; the most severe edema was not always found with the most severe nerve injury.</li> <li>• Nerve fiber injury, endoneurial edema, and lipid droplet formation were produced in dose-dependent fashion.</li> </ul>                                          |
| Kalichman et al. <sup>74</sup> | Rat    | 49    | Sciatic | <ul style="list-style-type: none"> <li>• Exposure to lidocaine, etidocaine, procaine, and chlorprocaine resulted in neuronal edema and lipid droplet scores greater than saline and water controls.</li> <li>• Nerve injury was significantly different than with controls only at the highest concentrations of each drug.</li> <li>• Etidocaine was the least toxic LA.</li> </ul>                                                                                                                                                                                                    |
| Myers et al. <sup>159</sup>    | Rat    | ?     | Sciatic | <ul style="list-style-type: none"> <li>• Direct application of tetracaine 1% and 2-chlorprocaine resulted consistently in subperineurial and endoneurial edema due to increased perineurial permeability.</li> <li>• Between 24 hours and 4 weeks, perineurial and endoneurial fibrotic changes were noted to varying degree as a result of increased perineurial permeability and endoneurial edema.</li> </ul>                                                                                                                                                                        |
| Selander et al. <sup>109</sup> | Rabbit | 56    | Sciatic | <ul style="list-style-type: none"> <li>• Topical application of clinically recommended concentrations of bupivacaine around a nerve caused no detectable nerve injury; intrafascicular injection caused considerable axonal degeneration and damaged the blood-nerve barrier.</li> <li>• Axonal degeneration was the same after injection of saline and bupivacaine 0.5% but increased with increasing bupivacaine concentration and especially with addition of adrenalin.</li> <li>• Acute effects of intrafascicular injection changed little upon addition of adrenalin.</li> </ul> |
| Williams et al. <sup>140</sup> | Rat    | 25/15 | Sciatic | <ul style="list-style-type: none"> <li>• Single injection or continuous infusion of bupivacaine or midazolam, combined with dexamethasone, clonidine, and buprenorphine, did not result in long-term neurologic deficits.</li> </ul>                                                                                                                                                                                                                                                                                                                                                    |

**Table E: Case reports of neurological dysfunction following peripheral nerve blocks.**

| Author                             | Block type        | Age/<br>Sex | Intraneural<br>injection<br>detected? | Risk factors                             | Single<br>shot/<br>catheter | Guidance<br>method | Procedural<br>problems                                  | EMG<br>findings                                                              | Presentation                                                                                   | Time of<br>resolution           | Pearson<br>score |
|------------------------------------|-------------------|-------------|---------------------------------------|------------------------------------------|-----------------------------|--------------------|---------------------------------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|---------------------------------|------------------|
| Al-Nasser & Palacios <sup>28</sup> | Psoas compartment | 60/F        | N/A                                   | None                                     | Catheter                    | NS                 | Intrathecal placement on first attempt                  | Severe femoral nerve injury at 24 hrs                                        | Dense motor and sensory block despite low LA concentration                                     | 12 mo. (6 mo. partial recovery) | 6                |
| Atchabahian & Brown <sup>30</sup>  | Fascia iliaca     | 78/F        | N/A                                   | None                                     | Single shot                 | Landmark           | None                                                    | N/A                                                                          | Complete anesthesia over anterior thigh and motor weakness                                     | POD 8                           | 4                |
| Barrington et al. <sup>33</sup>    | Infraclavicular   | 60/M        | No                                    | C8 radiculopathy, smoking, alcohol abuse | Catheter                    | US                 | None                                                    | Recent onset brachial plexopathy at 3 wks                                    | Sensory deficits in radial and medial antebrachial nerve; persisting paresthesia and allodynia | Did not resolve                 | 9                |
| Barutell et al. <sup>10</sup>      | Interscalene      | 49/F        | Possibly                              | Obesity                                  | Single shot                 | Landmark           | Paresthesia, loss of consciousness, respiratory failure | Total denervation in C8/T1 supply; partial denervation in C7 supply on POD 1 | Paralysis of extensor muscles of hand                                                          | Did not resolve                 | 7                |
| Ben-David & Stahl <sup>35</sup>    | Axillary          | 38/M        | N/A                                   | None                                     | Single shot                 | Landmark           | None                                                    | Neurapraxia at 4 wks                                                         | Sensory and motor changes in radial territory with pain                                        | 6 mo.                           | 3                |
| Blumenthal et al. <sup>39</sup>    | Femoral nerve     | 72/M        | N/A                                   | Subclinical poly-neuropathy              | Catheter                    | NS                 | None                                                    | Low-voltage denervation activities on POD 4                                  | Persistent quadriceps weakness and hypesthesia                                                 | Did not resolve                 | 7                |

|                                |                         |      |     |                             |             |          |                                               |                                                                                                                      |                                             |                                 |   |
|--------------------------------|-------------------------|------|-----|-----------------------------|-------------|----------|-----------------------------------------------|----------------------------------------------------------------------------------------------------------------------|---------------------------------------------|---------------------------------|---|
| Bonner & Pridie <sup>41</sup>  | Sciatic nerve           | 59/F | N/A | Peripheral vascular disease | Single shot | NS       | None                                          | Absent conduction in common peroneal and posterior tibial nerves at 2 wks                                            | Persistent weakness in sciatic distribution | 12 mo. (6 mo. partial recovery) | 4 |
| Cohen & Gray <sup>11</sup>     | Interscalene            | 36/M | Yes | None                        | Single shot | US       | None                                          | N/A                                                                                                                  | Persistent weakness below elbow             | 6 wks                           | 2 |
| Funk et al. <sup>54</sup>      | Interscalene            | 35/M | N/A | None                        | Single shot | NS       | High injection resistance, twitches at 0.1 mA | No electrical activity in triceps on POD 10                                                                          | Weakness and hypesthesia in dorsum of hand  | 18 mo.                          | 3 |
| Giabicani et al. <sup>57</sup> | Popliteal sciatic nerve | 54/F | N/A | Subclinical poly-neuropathy | Single shot | US       | None                                          | Decreased bilateral amplitudes of potentially prolonged distal latencies and slowing conduction velocities on POD 40 | Persistent sensory and motor block          | 2 yrs                           | 3 |
| Gungor et al. <sup>58</sup>    | Psoas compartment       | 44/M | N/A | None                        | Single shot | NS       | None                                          | Partial lesion of proximal femoral nerve (? POD)                                                                     | Weakness in knee extensors                  | 6 mo.                           | 4 |
| Imran et al. <sup>64</sup>     | Axillary                | 44/M | N/A | None                        | Single shot | Landmark | None                                          | Significant denervation of axillary nerve at 6 wks                                                                   | N/A                                         | Did not resolve                 | 2 |
| Jung et al. <sup>68</sup>      | Axillary                | 62/F | N/A | None                        | Single shot | US       | None                                          | Medial antebrachial nerve injury (? POD)                                                                             | Pain and numbness                           | Did not resolve                 | 8 |
|                                | Axillary                | 30/F | N/A | None                        | Single shot | US       | None                                          | Medial antebrachial nerve injury (? POD)                                                                             | Pain and numbness                           | Did not resolve                 |   |
| Kim et al. <sup>77</sup>       | Brachial plexus         | 54/F | N/A | None                        | Single      | ?        | Radiating pain                                | Median nerve                                                                                                         | Pain and                                    | ?                               | 2 |

|                              |                        |      |                                                     |                    |             |             |                                              |                                                                        |                                   |                                                   |   |
|------------------------------|------------------------|------|-----------------------------------------------------|--------------------|-------------|-------------|----------------------------------------------|------------------------------------------------------------------------|-----------------------------------|---------------------------------------------------|---|
|                              |                        |      |                                                     |                    | shot        |             | in median nerve territory upon injection     | injury at 1 mo.                                                        | numbness                          |                                                   |   |
| Koff et al. <sup>79</sup>    | Interscalene           | 65/M | No                                                  | Multiple sclerosis | Single shot | US+NS       | No                                           | Denervation of median and ulnar nerves (POD 4; 3 wks, 3 mo.)           | Weakness                          | Did not resolve                                   | 4 |
| Lim & Pereira <sup>87</sup>  | Supraclavicular        | 34/F | N/A                                                 | None               | Single shot | Paresthesia | Paresthesia                                  | Focal demyelination at level of cords at 1 wk.                         | Paralysis of hand and paresthesia | Lost to follow-up (resolving neuropathy at 8 wks) | 4 |
| Shah et al. <sup>17</sup>    | Anterior sciatic nerve | 51/F | ? (high injection pressure noted)                   | None               | Single shot | NS          | High injection pressure                      | Peroneal component of sciatic nerve injured at level of thigh at 4 wks | Weakness and hypesthesia          | Did not resolve                                   | 5 |
| Stark <sup>18</sup>          | Axillary               | 51/M | ? (disruption of fascicular anatomy on exploration) | None               | Single shot | NS          | N/A                                          | Median nerve damage at 6 wks                                           | Median nerve paralysis            | Did not resolve                                   | 2 |
|                              | Axillary               | 69/F | N/A                                                 | None               | Single shot | NS          | N/A                                          | Ulnar nerve demyelination at 6 wks                                     | Ulnar nerve paralysis             | Did not resolve                                   |   |
|                              | Axillary               | 55/M | N/A                                                 | Scleroderma        | Catheter    | NS          | N/A                                          | Ulnar nerve demyelination at 8 wks                                     | Ulnar nerve paralysis             | Did not resolve                                   |   |
| Uppal et al. <sup>129</sup>  | Sciatic nerve          | 46/M | N/A                                                 | None               | Single shot | NS          | Distended sciatic nerve noted during surgery | Severe axonal loss in sciatic nerve (? POD)                            | Sciatic nerve weakness/ foot drop | Did not resolve                                   | 2 |
| Walton et al. <sup>134</sup> | Interscalene           | 36/M | No                                                  | None               | Single shot | NS          | None                                         | Complete denervation of multiple nerves at 5 wks                       | Paresis and numbness              | 26 wks                                            | 3 |

