Nerve Injury Resulting from Intraneural Injection When Performing Peripheral Nerve Block

5

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Key Points

- A neuronal injury can be explained using an epidemiological triad model as an interaction between an injurious agent (local anesthetic/needle or pressure injury), a susceptible host (inadequately protected nerve), and a hazardous working environment (poor supervision/guidance for locating needle; unsafe practices, unintended exposure). In theory, elimination of one of the triad's components should prevent the occurrence of the event.
- Long-term neurologic complications (lasting more than 6 months) are rare following peripheral nerve blocks while the short-term neurologic symptoms although more common are known to resolve within a few weeks to 3 months.
- Most of the evidence regarding needle, pressure, and local anesthetic-related injuries comes from animal studies.
- In clinical practice, it is difficult to stay extraneurally all the time and intraneural injections do occur while performing PNB.
- To minimize the risk of neurological injury, one must evaluate the patient properly (preprocedural examination to ensure no preexisting neuropathy/risk factors), select equipment appropriately (needle gauge, type), and administer local anesthetic accordingly (lower concentration for nerves susceptible to insults).
- Allow a sufficient follow-up period particularly if paresthesia is noted during the procedure.
- Utilize all available guidance methods if possible for the performance of PNB including US, injection pressure monitoring, and neurostimulation.

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Introduction

Neurologic injuries following peripheral nerve blocks (PNB) are rare, ranging between 2.4 and 4 per 10,000 blocks, but they can be debilitating and, at times, devastating [1–6]. From a health perspective, a rare event can be defined as any event that occurs infrequently (≥1/10,000 to <1/1000) [7]. Rare events do not occur in a predictable pattern; thus, trying to deduce event rates may prove to be erroneous. Predicting neurologic complications following PNBs is subject to the same issues affecting other rare events, such as multiplicity of sources, difficulties in data collection, and variation in statistical analysis. The incidence of the event may be impacted further by any change in the target population or the definition of the problem. Unsurprisingly, no studies to date have investigated neurologic complications following regional anesthesia from a rare event perspective, likely due to the complex interactions of known and unknown factors that influence these complications. Although the use of ultrasound (US) has been shown to reduce the incidence of vascular puncture, LA systemic toxicity [7], and block success [8] we have yet to demonstrate improvements with the introduction of US.

Neurologic injury following PNB is complex and includes needle trauma, pressure injury [9], damage to the vasa nervosum resulting in hematoma formation or ischemia, and finally LA [10] or adjuvant-related toxicity. Other important factors also include patient characteristics [11, 12], type of surgery [13], and the anatomical location of injections. Given the complexity of possible interactions among various factors in regional anesthesia, the complication may be best explained using the same epidemiological principles of disease causation (Fig. 5.1).

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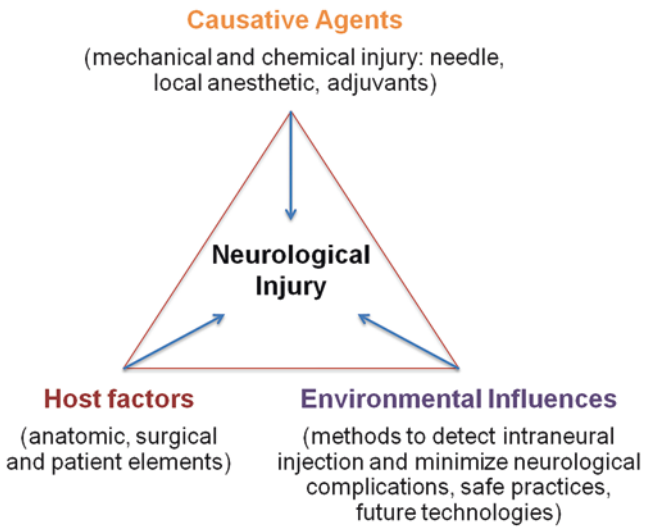

Fig. 5.1 Epidemiologic triangle demonstrating relationship between causative agents, host factors, and environmental influences on neurological injury

Epidemiological principles have been used to determine and study the interrelationship of various factors on the suspected cause of diseases so that control measures can be identified and implemented to prevent and minimize the disease. Typically, the event (complication) is said to occur when there is interaction among an injurious origin (causative agents), a susceptible host (host factors), and suitable circumstances (environmental influences) known popularly as the epidemiological triad [14, 15]. Using this model, risk factors can then be broadly classified to the host (anatomical and biological factors), the injurious agent (mechanical, pressure, and neurotoxic insults), and the environment (guidance techniques, supervision, safety culture). The neurological injury may represent the final result from the interaction between these risk factors. Elimination or minimization of one of the triangle's component may potentially, in theory, interrupt the interaction and prevent the event from occurring.

In fact, any discussion of epidemiology would be incomplete without mentioning John Snow, a pioneer anesthesiologist, who is also known as the "father of epidemiology" due to his well-known first epidemiological studies conducted in the 1850s [16]. In his studies, Snow used logic and common sense to study the interaction of factors causing disease and to develop preventative measures in ending the cholera outbreak. This work classically illustrates the effective use of epidemiological principles used even today to investigate and control disease and outbreaks. In this chapter, we, therefore, have performed a systematic review to evaluate the pertinent clinical and pathophysiological aspects of neurological complications following PNBs from the perspective of the epidemiological triangle."

Search Strategy and Selection of Studies

A systematic review of the medical literature (MEDLINE, OVID, and EMBASE) was performed during Nov–Dec 2015 using the search strategy described later. The MEDLINE search used a combination of the following medical subject headings: nerve injury, neurologic injury, peripheral nerve injury, neurologic deficit, paresthesia, neurologic sequelae, pathology, ultrastructure, anatomy, transient neurologic deficit, transient neurologic symptoms, paralysis, nerve block, peripheral nerve block, local anesthetic, local anesthesia, conduction anesthesia, and regional anesthesia. Subsequent searches combined the keywords intraneural injection, epineurium, subepineurial injections, perineurium, intrafascicular injection, extrafascicular injection, injection pressure, ultrasound, neurostimulation, and needles. EMBASE and OVID database searches were performed for the period 1975–2015. We started from the year 1975 since the very first investigations, looking into the factors important to the causation of nerve injury following regional anesthesia in a systematic way, began in 1977 [17].

Both human and animal studies were included in the review. Additional database searches included Cochrane, LILACS, DARE, IndMed, ERIC, NHS, HTA via Centre for Reviews and Dissemination (CRD; York University), which did not produce any additional unique results. The bibliographies of publications included for analysis were also reviewed manually for additional material that may have been missed by the database searches.

Literature Selection

The full text of all articles obtained from the searches was retrieved for critical appraisal. References of all articles were examined to ensure that no original research studies were missed. We included closed claimed analyses, meta-analyses, systematic reviews, randomized controlled trials (RCTs), controlled studies without randomization, observational studies, retrospective studies, comparative studies, and case series for this review. For the purposes of this review, RCTs were defined as such only when they included human subjects; randomized studies of animal subjects were not classified as RCTs. We did not include correspondences, pediatric population, or conference abstracts with incomplete data sets in this review.

Evidence Evaluation

Relevant full-text articles were separated based on literature type (database reviews, human and animal studies) and were subsequently reviewed independently in duplicate. Data

Table 5.1 Oxford Centre for Evidence-Based Medicine levels of evidence and grades of recommendation (adapted from www.cebm.net)

Level	Description
1a	Systematic review of RCTs or of prospective cohort studies
1b	Individual RCT or prospective cohort study with good follow-up[a]
1c	All or none studies
2a	Systematic review of cohort studies
2b	Individual cohort study (including retrospective)
2c	"Outcomes" research
3a	Systematic review of case–control studies
3b	Individual case–control study, nonconsecutive cohort study, or limited population
4	Case series
5	Expert opinion without explicit critical appraisal or based on physiology, bench research, or "first principles"
Grades of recommendation	
A	consistent level 1 studies
B	consistent level 2 or 3 studies *or* extrapolations[b] from level 1 studies
C	level 4 studies *or* extrapolations from level 2 or 3 studies
D	level 5 evidence *or* inconsistent or inconclusive studies of any level

[a]Defined as >80 % with adequate time for alternative diagnoses to emerge (e.g., 1–6 months acute; 1–5 years chronic)
[b]Where data is used in a situation that has potentially clinically important differences than the original study situation

were classified based on the epidemiologic triangle: (1) host factors (anatomic, surgical, and patient-specific elements), (2) damage-causing agents (needle, local anesthetic, adjuvants, pressure injury), and (3) environmental factors (methods to detect intraneural injection, safe practices, future technologies). Additionally, data relating to nerve injury and the incidence of unintentional intraneural injection were evaluated separately.

Data were extracted and entered into a database (Microsoft Excel, Microsoft Corp., Redmond, WA). Level of Evidence (Table 5.1) and Grades of Recommendation (Table 5.2) developed by the Oxford Centre for Evidence-Based Medicine were assigned to each study.

Furthermore, RCTs included in the current review were assigned Jadad scores (0–5) [18] while case reports were graded by Pierson scale [19] to assess scientific quality. Nonrandomized studies were not assessed for quality. Animal and cadaveric tissue studies were given a lower grade (Level of evidence 5; Grade D) irrespective of the study design.

Selected studies: A total of 3328 abstracts were retrieved from the MEDLINE, OVID, and EMBASE databases. After elimination of 62 duplicates, 3266 articles were screened for eligibility, 206 of which were selected for full-text review. Seven additional articles identified from a manual search of references from relevant articles were included. Seventy nine studies were excluded based on the criteria earlier, leaving 134 full-text articles for review (Fig. 5.1).

A total of 43 animal [9, 17, 20–59] studies (Table 5.2), 60 human [1–6, 60–113], and 8 cadaver/laboratory studies [114–121] (Tables 5.3 and 5.4) 21 case reports/case series (Table 5.5) [122–143] were included for this review. The statement of evaluated outcomes has been summarized in Table 5.6.

Among animal studies, eight studies evaluated the impact of needle design on nerve trauma, while seven studies reported on the injection pressure, 21 studies evaluated neurotoxicity of LA/adjuvants, and seven studies evaluated guidance methods such as neurostimulation/US. Of the human studies, six studies evaluated the incidence of unintentional intraneural injections while four studies evaluated the impact of deliberate intraneural injections. A total of 38 studies reported on neurologic complications in relation to PNB, while the remaining 9 reported on methods to detect or avoid intraneural injection.

Incidence of Neurologic Complications Following PNB

Transient neurologic dysfunction following PNBs are more common than long-term dysfunction and usually resolve with time (*LOE 1b*; *Grade A*). *Long-term postoperative neurologic dysfunction is rare following peripheral nerve blocks* (*LOE 1b*; *Grade A*). *Procedure-induced paresthesia may increase the risk of postoperative neurologic dysfunction* (*LOE 1b*; *Grade A*). *The safety of performing PNB under general anesthesia and its impact on neurologic outcomes is currently unknown* (*LOE 2b*; *Grade C*).

Retrospective reviews tend to under-report the incidence of neurologic complications due to selection, information, and recall bias, whereas the medico-legal databases may overestimate the incidence due to over-reporting and a lack of denominator for the incidents (Table 5.4). Early attempts to determine the incidence of neurologic sequelae following regional anesthesia came from ASA closed claims analyses [69, 88]. The first closed claims analysis included spinal anesthesia, ophthalmic blocks, and chronic pain blocks, while the latter looked specifically for neurologic complications following PNB. Closed claims analyses of PNBs have shown a trend toward a rise in nerve injury claims over the years (31–51 %), but only a few are thought to be related to the PNB itself [88, 89]. This ambiguity necessitated several prospective studies of block-related neurologic sequelae.

Prospective studies estimate the incidence of long-term neurologic injury following peripheral nerve blocks to be in the range of 2.4–4 per 10,000 blocks [2, 65–68, 144]. Transient neurologic deficits lasting up to 2 weeks occur more frequently following PNB, with an incidence varying

Table 5.2 Assessment of animal studies investigating neurological injury

Study	Animal model	Number of blocks/ attempts	Block type	Key findings	LOE[a]
Hadzic et al. [9]	Dog	14	Sciatic	• Perineural injections required low injection pressure (<4 psi) while 4/7 intraneural injections required high injection pressure (>25 psi)	5
				• High injection pressures resulted in severe persistent motor deficits throughout the study period (7 days) and histological changes of nerve injury	
Selander et al. [43]	Rabbit	20	Sciatic	• Intrafascicular injection required higher injection pressures (>600 mmHg) and showed a rapid longitudinal spread within the fascicle	5
				• Rupture of the perineurium occurred at pressures between 125 and 900 mmHg	
Selander et al. [16]	Rabbit	30	Sciatic	• Nerve fascicles slid or rolled away easily from the needle tip, especially with short-bevel needles	5
				• The most severe fascicular injuries occurred more frequently with long-bevel (14°) than with short-bevel (45°) needles	
Macias et al. [37]	Rat	12	Sciatic	• 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	5
				• Four animals in the short bevel group showed a decrease in movement and flexion tendency	
Steinfeldt et al. [44]	Pig	40	Brachial plexus	• Nerve damage (hematoma and myelin damage) and injury scores were greater with larger needle diameter after intentional nerve perforation	5
Maryuama et al. [36]	Rabbit	90	Sciatic	• 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	5
				• The number of damaged axons was reduced significantly by inserting the beveled needle parallel to the nerve fibers	
Steinfeldt et al. [45]	Pig	58	Brachial plexus	• No significant difference with regard to incidence of intraneural hematoma or myelin damage after both needle injuries	5
				• 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	
Rice et al. [41]	Rat	63	Sciatic	• After deliberate intrafascicular needle insertion, short-bevel needles caused more axonal damage and neuronal edema compared to long-bevel needles	5
				• 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	
Kapur et al. [33]	Dog	30	Sciatic	• High injection pressures during intraneural injection may be indicative of intrafascicular injection and usually result in functional and histological changes indicative of nerve injury	5
				• Intraneural injections with low pressure resulted in significantly longer duration of sensory motor blockade	
Gentili et al. [25]	Rat	140	Sciatic	• 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	5
				• Damage by lidocaine with or without epinephrine was mild and least with bupivacaine and mepivacaine without epinephrine	

Yang et al. [58]	Rat	16	Sciatic	• Local anesthetics cause Schwann cell death in vitro in a time- and concentration-dependent manner	5
				• Prolonged exposure of nerves in vivo to continuous infusions of bupivacaine causes damage to myelin as well as infiltration and activation of macrophages	
Lupu et al. [35]	Pig	20	Median	• 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	5
Iohom et al. [27]	Rat	52	Sciatic	• Intraneural injection of ropivacaine at concentrations routinely used in clinical practice had no deleterious effect on sciatic nerve motor function	5
Myers et al. [39]	Rat	48	Sciatic	• 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	5
Bouaziz et al. [22]	Rat	48	Sciatic	• All local anesthetics studied decrease NBF	5
				• The greatest decrease was noted with ropivacaine followed by levobupivacaine (0.75 %) and then by the rest	
				• Addition of epinephrine did not result in further decrease in NBF	
				• Although significant, the reduction in NBF did not result in subsequent histopathological changes of neurotoxicity	
Partridge et al. [21]	Rat	90	Sciatic	• Epinephrine + lidocaine causes dose-dependent reduction in NBF which continues after washout	5
				• Bupivacaine causes dose-dependent improvements in NBF and is reversed by washout	
				• Tetracaine results in no significant change in NBF	
Whitlock et al. [54]	Rat	54	Sciatic	• 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	5
Williams et al. [57]	Cultured rat neurons	n/a	n/a	• Ropivacaine (2.5 mg/mL) is more neurotoxic than high concentrations of preservative-free adjuvants, clonidine, buprenorphine, dexamethasone, and midazolam	5
				• Midazolam increased the neurotoxic potential of ropivacaine	
Tüfek et al. [49]	Rat	40	Sciatic	• 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	5
				• No difference in total oxidant status between the sham, saline, and dexmedetomidine groups but significant increase in the bupivacaine group	
Chan et al. [23]	Pig	28	Brachial plexus	• 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 %	5
				• Intrafascicular injection occurred in 2/24 injections	
Tsai et al. [173]	Pig	40	Sciatic	• Type I motor response was obtainable only when needles were positioned 0.1 cm from the nerve or closer.	5
				• Distance: current: frequency was 0.1 cm: 0.92 ± 0.33 mA: 70 %	
				• On epineurium = 0.39 ± 0.33 mA: 95 %; Intraneural = 0.56 ± 0.54 mA: 100 %	
Altermatt et al. [19]	Pig	24	Brachial plexus, femoral	• The diameter increased by more than 50 % compared with preintervention images	5
				• The current required to elicit a motor response was variable (0.2–3.3 mA)	
				• Minimum current threshold was ≤0.5 mA in 75 % of cases and >1.0 mA in 17 % of cases	

(continued)

Table 5.2 (continued)

Study	Animal model	Number of blocks/ attempts	Block type	Key findings	LOE[a]
Wiesmann et al. [55]	Pig	50	Brachial plexus	• Nerve contact and intraneural needle placement showed similar threshold current intensities (≤0.2 mA), irrespective of the pulse duration	5
				• No significant difference between needle–nerve contact and intraneural needle tip positions	
				• Control nerve stimulation required significantly higher threshold current, regardless of applied pulse duration	
Vuckovic et al. [53]	Rat	24	Median	• 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 (86.552 ± 13.262) kPa in comparison to 25.128 ± 3.49 kPa for paraneural injection	5
Vuckovic et al. [52]	Rats & stillborn human fetuses	48	Median	• All perineural injections resulted in pressure ≤27.92 kPa, while the majority of intraneural injections had injection pressure ≥ 69.8 kPa	5
Rigaud et al. [42]	Dog	24	Sciatic	• Ink distribution patterns were not different between low and high stimulation threshold groups	5
				• One intraneural injection occurred in the high threshold group	
				• 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	
Kroin et al. [34]	Rat	n/a	Sciatic	• All of the local anesthetic solutions produced a longer mean duration of sensory nerve block in diabetic rats versus nondiabetic rats	5
				• None of the sciatic nerves examined in the percutaneous injection study showed >3 % nerve fiber degeneration overall	
Belda et al. [20]	Piglet	12	Sciatic	• Cross-sectional area and relative echogenicity values were different immediately after the injections and returned to prepuncture values within 4 days	5
				• Injections did not exceed >20 psi or result in motor deficits	
				• Histology showed intact perineurium and signs of inflammation immediately and on days 1 and 2 postinjection	
Voelckel et al. [51]	Pig	20	Sciatic	• Motor response to currents >0.5 mA ensures extraneural injections while low current (<0.2 mA) is specific for intraneural injections	5
				• The mean ± SD current required to obtain a motor response was 0.4 ± 0.05 mA in the standard current group and 0.15 ± 0.04 mA in the low current group	
				• Standard current group showed no signs of inflammation. In 5/10 low current group animals, inflammation was found sub-, peri-, and intraneurally	
				• One sciatic nerve specimen of the low current group revealed disruption of perineurium and axons	
Steinfeldt et al. [46]	Pig	42	Sciatic	• Myelin damage following perineural hematoma was seen in 15 % of cases	5
				• Both blood and albumin around the nerve result in aseptic inflammation of the nerves and severe structural nerve injury/inflammation	
Steinfeldt et al. [47]	Pig	50	Brachial plexus	• 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	5

Vassiliou et al. [50]	Pig	611	Brachial plexus, sciatic	• Dual guidance showed greater accuracy of needle tip placement in proximity to the nerve (98.5 %) and fewer intraneural needle placements (0.5 %)	5
				• Significant differences in close needle placement: US+NS (98.5 %); NS group (90.1 %), and US group (81.6 %)	
				• 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	
				• Puncture-related hematomas more frequent with NS (10.8 %) compared with US (2.5 %) or dual guidance (1.5 %)	
Farber et al. [24]	Rat	16	Sciatic	• Animals that received intrafascicular injections showed increased severity of injury compared to control animals	5
				• A layering of severity of injury was found with most severely injured areas closest to and uninjured areas furthest from the injection site	
				• Bupivacaine caused more damage to large fibers than the other local anesthetics	
Hirasawa et al. [26]	Rabbit	50	Sciatic	• Least disturbance/damage from tapered needle	5
				• Followed in increasing order of damage by short bevel/parallel insertion, long bevel/parallel insertion, short bevel/perpendicular insertion, long bevel/perpendicular insertion	
Kalichman et al. [28]	Rat	20	Sciatic	• Streptozotocin-induced diabetic rats had lower motor nerve conduction velocity compared to normal rats	5
				• Extraneurally placed LA caused neural edema, which was more pronounced with lidocaine 4 % than saline or lidocaine 2 % in diabetic rats	
				• Nerve fiber injury scores were greater in diabetic rats compared to control groups	
Kalichman et al. [29]	Rat	?	Sciatic	• Procaine (10 %) but not saline, 80 % ethanol, or 80 % glycerol induced statistically significant decreases in nerve blood flow	5
				• Procaine and cocaine were associated with dose-dependent decreases in nerve blood flow, but cocaine was more potent	
				• At 48 h, injury scores were elevated significantly for 80 % ethanol and 10 % procaine; nerve injury from procaine and cocaine was dose dependent	
Kalichman et al. [30]	Rat	60	Sciatic	• Etidocaine, lidocaine, chloroprocaine, and procaine caused concentration-dependent nerve injury	5
				• The highest concentration of LA caused endoneurial edema, especially in larger fascicles	
Kalichman et al. [31]	Rat	83	Sciatic	• Nerve fiber injury and disturbances of endoneurial microenvironment occur after 48 h exposure to various LAs	5
				• Degree and extent of nerve injury varied among the LAs	
				• 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	
				• Nerve fiber injury, endoneurial edema, and lipid droplet formation were produced in dose-dependent fashion	
Kalichman et al. [32]	Rat	49	Sciatic	• Exposure to lidocaine, etidocaine, procaine, and chloroprocaine resulted in neuronal edema and lipid droplet scores greater than saline and water controls	5
				• Nerve injury was significantly different than with controls only at the highest concentrations of each drug	
				• Etidocaine was the least toxic LA	

(continued)

Table 5.2 (continued)

Study	Animal model	Number of blocks/ attempts	Block type	Key findings	LOE[a]
Myers et al. [38]	Rat	?	Sciatic	• Direct application of tetracaine 1 % and 2-chlorprocaine resulted consistently in subperineurial and endoneurial edema due to increased perineurial permeability	5
				• Between 24 h and 4 weeks, perineurial and endoneurial fibrotic changes were noted to varying degree as a result of increased perineurial permeability and endoneurial edema	
Selander et al. [43]	Rabbit	56	Sciatic	• 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	5
				• 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	
				• Acute effects of intrafascicular injection changed little upon addition of adrenalin	
Williams et al. [56]	Rat	25/15	Sciatic	• Single injection or continuous infusion of bupivacaine or midazolam, combined with dexamethasone, clonidine, and buprenorphine, did not result in long-term neurologic deficits	5

[a]All studies using an animal model were assigned an LOE of 5, regardless of study design

Table 5.3 Assessment of human studies investigating neurological injury

Study	Type of study (Jadad score)	Guidance method	Block type	Key findings	LOE
Liu et al. [91]	Cohort study	US	Supraclavicular, interscalene	• Unintentional intraneural injection is common following supraclavicular or interscalene blocks (17 %)	2b
				• Incidence of temporary nerve injury was 0 % at both 1 and 4–6 week periods	
Hara et al. [78]	Cohort study	US + NS	Sciatic	• Unintentional intraneural injection is common following US-guided subgluteal sciatic nerve blocks (17 %) and may not necessarily result in neurological complications	2b
				• Intraneural injections have a fast block onset compared to extraneural injections, with no effect on block duration	
Ruiz et al. [98]	RCT (4)	US + NS	Femoral	• 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	1b
				• No differences between the groups regarding incidence of paresthesia or nerve injury	
Robards et al. [97]	Cohort study	US + NS	Sciatic	• Deliberate intraneural injection during popliteal sciatic nerve block with injection pressures <20 psi does not result in immediate neurological dysfunction	2b
				• Motor response was absent in 16.7 % with current up to 1.5 mA even when needle was intraneural on US	
Sala-Blanch et al. [99]	Cohort study	NS	Sciatic	• Intraneural (subepineurial) injection during nerve stimulation-guided popliteal sciatic nerve block may occur commonly (up to 66 %) without imminent neurological injury	2b
				• Intraneural injections may have a faster block onset	
Sala-Blanch et al. [100]	Lab study	Direct vision	Sciatic	• Intraneural needles likely traverse connective tissue rather than fascicular tissue	5
				• 30° bevel needles did not result in fascicular injury; incidence of fascicular injury after insertion of 15° bevel needles was ~3 %	
Sauter et al. [178]	Cohort study	US	Radial, ulnar	• 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	2b
Gadsden et al. [75]	Cohort study	US	Interscalene	• All extraneural injections had opening injection pressure <15 psi	2b
				• Limiting injection pressure to 15 psi prevented injection upon needle–nerve contact in all but one instance	
				• Monitoring of opening injection pressure may be helpful in detecting needle–nerve contact	
Bigeleisen et al. [63]	Cohort study	US	Supraclavicular	• Ultrasound was able to detect the location of the needle tip clearly in 69 % of cases	2b
				• Stimulation currents of ≤0.2 mA detect intraneural position of the needle reliably	
				• Stimulation thresholds >0.2 and ≤0.5 mA could not rule out intraneural needle tip placement	
				• 10 % of patients had temporary neurological symptoms mostly unrelated to nerve blocks	
				• Diabetic patients require higher stimulation thresholds both outside and inside the nerve to elicit a motor response	
Moayeri et al. [93]	Cohort study	US	Supraclavicular, sciatic	• Intraneural injection can be detected on US by injecting a small amount of injectate	2b
				• The ultrasonographic criterion 'increase in cross-sectional surface area together with change in echogenicity' identified intraneural injection with 94 % precision	
				• Cross-sectional surface area increased 8–9 % in both brachial plexus and sciatic nerve	

(continued)

Table 5.3 (continued)

Study	Type of study (Jadad score)	Guidance method	Block type	Key findings	LOE
Morau et al. [94]	Cohort study	NS	Sciatic	• Intraneural spread of local anesthetic was common following NS-guided popliteal sciatic block (39 % had a nerve surface area increase of 15 %)	2b
				• Patients with intraneural injections had faster block onset and better success rate	
Bigeleisen et al. [62]	Cohort study	US	Axillary	• Deliberate intraneural injection during axillary brachial plexus block did not result in long-term neurological dysfunction	2b
Moayeri et al. [115]	Cohort study	n/a	n/a	• The area of the connective tissue compartment surrounding the brachial plexus increased proximally to distally, while the neural component remained the same	2b
				• Ratio of connective to neural tissue increases progressively from proximal to distal part of brachial plexus	
Moayeri et al. [116]	Cohort study	n/a	Sciatic	• Ratio of neural to nonneural tissue in sciatic nerve changes significantly from 2:1 (midgluteal and subgluteal) to 1:1 (midfemoral and popliteal)	2b
Dufour et al. [73]	Cohort study	NS	Median	• NS-guided median nerve block has ~43 % incidence of intraneural injection	2b
				• In the absence of intraneural injection, presence of circumferential local anesthetic spread seemed predictive of successful sensory block in ~75 % of cases	
Krediet et al. [86]	Cohort study	US	Sciatic	• 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	2b
				• Assessments by both groups were highly specific (98 %) for intraneural injections	
				• Among novices, 20–50 % of all intraneural injections were missed	
Sala Blanch et al. [100]	Cohort study	NS	Sciatic	• None of the patients exhibited clinical or electrophysiological evidence of neurological injury after deliberate intraneural injection	2b
				• 16/17 (94 %) patients had US criteria of intraneural injection after deliberate NS-guided intraneural injection	
				• Average increase in postinjection nerve area was 45 %	
Orebaugh et al. [117]	Lab study (Cadaver)	US	Interscalene	• With US-guided needle tip placement in the interscalene region, frequency of intraepineurial injection was relatively high (50 %)	5
				• In cases with intraepineurial needle placement, there was no evidence of fascicular injection or axonal damage	
Sunderland and Ray [120]	Cohort study	n/a	Sciatic	• No exchange of bundles between the two popliteal divisions of the sciatic trunk	2b
				• Direct relationship found between number of fascicles and thickness of nerves (cross-sectional area)	
				• Branching of fascicles varied greatly among nerves at any given level	
Tran et al. [108]	RCT (3)	US	Sciatic	• 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	1b
				• None of the 45 patients followed up at 1 week showed sensory or motor deficit	
Theron et al. [107]	Cohort study	n/a	n/a	• Syringe feel cannot help anesthesiologists determine reliably whether needle tip is placed intraneurally irrespective of operator experience	5
				• 30 % of subjects correctly identified the nerve	
				• 30 % of self-identified experienced regional anesthesiologists correctly identified the nerve	

Tsui et al. [109]	Lab study	n/a	n/a	• When tested on nine different needle–syringe combinations, CAIT effectively maintained injection pressures below 1034 mmHg in an in vitro system	5
Claudio et al. [114]	Cohort study	n/a	n/a	• Anesthesiologists vary widely in perception of "normal" pressure and speed during simulated PNB injection	2b
				• Pressures varied as much as 20X among needles of the same gauge/length	
				• Pressure >20 psi was generated 70 % of the time; >25 psi, 50 % of the time; >30 psi, 10 % of the time	
Tsui et al. [121]	Cohort study	n/a	n/a	• No anesthesiologist generated pressures >1034 mmHg using CAIT	2b
				• 29/30 subjects generated pressures >1034 mmHg at some point when using 'syringe feel' method	
				• Mean pressure using CAIT was lower (636 ± 71 vs. 1378 ± 194 mmHg, $p = 0.03$); 'syringe feel' method resulted in higher peak pressures (1875 ± 206 vs. 715 ± 104 mmHg, $p < 0.001$)	
Sunderland [152]	Cohort study	n/a	Median, radial, ulnar	• Fascicular pattern changed along the entire length of each nerve	2b
				• The longest section of any nerve with a constant pattern was 15 mm	
				• Size and number of fascicles were inversely related at any one level	
				• There was no constant or characteristic fascicular pattern for any nerve. There was no constant or characteristic fascicular pattern for any nerve	
Choyce et al. [70]	Cohort study	Paresthesia	Axillary	• After paresthesia, 77 % of needle placements produced motor activity ≤0.5 mA (median 0.17 mA; range 0.03–3.3 mA)	2b
Kaiser et al. [83]	RCT (3)	NS	Sciatic	• Complete paralysis was achieved in all patients only with low current (0.1 mA)	1b
Keschner et al. [84]	Cohort study	NS	Infraclavicular	• Block success rate of 94 % with stimulating current <0.3 mA, with no neurological complications noted on first postoperative visit	2b
Seidel et al. [101]	RCT (3)	US vs. NS	Sciatic	• Success rate was significantly higher in the US group (94.9 % vs. 61.9 %, $p<0.001$). Paresthesia was more common in US group (51.7 %) vs. NS group (23.7 %)	1b
				• Paresthesias indicated an intraneural needle position with an odds ratio of 27.4 (specificity 98.8 %, sensitivity 45.9 %)	

Table 5.4 Incidence of neurological complications following peripheral nerve blocks

Study	Type of study[a]	Follow-up period	Number of PNB or claims (CC)	Incidence of temporary nerve injury (<6 months)	Incidence of long-term injury (>6 months)	Key findings	LOE
Barrington et al. [1]	P	6–10 days or 6 weeks for new onset neurological symptoms	8189	0.04 %	0 %	• Incidence attributable to nerve block is 0.04 % • 2/3 blocks with nerve injury related to PNB were done using NS alone; other used US+NS (not significant)	1b
Fredrickson et al. [3]	P	2nd to 4th weeks post-op	1010	8.2 %, 3.7 %, and 0.6 % at 10 days, 1 month, and 6 months, respectively	–	• Most common causes of postoperative neurological dysfunction are unrelated to PNB • Elicitation of paresthesia was associated with an increased odds ratio for development of new neurological symptoms	1b
Kroll et al. [87]	CC	N/A	1541	Most claims were for disabling injury	–	• GA (61 %) was more commonly associated with nerve damage claims compared to RA (36 %) • GA was involved in a majority of ulnar nerve injuries (85 %)	2b
Cheney et al. [69]	CC	N/A	4813	–	–	• RA was more frequently associated with nerve damage claims compared to GA • Ulnar nerve injury occurred predominantly in men (75 %) • Increase in spinal cord complications compared to previous analysis	2b
Lee et al. [88]	CC	N/A	189	–	–	• 51 % of claims were for nerve damage • 68 % of claims were for temporary or nondisabling injury • 32 % of claims were associated with permanent and/or disabling injuries • 6/8 spinal cord injury claims related to interscalene blocks with cervical spinal cord damage; 4 of these 6 blocks were performed under GA	2b
Lee et al. [89]	CC	N/A	1005	• 51 % of claims were for nerve damage • 68 % were for temporary or nondisabling injury • 32 % were associated with permanent and/or disabling injuries	6/8 spinal cord injury claims related to interscalene block and 4/6 blocks performed under GA	• Majority of claims (72 %) associated with temporary or nondisabling injuries • 1/4 of claims involved disabling injuries • Majority of claims were associated with outpatient procedures (66 %)	2b
Auroy et al. [2]	P (multicenter)	N/A	158,083	Incidence: • Popliteal (0.315 %) • Interscalene (0.029 %) • Femoral (0.029 %) • Sciatic (0.024 %) • Axillary (0.018 %) • Mid-humeral (0.014 %)	7/158,083	• Lidocaine spinals associated with more complications than bupivacaine spinals • Of 12 complications that occurred after PNB, 9 were done using NS	1b

Borgeat et al. [65]	P	days 1–5, 10; months 1, 3, 6, 9	520	14 %	0.4 %	• Up to 14 % and 7.9 % of patients have neurological symptoms not related to shoulder surgery at 10 days and 1 month, respectively • All symptoms appeared within 23 days after the block; 10 % developed symptoms between days 10 and 23, but most resolved spontaneously • Long-term neurological dysfunction due to interscalene block is rare (0.4 %); treatable causes (e.g., sulcus ulnaris syndrome) need to be identified early	1b
Jacob et al. [82]	R	N/A	3883	–	–	• 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 • Patients with nerve injury who underwent PNB were less likely to have complete neurologic recovery	2b
Welch et al. [112]	R	N/A	6685	–	–	• 0.3 % incidence of iatrogenic injuries • Significant association of iatrogenic injuries with certain types of surgery, GA, and epidural anesthesia but a similar association was not found with PNB	2b
Jacob et al. [81]	R		2444	–	–	• Nerve injury following hip arthroplasty was not associated with type of anesthesia or PNB • The risk for nerve injury was associated with younger age, female gender, longer operations, and posterior surgical approach	2b
Candido et al. [144]	P	24 and 48 h, 2 and 4 weeks, and 3 months	693	3.3 %	0.1 %	• Incidence of neurologic sequelae in brachial plexus distribution after interscalene block was 3.3 % and 0.1 % at 1 and 3 months • Pain/paresthesia at the block site are independent predictors of neurological sequelae	1b
Sviggum et al. [104]	R	N/A	1138	–	–	• Use of interscalene block does not increase the risk of nerve injury in patients undergoing TSA • Use of interscalene block was associated with significantly lower odds for nerve injury (0.44; 95 % CI = 0.22–0.86) • Incidence of nerve injury after elective TSA was ~2.2 %	2b
Hebl et al. [79]	R	2, 3, and 6 weeks post-op	100	6/100 receiving axillary block and 4/100 receiving GA at 2–3 weeks. follow-up	–	• RA does not seem to worsen neurologic outcome in patients with preexisting ulnar neuropathy who undergo ulnar nerve transposition	2b
Borgeat et al. [66]	P	Days 1–5 and 10 post-op; 1, 3, and 6 months	700	8 % on day 10; 2.4 % at 1 month	0 %	• Minor neurologic complications of 2.4 %, 0.3 %, and 0 % at 1, 3, and 6 months, respectively, using lateral modified approach for interscalene block • Two patients had a severe and prolonged sensory-motor deficit involving the middle and lower trunks; these patients needed 19 and 28 weeks to recover, respectively	1b

(continued)

Table 5.4 (continued)

Study	Type of study[a]	Follow-up period	Number of PNB or claims (CC)	Incidence of temporary nerve injury (<6 months)	Incidence of long-term injury (>6 months)	Key findings	LOE
Capdevila et al. [68]	P (multicenter)	Post-op period, 2 weeks, 6 weeks, and 3 months	1416	0.21 %	0 %	• Incidence of short-term neurological dysfunction following continuous PNB is ~0.21 % for femoral nerve block	1b
						• Minor symptoms such as dysesthesia range between 1.5 and 3 %	
						• High risk for neurological dysfunction include intensive care unit stay, patient age <40 years, and bupivacaine infusion	
Brull et al. [67]	Systematic review of P and R studies	N/A	50,117	1.8 %	0.004 %	• Transient postblock neuropathy has an overall incidence of 1.8 % with the highest risk being with interscalene and axillary blocks followed by proximal sciatic, femoral, and popliteal blocks	2a
Orebaugh et al. [4]	R	24 h or until the block resolved	5436	N/A	0.09 %	• 3 EMG-confirmed cases of nerve injury with landmark-NS technique vs. no long-term injury with US technique	2b
						• No statistically significant difference between the two groups in frequency of neurologic injury	
Ecoffey et al. [74]	P (multicenter)	10 days	27,031	0.37 per 10,000 (none attributed to regional anesthesia)	N/A	• After US-guided axillary block, overall incidence of postoperative neurologic symptoms was 0.37/10,000	1b
						• Most were mild in nature and unrelated to the block	
Sites et al. [6]	R	5 days–6 months	12,668	• Femoral 0.09 % [95 % CI = 0.02–0.23]	• Femoral 0.02 % [95 % CI = 0–1.2]	• Overall incidence of short-term (lasting up to 5 days) symptoms following PNB was 0.18 %	2b
				• Interscalene 0.35 % [95 % CI = 0.14–0.73]	• Interscalene 0.25 % [95 % CI = 0.08–0.58]		
				• Supraclavicular 0.20 % [95 % CI = 0.04–0.58]	• Supraclavicular 0 % [95 % CI = 0–0.24]		
				• Popliteal 0.40 % [95 % CI = 0.11–1.04]	• Popliteal 0.31 % [95 % CI = 0.06–0.89]	• Symptoms lasting >6 months was 0.09 %	
				• Femoral (continuous) 0.1 % [95 % CI = 0.11–1.04]	• Femoral (continuous) 0.1 % [95 % CI = 0.11–1.04]		
				• Interscalene (continuous) 1.2 % [95 % CI = 0.27–3.76]	• Interscalene (continuous) 0.87 % [95 % CI = 0.10–3.11]		
				• Axillary 2.3 [95 % CI =0.06–12.57]	• Axillary 0 % [95 % CI = 0–8.4]		
Orebaugh et al. [5]	R	1 year	9069	4/9069 at 6–12 months	1/9069 at >12 months	• Nerve injuries lasting 6–12 months were more frequent with NS-guided blocks compared to US-guided blocks	2b
						• Long-term nerve injuries (>12 months) were no different between NS- or US-guided blocks	
Szypula et al. [106]	CC	N/A	366			• Claims related to PNB constituted 3 % of the total closed claims and 13 % of all regional anesthesia claims	2b
						• Epidural (72 %), spinal (15 %) and combined spinal/epidural (2 %) constituted most of the claims and were mostly related to obstetrics	
						• Nonobstetric claims had worse outcomes compared to obstetric claims	

Auroy et al. [60]	P	N/A	21,278	Spinals (70.58 %) Epidurals (17.64 %) PNB (11.76 %)		• 4 neurological injuries total; incidence of 1.9/10,000 blocks	1b
Bogdanov et al. [64]	R	4–8 weeks	548	None	None	• Modification of Winnie's technique allows interscalene block to be performed safely on anesthetized patients	2b
Klein et al. [85]	P	day 7 and further work-up	2382	0.17 %	–	• Neurological injury occurs infrequently with the use of long-acting LA	1b
Lenters et al. [90]	RNeurologic complications, PNB:retrospective review	N/A	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)	• ISB is associated with a 0.73 % incidence of neurological dysfunction and 0.16 % incidence of chronic neuropathy	2b
Weigel et al. [113]	R	Third month post-op	1398	12 (0.9 %) had transient neurological deficits	One permanent neurological injury noted after femoral nerve block	• Major complications after CPNB are rare, but minor transient adverse effects are not uncommon after CPNB	2b
Watts et al. [110]	P	Day 10–12 post-op	1065	13/1065 (1.22 %)	2/1065 (0.22 %) had long-term injury (>6 months)	• 30 % blocks performed on awake patients; 25.6 % under sedation, and 44.4 % under GA • Catheters used in 7/13 blocks associated with neurological dysfunction	1b
Weber et al. [111]	R	N/A	218	2/218 (0.91 %)	–	• Two patients had temporary neurologic injuries that persisted at 6 weeks • One patient had long-term nerve damage (>1 year)	2b
Cuvillon et al. [72]	P	N/A	211	–	0.4 %	• 0.48 % incidence following 48 h infusion through femoral catheter	1b
Hajek et al. [77]	R	N/A	157	–	1.26 %	• Higher prevalence of neurological dysfunction and long-term neuropathy compared to other studies with 72-h CPNB	2b
Compere et al. [71]	P	3, 6 and 12 months	400	–	2/400 (0.05 %)	• One complication resolved at 18 months, and the other persisted; paresthesia was noted during block placement in the latter patient	1b
Neuberger et al. [95]	P	N/A	3491	0.3 % at <6 weeks; 6 patients (0.2 %) had symptoms lasting >6 weeks	–	• Neurological complications following PNB catheters are rare	1b
Nye et al. [96]	R	surgery clinic follow-up	213	6.6 %	1.9 %	• High incidence of temporary (6.6 %) neurological dysfunction following 72-h lumbar plexus catheters	2b
Selander et al. [102]	Cohort study	N/A	533	1.9 % (8 in paresthesia-guidance group and 2 in artery-guidance group)	3/533 (0.56 %) (1.03 % in paresthesia group) had symptoms lasting >1 year	• Difficult to avoid paresthesia in the artery group • All 10 patients with complications reported painful paresthesia during block procedure	2b
Sharma et al. [103]	R	2, 6, 12 weeks and 1 year	709	0.66 %	0.13 %	• Overall rate of femoral neuropathy/neuritis was 0.59 % • In all but one patient, neurologic deficits resolved within 1 year of TKA	2b
Swenson et al. [105]	R	N/A	620	2/620 (0.3 %)	–	• In both patients reporting neurological dysfunction, complications resolved within 6 weeks	2b

a*P* prospective study, *R* retrospective review, *CC* closed claims analysis

Table 5.5 Case reports of neurological dysfunction following peripheral nerve blocks

Author	Block type	Age/Sex	Intraneural injection detected?	Risk factors	Single shot/ catheter	Guidance method	Procedural problems	EMG findings	Presentation	Time of resolution	Pearson score
Al-Nasser and Palacios [122]	Psoas compartment	60/F	N/A	None	Catheter	NS	Intrathecal placement on first attempt	Severe femoral nerve injury at 24 h	Dense motor and sensory block despite low LA concentration	12 months (6 months partial recovery)	6
Atchabahian and Brown [124]	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. [125]	Infraclavicular	60/M	No	C8 radiculopathy, smoking, alcohol abuse	Catheter	US	None	Recent onset brachial plexopathy at 3 weeks	Sensory deficits in radial and medial antebrachial nerve; persisting paresthesia and allodynia	Did not resolve	9
Barutell et al. [126]	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 and Stahl [127]	Axillary	38/M	N/A	None	Single shot	Landmark	None	Neurapraxia at 4 weeks	Sensory and motor changes in radial territory with pain	6 months	3
Blumenthal et al. [128]	Femoral nerve	72/M	N/A	Subclinical polyneuropathy	Catheter	NS	None	Low-voltage denervation activities on POD 4	Persistent quadriceps weakness and hypesthesia	Did not resolve	7
Bonner and Pridie [129]	Sciatic nerve	59/F	N/A	Peripheral vascular disease	Single shot	NS	None	Absent conduction in common peroneal and posterior tibial nerves at 2 weeks	Persistent weakness in sciatic distribution	12 months (6 months partial recovery)	4
Cohen and Gray [130]	Interscalene	36/M	Yes	None	Single shot	US	None	N/A	Persistent weakness below elbow	6 weeks	2
Funk et al. [131]	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 months	3
Giabicani et al. [132]	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 years	3
Gungor et al. [133]	Psoas compartment	44/M	N/A	None	Single shot	NS	None	Partial lesion of proximal femoral nerve (? POD)	Weakness in knee extensors	6 months	4
Imran et al. [134]	Axillary	44/M	N/A	None	Single shot	Landmark	None	Significant denervation of axillary nerve at 6 weeks	N/A	Did not resolve	2
Jung et al. [135]	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. [136]	Brachial plexus	54/F	N/A	None	Single shot	?	Radiating pain in median nerve territory upon injection	Median nerve injury at 1 month	Pain and numbness	?	2
Koff et al. [143]	Interscalene	65/M	No	Multiple sclerosis	Single shot	US+NS	No	Denervation of median and ulnar nerves (POD 4; 3 weeks, 3 months)	Weakness	Did not resolve	4

Lim and Pereira [137]	Supraclavicular	34/F	N/A	None	Single shot	Paresthesia	Paresthesia	Focal demyelination at level of cords at 1 week	Paralysis of hand and paresthesia	Lost to follow-up (resolving neuropathy at 8 weeks)	4
Shah et al. [139]	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 weeks	Weakness and hypesthesia	Did not resolve	5
Stark [140]	Axillary	51/M	? (disruption of fascicular anatomy on exploration)	None	Single shot	NS	N/A	Median nerve damage at 6 weeks	Median nerve paralysis	Did not resolve	2
	Axillary	69/F	N/A	None	Single shot	NS	N/A	Ulnar nerve demyelination at 6 weeks	Ulnar nerve paralysis	Did not resolve	
	Axillary	55/M	N/A	Scleroderma	Catheter	NS	N/A	Ulnar nerve demyelination at 8 weeks	Ulnar nerve paralysis	Did not resolve	
Uppal et al. [141]	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. [142]	Interscalene	36/M	No	None	Single shot	NS	None	Complete denervation of multiple nerves at 5 weeks	Paresis and numbness	26 weeks	3

Table 5.6 Summary of evaluated outcomes with statements of evidence and grades of recommendation

Evaluated outcomes	Level of evidence	Grade of recommendation	References
Host factors			
Anatomical factors			
• Intraneural fascicular topography has wide variability with no consistent pattern of branching or anastomosis at any given site	2b	B	[115, 116, 120]
• The connective tissue content of a peripheral nerve varies depending on the number of fascicles at a given site	2b	B	[120, 152]
• Neural connective tissue and number of fascicles increase from proximal part of the nerve distally	2b	B	[115, 116]
Surgical factors			
• Certain types of surgery are associated with a higher risk of postoperative nerve injury	2b	B	[112]
Peripheral nerve blocks do not increase the risk of postoperative neurological dysfunction	2b	B	[66, 104, 112, 144]
Neuropathy			
• Preexisting neuropathy is thought to increase the risk of postoperative neurological dysfunction following PNB	5	D	[11, 125, 128, 129, 132, 140, 143, 162]
• Neuropathic nerves are more prone to the prolonged effects of local anesthetics	5	D	[29, 35]
Causative agents			
Mechanical agent: *needle trauma*			
• Nerve trunks usually slide under an advancing short-bevel needle compared to long-bevel needles	5	D	[17, 38, 119]
• Long-bevel needles cause more functional or histological damage compared to short-bevel, pencil-tip, or Tuohy needles but the superiority among the latter three needle types is currently unknown	5	D	[37, 38, 45, 46, 119]
• Needle gauge may in itself influence the degree of damage irrespective of needle type	5	D	[45]
• When short-bevel needles do penetrate perineurium, the resulting nerve damage is greater than that of long-bevel needles	5	D	[42]
• The amount of damage is smaller when the needle bevel is parallel than when it is perpendicular to the nerve fibers	5	D	[17, 27, 37]
Mechanical agent: *pressure injury*			
• Perineural injections require the least injection pressure followed by extrafascicular injection, while intrafascicular injections generate high injection pressure	5	D	[53, 54, 167]
• While high injection pressures result in functional and histological nerve damage , intraneural injection with low injection pressures may not necessarily result in nerve damage	2b	C	[9, 21, 34, 97]
Chemical agent: *neurotoxicity*			
• Both extra- and intrafascicular injection of local anesthetic can result in histological damage, but is far greater following intrafascicular injection leading to functional injury as well	5	D	[22, 23, 25, 26, 28–33, 35, 36, 39, 40, 44, 50, 57]
• All local anesthetics are neurotoxic in increasing concentrations and individual local anesthetics differ in their neurotoxic potential	5	D	[25, 26, 44, 55, 58, 59]
• Both epinephrine and local anesthetics decrease neural blood flow, and their combination has synergistic effects	5	D	[22, 23, 25, 26, 39]

Chemical agent: adjuvants			
• Local anesthetics are more neurotoxic than their adjuvants, but while some adjuvants may have neurotoxic potential, others may be neuroprotective	5	D	[50, 57, 58, 173]
Environmental influences			
Nerve stimulation			
• Nerve stimulation has low sensitivity but high specificity for proximity of the needle tip to the target nerve when stimulation is present at low currents	2b	B	[52, 70, 97]
• Nerve stimulation cannot differentiate between intraneural needle placement and needle–nerve contact	5	D	[56]
• Diabetic nerves require higher stimulating currents for both intra- and extraneural needle placement	2b	C	[43, 63]
Injection pressure monitoring			
• High injection pressures are often reached unknowingly by experienced and nonexperienced practitioners	2b	B	[109, 114]
• Syringe feel is inaccurate in differentiating tissues, and higher pressures are generated by performers unknowingly	2b	B	[107]
• Injection pressure can be kept within safe limits reliably by using CAIT or pressure measurement devices	2b	C	[109, 121]
• Opening pressure can detect needle nerve contact reliably	2b	C	[75]
Ultrasound			
• Ultrasound guidance can detect intraneural injection but is dependent on the operator experience	2b	B	[63, 78, 86, 91, 98, 117]
• Use of ultrasonography does not prevent intraneural injection	2b	B	[63, 78, 91, 98]
• Neurological complications following PNB have not declined as a result of US guidance	2b	B	[4, 5, 92]
Neurological injury and regional anesthesia			
Incidence of intraneural injection			
• Unintentional intraneural injections happen more often than previously expected	2b	B	[63, 78, 91, 94, 98, 99]
• Intraneural injections may not necessarily result in neurological dysfunction	2b	B	[62, 63, 78, 91, 94, 97–100, 108]
• Intraneural injections have a fast onset	2b	B	[78, 94, 99]
Incidence of neurological complications following PNB			
• Transient neurological dysfunction following peripheral nerve blocks are more common than long-term dysfunction and usually resolves with time	1b	A	[2, 3, 65–68, 144, 145]
• Procedure-induced paresthesia may increase the risk of postoperative neurological dysfunction	1b	A	[3, 102, 144]
• The safety of performing PNB under general anesthesia and its impact on neurological outcomes is currently unknown	2b	C	[64, 110]

between 8.2 and 15 % [3, 145]. Transient neurologic symptoms are known to resolve by 6 months to 1 year [3, 66]. Neither ultrasound nor nerve stimulation guidance affected the incidence of short- or long-term neurologic dysfunction following PNB in one retrospective review [5], although a recent update of the same database showed a lower incidence of short-term neurologic dysfunction with the use of ultrasound guidance [4]. A retrospective database review of ultrasound-guided blocks showed an incidence of long-term neurologic dysfunction of 0.9/1000 [6], which is about 22 times higher than those reported by others [1–3, 67]. Various definitions of long-term neurologic dysfunction (e.g., >6 vs. >12 months) may have accounted for the difference in incidence between these studies.

Procedure-induced paresthesia may increase the likelihood of transient neurologic symptoms following PNB as reported in three prospective cohort studies [3, 102, 144]. Certain peripheral nerve blocks have a predilection for neurologic complications than others. In a retrospective review of 12,668 patients undergoing ultrasound-guided nerve blocks, Sites et al. [6] reported short-term neurologic dysfunction being highest with axillary nerve block (2.3 %), followed by interscalene catheter (1.2 %), popliteal sciatic block (0.4 %), single-injection interscalene block (0.35 %), supraclavicular block (0.2 %), and femoral nerve block (0.1 %). Long-term dysfunction was again common with interscalene catheters (0.87 %), popliteal sciatic block (0.31 %), and single-injection interscalene block (0.25 %). In contrast, supraclavicular, axillary, and femoral nerve blocks rarely caused long-term problems. In an internet-based survey of 36 centers (27,031 patients), Ecoffey et al. [74] reported an overall incidence of postoperative neurologic symptoms of around 0.37 per 10,000 following ultrasound-guided axillary brachial plexus block, most of which were thought to be unrelated to the block. Although the reported incidence indicates a decrease in block-related neurologic symptoms compared to other studies [6], whether or not the observed results are due to ultrasound guidance cannot be extrapolated.

Neurologic complications must increase following prolonged exposure to nerves according to lab studies but there has been conflicting evidence regarding this. While some studies have noted a higher than normal incidence of neurologic complications with the use of catheter in psoas compartment blocks, popliteal sciatic nerve blocks [77, 96], other studies note a very low complication rate [68, 71, 72, 95, 105, 113]. This may be related to the method of data collection and the definition of neuropathy. Future prospective data collection methods are needed to address this issue.

Although there are articles reporting low incidence of neurologic complications following PNB performed under general anesthesia [64, 110], there is limited information on whether blocks performed under general anesthesia increase the risk of postoperative neurologic dysfunction. A retrospective review by Bogdanov et al. [64] did not report neurologic complications following interscalene blocks performed under general anesthesia but two patients in the study by Watts et al. [110] reported long-term neurologic dysfunction. The details of whether these blocks were performed under sedation or general anesthesia are not known from the study. To date, there is no known pathological reason why general anesthesia would directly increase the patient's susceptibly (host factor) in neurologic injury when receiving regional anesthesia. However, one would expect that general anesthesia would compromise the patient's (environmental influences) ability to communicate and provide feedback of either early symptoms of LAST or paresthesia from needle–nerve contact. In a recent report, threshold currents that are needed to generate a motor response were higher in an anesthetized patient than those in awake patients. This observation may suggest that there is a possibility of potential error which can be made when using nerve stimulation to locate the nerve when a patient is under general anesthesia [146].

Nevertheless, the current ASRA advisory panel suggested that a conscious patient is preferred while performing PNBs unless in selected patient populations (e.g., dementia and developmental delay) where the risk-to-benefit ratio of performing regional anesthesia under general anesthesia may improve [147].

Lessons from Case Reports

Case reports identify the patient and performance characteristics, neurologic presentation, and subsequent outcomes. A total of 21 case reports/series reported on the occurrence of neurologic complication in 24 patients following PNB (Table 5.5). The majority was middle aged (Median age 50.5 years) and consisted of 12 males and 12 females. Only four of the 24 cases had some signs of intraneural injections while the rest of the cases did not mention the possibility. It is not only those with some form of subclinical or overt neuropathy ($n = 5/24$ patients) who are susceptible, but quite often it is an otherwise healthy patient who suffers this unfortunate complications. The presence of risk factors may be a bad prognostic sign since only two of these 5 patients had recovery of some nerve function after a prolonged period of time. The most common presentation was persistent weakness (16 cases) followed by pain and paresthesia (three cases) and a combination of both in the remaining. Only 4 patients had catheters placed while the rest had single shot blocks. A total of 12 patients did not have recovery of nerve function back to normal while the rest of the patients had recovery ranging anywhere from 1 week to 2 years. Five blocks were performed under US guidance while 11 cases utilized neurostimulation, 1 case

used the combined US+NS technique, 1 case did not document the guidance method used, and 5 cases used the landmark/paresthesia technique.

Benumof [148] reported a case of spinal cord injury following an interscalene block performed under general anesthesia. This case report is an invaluable reminder of the risks associated with RA but is not strictly speaking PN injuries.

Analyzing Neurologic Injury from the Perspective of Disease Causation

Given their complexity, neurologic complications can best be evaluated by the same epidemiological principles of event causation (Fig. 5.1). The epidemiological triangle is a common injury model used to describe the relationship between an agent, a host, and the environment [14, 15]. A neuronal injury is more likely to occur when there is interaction between a susceptible host (inadequately protected nerve), an injurious agent (local anesthetic, needle, or injection pressure), and a hazardous working environment (poor supervision/guidance for locating needle, unsafe practices, unintended exposure). Elimination of one of the triangle's components should, in theory, prevent the occurrence of the event. Hence, the safest approach appears to be identification of potential risk factors and prevention of their interaction.

Epidemiological Triangle

Host/Biological Factors

The history of neurologic complications is as old as the field of regional anesthesia itself. Early performers of regional anesthesia acknowledged both the possibility of neurologic complications following PNB [149, 150] and the lack of complications following deliberate needle–nerve contact [151]. Various anatomical, surgical, and patient factors may affect the incidence of postoperative nerve injury and include the type of surgery, associated comorbidities, the presence of preexisting neuropathy, and whether temporary or permanent injury is being considered.

Anatomy and Physiology

Not all nerves or nerve blocks are the same since intraneural fascicular topography shows wide variability (*LOE 2b*; *Grade B*). *The connective tissue content of a peripheral nerve varies depending on the number of fascicles at a given site* (*LOE 2b*; *Grade B*). *Neural connective tissue and number of fascicles increase from proximal part of the nerve distally* (*LOE 2b*; *Grade B*).

A total of three studies looked into the neural anatomy with relevance to PNB [115, 116, 120]. In most cases, a peripheral nerve is a mixed entity consisting of both sensory and motor components and has both myelinated and unmyelinated axons. Connective tissue covering the axons is present in different layers, providing support and nutrition to the nerves and acting as a protective barrier to the axon (Fig. 5.2). The three protective covers are the epineurium which covers the nerve overall and separates the fascicles, perineurium which lines the fascicles, and the endoneurium which lies inside the fascicles and surrounds the axons. The epineurium—the outer covering of the nerve—encases the fascicular bundles within a connective tissue network known as interfascicular epineurium. The adipose tissue in the interfascicular epineurium acts as a cushion for the fascicles and causes them to slide under or over a slowly advancing needle, protecting the fascicles from needle trauma. The fascicular bundle is in turn encased by multiple layers of cells, known as the perineurium, which act as a functional barrier for the axons and protects against physical and chemical

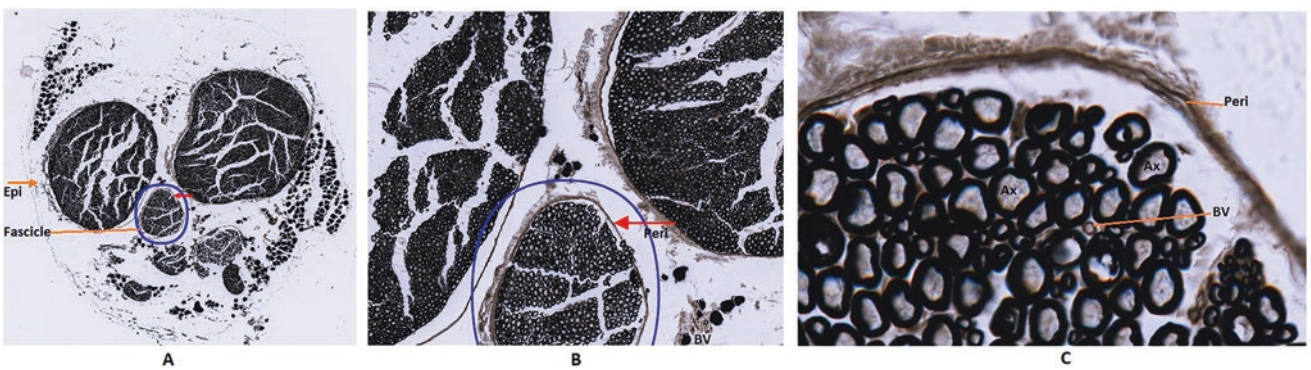

Fig. 5.2 Electron micrograph of a peripheral nerve stained with osmic acid. (a) The entire nerve is encased in a connective tissue layer, the epineurium (Epi), and the nerve fibers are arranged in fascicles. (b) Each fascicle is surrounded by a cellular layer, the perineurium (*red arrow*). Blood vessels (BV) can be seen collapsed in the interfascicular epineurium. (c) Axons (Ax) within the fascicle are in an endoneurial network, interspersed with nonfenestrated blood vessels (BV). (Reproduced with permission from the Department of Anatomy and Cell Biology, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada. http://slides.uwo.ca/spinal_cord.html)

insults. The perineurium bathes the axons in an interstitial fluid which is similar to CSF in composition and is continuous with the neuraxis [152, 153]. Inside the fascicle, myelinated or unmyelinated axons are supported by a network of connective tissue known as endoneurium which also contains the nonfenestrated capillaries that provide nutrition to these tissues. The endoneurium serves a vital role in nerve regeneration by aligning the regrowing axons toward its target. The perineurium maintains an intrafascicular pressure which is reflected in the intracellular pressure of the axons [154, 155]; thus, injection deep to the perineurium generally requires greater injection pressure compared to injection within the epineurium.

Nerve composition varies among different nerve types and also within a given nerve. Sunderland [152] noted that, in the upper limb, the fascicular topography of the radial, median, and ulnar nerves varied every 0.25–0.5 mm segment, and the branching pattern was not constant for a given nerve at a given site. While the sizes of individual fascicles are inversely related to their number at a given location along the nerve [152], the connective tissue content and cross-sectional area of a nerve are directly proportional [120]. This suggests that the amount of injury following intraneural injection depends not only on the characteristics of the insult but also on how protected a nerve is at the site of injection. Nerves are thought to be oligofascicular at the level of nerve roots and polyfascicular in areas prone to physical stress, such as the joints. Hence it is common to see hypoechoic (mono/oligofascicular) nerves at the level of roots (interscalene block) whereas they are hyperechoic (multifascicular) near a joint (popliteal nerve block). Moayeri et al. noted a proximal oligofascicular pattern progressing to a polyfascicular pattern in the brachial plexus [115] and sciatic nerve [116]; Sunderland and Ray [120] noted a wide variation in the fascicular pattern of the sciatic and forearm nerves with no consistent pattern in any part of the nerve. Whether neurologic complications are related to the fascicular morphology is currently unknown [97, 99] since proximal blocks (ISB, subgluteal sciatic nerve block) are known to have similar complications as distal blocks (popliteal sciatic, axillary brachial plexus block). Although the connective tissue content increases with age due to endothelial proliferation as a reaction to decreased vascularity of the nerves [156]. This may influence block onset and recovery, but its implications for neurologic injury are currently unknown. Since we did not anticipate any differences between cadaver and live tissue in terms of nerve composition, cadaver studies provided good evidence to support the earlier statements even in the absence of studies of live human tissue.

Surgical Factors

Certain types of surgery are associated with a higher risk of postoperative nerve injury (*LOE 2b*; *Grade B*). *Peripheral nerve blocks do not increase the risk of postoperative neurologic dysfunction*. (*LOE 2b*; *Grade D*).

Some surgeries are more prone to nerve injuries than others, especially those involving excessive neural stretch [157], trauma [158], inflammation [80], or ischemia [127] including a prolonged tourniquet time [82, 159]. In a retrospective review of 380,680 anesthetics during a 10-year period, Welch et al. [112] found a 0.3 % incidence of iatrogenic injuries. There was a significant association of iatrogenic injuries with certain types of surgeries, general anesthesia, and epidural anesthesia but a similar association was not found with peripheral nerve blocks. The lack of association between regional anesthetic nerve blocks and iatrogenic injuries is also confirmed by other studies in shoulder [65, 66, 144], knee [82], and hip surgeries [81]. Shoulder surgeries have a predilection for iatrogenic nerve injuries [13, 160] and the incidence can be as high as 8.2 % following anterior stabilization, around 1–4 % following shoulder arthroplasty or 1–2 % following rotator cuff repairs [161]. While Borgeat et al. [66] and Candido et al. [144] noted different incidences of persistent neurologic sequelae unrelated to surgery 1 month after ISB (7.9 % vs. 3.3 %), most of these complications were unrelated to ISB. Further, a retrospective review of 1569 patients undergoing total shoulder arthroplasty by Sviggum et al. also noted no such relationship between interscalene block and nerve injury [104]. While some studies indicate that the likelihood of complete recovery from peripheral nerve injury is lower when the patient had a PNB [82], other studies have not shown a similar association [82].

Neuropathy

Preexisting neuropathy is thought to increase the risk of postoperative neurologic dysfunction following PNB (*LOE 5*; *Grade D*). *Neuropathic nerves are more prone to the prolonged effects of local anesthetics* (*LOE 5*; *Grade D*).

Currently, there is no high-quality evidence regarding cause and effect of neurologic sequelae following nerve blocks but most anesthesiologists have a tendency to avoid PNB in patients with neuropathy. Although a retrospective cohort study [79] did not demonstrate worsening of neurologic outcomes following PNB in patients with preexisting neuropathy, a number of case reports [125, 128, 129, 132, 140, 143] indicate that either subclinical or overt preexisting neuropathy may make them susceptible to long-term nerve damage. Hence, the expert opinion regarding regional anesthesia in patients with neurologic disease tends to err toward caution [11, 162]. The degree of neural dysfunction in a chronically compromised nerve may be clinical or subclinical, and any secondary insults such as hypoxia or ischemia, local anesthetic neurotoxicity, or direct mechanical trauma following nerve blockade is thought to exacerbate it [162]. Importantly, the secondary insult need not be at the site of the neural compromise itself, a phenomenon known as "double-crush syndrome" [163]. In fact, a double-crush injury in the form of two distinct low-grade insults has been shown to be more damaging to the nerve compared to an

insult at a single site [164]. Thus, when suspecting underlying chronic neuropathy such as in patients with peripheral vascular disease, mechanical compression, metabolic derangements (diabetes mellitus) or postchemotherapy (cisplatin neurotoxicity), the decision to perform a PNB should be made on a case-by-case basis after thorough physical examination and discussion with the patient and the surgical team [162, 165]. It is generally thought that any evolving lesions or active inflammation of the nerves is a contraindication for PNB [162].

Two animal models of diabetic neuropathy have been tested for local anesthetic neurotoxicity [29, 35]. In the study by Kroin et al., local anesthetics produced a longer mean duration of sensory nerve block in diabetic rats versus nondiabetic rats [35]. Doses of lidocaine (with or without adjuvants) or ropivacaine that did not cause noteworthy nerve fiber damage in nondiabetic rats also failed to produce major pathology in nerves of rats with streptozotocin-induced diabetic neuropathy. The study by Kalichman [29] not only showed a lower conduction velocity in diabetic nerves, but also it had neuronal edema subsequent to extraneurally placed LA in a concentration-dependent fashion. This study along with others indicating that local anesthetic neurotoxicity is directly proportional to the dose and duration of local anesthetic exposure [59, 166], higher LA concentrations should be strongly discouraged for neuropathic patients and deliberate intraneural injections should be avoided based on conventional wisdom.

Causative Agent Factors

The insulting injury to a nerve can be as a result of direct needle trauma, pressure injury, or local anesthetic neurotoxicity. A majority of these factors have been evaluated in animal studies since human studies are not feasible due to obvious ethical concerns and hence most of the evidence is extrapolated to humans. It is difficult to judge as to which factor is the most damaging since most of the evidence originated from different animal models and more than one injurious agent may be evaluated in these studies.

Mechanical Agents

Needle Trauma

Nerve trunks usually slide under an advancing short-bevel needle compared to long-bevel needles (*LOE 5*; *Grade D*). *Long-bevel needles cause more functional or histological damage compared to short-bevel*, *pencil-tip*, *or Tuohy needles but the superiority among the latter three needle types is currently unknown* (*LOE 5*; *Grade D*). *Needle gauge may in itself influence the degree of damage irrespective of needle type* (*LOE 5*; *Grade D*). *When short-bevel needles do penetrate the perineurium*, *the resultant nerve damage is greater than that of long-bevel needles* (*LOE 5*; *Grade D*). *The amount of damage is greater when the needle bevel is perpendicular to nerve fibers than when it is parallel* (*LOE 5*; *Grade D*).

Eight animal studies and one cadaveric study evaluated the impact of needle design on nerve injury. The degree of nerve damage from needle trauma depends on the bevel type, the angle of needle insertion, and the needle size (gauge). Long-bevel (14° angle) needles penetrate fascicular bundles through the perineurium, while these fascicles slide under or away from short-bevel (45° angle) needles [17]. Animal [38] and human cadaver [119] studies demonstrate that injection with a long-bevel needle has a greater chance of being intrafascicular and resulting in nerve injury. One animal study showed that even in the absence of direct neural trauma, the presence of perineural hematoma might in itself result in inflammation and structural injury to the nearby nerves [48] and this has been implicated as a possible cause of injury in a case report [127]. Using cadaveric tissue, Sala-Blanch et al. [119] showed that, although fascicular contact is fairly common with intraneural injections, injury to these fascicles rarely occurs. Of the 134 fascicles contacted by the needle, only four were damaged, all from long-bevel needles. In animal studies, needles with a tapered end, such as Whitacre and Sprotte needles, are comparable to each other [37] and to Tuohy needles with respect to neural damage [37, 45, 46]. While two studies show superiority of tapered-tip needles over short-bevel needles in terms of neural damage caused [27, 37], and its effect on nerve conduction [27] another study reported similar neural perforations with tapered-tip and short-bevel needles of the same gauge [46].

The amount of nerve damage following intraneural needle placement is also higher when the bevel is inserted transversely to the nerve fiber compared to insertion along the long axis of the nerve [17, 27, 37]. Regardless of the type, needle gauge is directly proportional to the extent of nerve damage, as demonstrated by the stark difference in the extent of fascicular damage from 22G needles (3 %) and 17/18G needles (40 %) [45]. In general, short-bevel needles are preferred for PNB since they have difficulty penetrating perineurium; however, when short-bevel needles do penetrate the perineurium, the amount of mechanical trauma far exceeds that done by a long-bevel needle [42].

It is important to point out that basic science research using animals or cadaver tissue as a study model, such as the ones described earlier, were considered to be level 5 evidence and given a grade D recommendation irrespective of study design. This is because these studies arguably do not provide direct research evidence in live human subjects, although ethical issues and other difficulties obviously preclude doing these studies in live subjects. Nevertheless, the available evidence is quite convincing despite having a lower grade.

Pressure Injury

Perineural injections require the least injection pressure followed by extrafascicular injection, while intrafascicular injections generate high injection pressure (*LOE 5*; *Grade D*). *While high injection pressures result in functional and histological nerve damage, intraneural injection with low injection pressures may not necessarily result in nerve damage* (*LOE 2b*; *Grade C*).

The axons inside the fascicles are under pressure created by the perineurium and hence any injection into the perineurium will probably require higher injection pressure subsequently resulting in pressure injury. The evidence for pressure injury is purely based on animal models [9, 17, 21, 34, 53, 54, 167] and the human evidence is limited to studies looking at pressure monitoring during PNB [75]. In animal studies, low injection pressures (<25.1–27.9 kPa) are noted for injection performed around the nerve without penetration of the outer epineurium, while injection pressures increase slightly (69.8–86.5 kPa) upon entering the epineurium [53, 54]. Selander et al. [167], in a study of intraneural injection at different locations within the rabbit sciatic nerve, showed that a relatively low injection pressure (25–60 mmHg [3.3–7.9 kPa]) was required for subepineurial (extrafascicular) injections and resulted in limited spread of injectate, whereas intrafascicular injections required higher pressures (300–750 mmHg [39.9–99.7 kPa]) and resulted in rapid spread of injectate over long distances within the fascicle. To study the clinical consequence of such injections, Hadzic et al. [9] performed intraneural injections with 4 mL lidocaine in the canine sciatic nerve. Low-pressure (<4 psi) injections (3/7) were extrafascicular while high pressure injection (25–45 psi) (4/7) were intrafascicular in location which was similar to that noted by Selander et al. [167]. In a similar study design, Kapur et al. [34] showed that all intrafascicular injections resulted in clinical deficits in the form of paresis or disability while none of the extrafascicular injections resulted in any neural dysfunction. A study of ultrasound-guided deliberate intraneural injections in piglets with injection pressures <20 psi (~138 kPa) also showed that none of the injected nerves had a breach in the perineurium. Although the nerves showed signs of inflammation for up to 2 days postinjection and changes in nerve architecture under ultrasound for up to 4 days, none of the animals developed any functional deficits [21]. A similar evidence from a human study also showed that a low injection pressure during deliberate intraneural popliteal sciatic nerve block does not necessarily lead to early postoperative neurologic dysfunction [97] but further studies on injection pressure in clinical practice are needed. The pressure measurements following subepineurial injections are similar between those obtained by Vuckovic et al. [53, 54] and Hadzic et al. [9] but are higher than those reported by Selander et al. [167]. This could be related to differences in animal models, syringe, and injectate volumes used in the two studies. Although injection pressures <15 psi is recommended safe in clinical practice, this needs to be further validated.

The generation of high injection pressures during intrafascicular injection can be explained by the high intrafascicular pressure created by the perineurium and may also lead to pressure injury. The low injection pressures needed for perineural injection compared to subepineurial and intrafascicular injections show the potential utility of continuous monitoring of injection pressures during PNB. There is a need for further evidence regarding the short- and long-term safety of low-pressure intraneural injections.

Similar to studies related to needle design (see earlier), it would be difficult and unethical to perform studies in live humans to evaluate injury from high pressure injection. Thus, the published evidence is limited to basic science research using animals and cadaver tissue as study models. However, as with studies of needle design, the available evidence is fairly persuasive despite being assigned a lower grade.

Chemical Agents

Neurotoxicity

All local anesthetics are neurotoxic in increasing concentrations and individual local anesthetics differ in their neurotoxic potential (*LOE 5*; *Grade D*). *Both extra- and intrafascicular injection of local anesthetic can result in histological damage, but is far greater following intrafascicular injection leading to functional injury as well* (*LOE 5*; *Grade D*). *Both epinephrine and local anesthetics decrease neural blood flow, and their combination has synergistic effects* (*LOE 5*; *Grade D*).

A total of 21 studies evaluated the neurotoxicity of LA in different animal models. Broadly, the studies looked at comparative neurotoxicity of different LA solutions with or without adjuvants [25, 26, 44, 55, 58, 59], the impact of topical application of LA [22, 23, 29–33, 39, 40, 50, 57], or their intraneural injection [25, 26, 28, 35, 36, 44]. Intraneurally injected LA may often result in histological changes without any functional neuropathy [28, 35, 36]. While there is a general agreement over the increased amount of nerve damage following intrafascicular injection of LA as compared to topical application [44], whether or not LA solutions are more toxic than saline intrafascicularly is currently debated. While Farber et al. [25] in a study of Lewis rats noted intrafascicular injection of LA was more damaging than saline [25], a study by Selander et al. [44] on rabbits showed both saline and 0.5 % bupivacaine to cause equal amount of axonal damage. Although the amount of damage was greater with increasing concentrations of LA indicating that the

pressure injury is far more damaging than LA neurotoxicity. The damage following intrafascicular injections is a result of a breach in the blood–nerve barrier and the loss of internal hypertonic milieu [25] compounded by pressure injury, interstitial edema, and direct neurotoxicity, resulting in clinical nerve damage.

At therapeutic doses, all local anesthetic agents exhibit neurotoxic potential [168] and, although debatable, some drugs may be more neurotoxic than others. The direct neurotoxicity of local anesthetics is thought to be related to prolonged increases in cytosolic Ca^{2+} leading to depletion of adenosine triphosphate, mitochondrial injury, membrane dysfunction, and, ultimately, cell death [169, 170]. Transient neurologic symptoms following spinal anesthesia are thought to represent a mild consequence of local anesthetic neurotoxicity [171], and transient neurologic symptoms following PNB may represent a similar event, with small-diameter axons (pain and temperature) being more affected than large-diameter axons (motor and proprioception) [172].

The neurotoxic effect of local anesthetics is time and concentration dependent in an animal study and in vitro models of cell cultures [59] but whether this holds true in human subjects is not known. While long-acting LA [85] and continuous catheters [6, 68, 72] have been employed safely with a low incidence of long-term nerve damage, some catheter studies [3, 77, 95, 96] and case reports [122, 125, 128, 140] do point toward a fairly high incidence of nerve dysfunction. While Capdevilla et al. [68] in a study of continuous catheters noted a low incidence of long-term neuropathy, bupivacaine infusion was one of the risk factors for the same along with ICU stay and age <40 years. Further prospective studies are needed to know whether prolonged exposure of nerves to different concentrations of LA is safe or neurotoxic.

The local anesthetic neurotoxic potential of individual agents differs depending on the animal model and study methodology but in general, most local anesthetics have vasoconstrictive properties and that includes the common agents such as lidocaine [39], levobupivacaine, and ropivacaine [23], hence making them both directly neurotoxic and have neuronal ischemic effects. Although bupivacaine has a vasodilatory effect on intraneural blood flow [22] and is thought to be less neurotoxic following intraneural injection according to one study [26], another study found it to be more neurotoxic than lidocaine or ropivacaine when injected into the fascicle [25]. Given that local anesthetic neurotoxicity is well documented, deliberate intraneural injection of local anesthetic is still strongly discouraged, despite the fact that most of the evidence comes from animal studies.

Adjuvants

Local anesthetics are more neurotoxic than adjuvants and, while some adjuvants may have neurotoxic potential, others may be neuroprotective (*LOE 5*; *Grade D*).

The neurotoxic potential of local anesthetics far exceeds that of any adjuvants used in regional anesthesia [57, 58], and effects on nerve tissue depend on the individual agent. While adjuvants, including opioids, clonidine, dexamethasone, and neostigmine, do not influence the neurotoxic potential of local anesthetics in vitro, drugs such as ketamine and midazolam may themselves be neurotoxic at higher doses [173]. On the other hand, dexmedetomidine was shown to be neuroprotective in rats following intraneural sciatic nerve injection [50]. It was postulated that dexmedetomidine decreased the neurotoxic potential of bupivacaine by decreasing mast cell degranulation at the site of injury. Nevertheless, the current evidence is limited to studies in animal models.

Intraneural Injections

Unintentional intraneural injections occur more often than previously expected (*LOE 2b*; *Grade B*), *but they may not necessarily result in neurologic dysfunction* (*LOE 2b*; *Grade B*). *Intraneural injections have a rapid block onset* (*LOE 2b*, *Grade B*).

Six trials studied the incidence of unintentional intraneural injection [73, 78, 91, 94, 98, 99]. Three were performed with the aid of nerve stimulation alone, one was done with ultrasound guidance alone, and two used dual guidance. The results showed that unintentional intraneural injection occurs frequently in both upper and lower limb blocks, with the incidence varying from ~17 % to as high as 66 % [73, 78, 91, 94, 98, 99]. Intraneural injections were also shown to hasten block onset [78, 94, 99], improve block success [108], and have also been shown to prolong block duration in animal models [34]. The incidence of needle nerve contact could possibly be higher with an out-of-plane (OOP) approach (64 % for femoral nerve block) [98] but whether or not this results in an increased incidence of intraneural injections is currently unknown. OOP approaches although have not been shown to increase the incidence of neurologic complications [3].

Irrespective of unintentional or targeted intraneural injections using either low current neurostimulation or US guidance, none of the trials reported long-term postoperative neurologic dysfunction related to PNB [62, 63, 78, 94, 97–100, 108]. However, the follow-up period in some of these studies was not long enough to allow symptoms to develop, and none of the studies were sufficiently powered to assess the incidence of neurologic dysfunction or nerve injury. Hence, it cannot be recommended as safe practice to perform deliberate intraneural injections until data from larger studies are available.

Five studies investigated deliberate intraneural injection [62, 97, 100, 108]. In each one, ultrasound was used to identify intraneural injection, and one study used nerve stimulation in addition to ultrasound [97]. A 10 % incidence of transient neurologic deficit was observed in one of

the studies [63], and another study evaluating the deliberate intraneural injections performed under ultrasound versus neurostimulation showed an increased success rate with US but resulted in a higher incidence of paresthesia [101]. None of the studies revealed any increase in neurologic complications during follow-up (1–4 weeks after the procedure). A cadaveric study of interscalene blocks reported a 50 % incidence of subepineural injection when the needle tip was placed adjacent to the brachial plexus trunks [117]. While the results of these studies do not imply that intraneural injection is a safe procedure, they do show that it is a fairly common occurrence and does not always lead to neurologic complications.

The take-home message is not to think that deliberate intraneural injections are safe to perform but to think that it is fairly common in clinical practice to note intraneural injections and it does not necessarily result in neurologic complications. The occurrence of neurologic complications may increase following intrafascicular (subperineural) injections but currently most of the evidence for this is based on animal studies and case reports.

Environmental Influences

The time-honored statement that "an ounce of prevention is worth a pound of cure" is essential when considering the ways to minimize adverse outcomes following intraneural injection. To help reduce or prevent the possibility of intraneural injection, an effective method of detecting and monitoring the presence and extent of intraneural injection is critical, as is the skill and willingness to use it in regional anesthesia practice.

Nerve Stimulation

When used at low currents, *nerve stimulation has low sensitivity but high specificity for detecting proximity of the needle tip to the target nerve* (*LOE 2b*; *Grade B*). *Nerve stimulation cannot differentiate between intraneural needle placement and needle–nerve contact* (*LOE 5*; *Grade D*). *Higher stimulating currents are required in diabetic patients for detecting intra- and extraneural needle placement* (*LOE 2b*; *Grade C*).

For electrical nerve stimulation, the minimal stimulating current intensity is proportional to the square root of the distance between the needle tip and the nerve, provided there is a constant magnitude of charge between the two points. In animal studies, a low stimulating current requirement (<0.2 mA) was originally shown to correlate with histological evidence of nerve injury in 50 % of the study animals, while current intensity >0.5 mA implied extraneural placement [52]. A similar study in humans employing noninsulated needles showed that the median (Range) stimulating current noted when a deliberate paresthesia is obtained was 0.17 (0.03–3.3 mA) [70]. This led to the popular practice of eliciting motor response at stimulating currents between 0.2 and 0.5 mA and deliberately withdrawing the needle when stimulation is obtained at currents <0.2 mA. A number of studies later showed the inaccuracies of neurostimulation both at low and high current stimulation. Even the studies which established the notion that an MSC of <0.2 mA was specific but not sensitive indicator of intraneural needle placement possibly had extraneural needle placements as evidenced by an extraneural injection in 50 % of injections in the animal study [52] and the wide range of MSC noted with the human study [70]. Animal studies have shown that higher stimulating currents are sometimes needed to elicit a motor response following intraneural needle placement [20, 24, 174]. The same phenomenon was observed in 16.7 % of patients receiving deliberate low-pressure intraneural injections during popliteal sciatic nerve block [97]. On the contrary, low stimulation currents have been employed for performing sciatic nerve block [83] and infraclavicular block [84] without evidence of nerve damage.

Recently, Weismann et al. [56] showed that a low stimulating current may indicate either needle–nerve contact or intraneural placement. Hence, a low stimulating current, if present, may only indicate that the needle tip is too close to or within the nerve, rather than differentiating between the two. The noncorrelation of needle tip location and nerve stimulation is due to a variety of factors influencing motor response following stimulation. The stimulating current is influenced by pulse width, interaction of the needle tip with the fascicles, and the degree to which a depolarization or hyperpolarization occurs as a result of the stimulating current [175–177]. Since the minimal stimulating current for each nerve is different [178], a single value cannot be extrapolated for all nerves.

Evidence regarding whether or not diabetic individuals require a higher stimulation threshold is evolving. In animal models of hyperglycemia, when a low stimulation threshold was used to guide the needle, all injections were intraneural, while none of the low current stimulation injections in normoglycemic animals had the same pattern of injectate dispersion [43]. A significant number of diabetic patients undergoing supraclavicular brachial plexus block required a higher stimulation threshold when the needle was placed perineurally (57 % required currents >1.0 mA vs. 9 % nondiabetic) or intraneurally (29 % required currents of 0.5–1.0 mA vs. 2 % nondiabetic) [63]. It has been reported and is worth pointing out that it also has been that the threshold currents used for motor response from nerve stimulation under general anesthesia might be higher than those in awake patients [146]. Thus, their result also suggested that using nerve stimulation as a technique to warn for intraneural placement in patients under general anesthesia may require different parameters compared with patients who are not under general anesthesia.

Injection Pressure Monitoring

High injection pressures are often reached unknowingly by experienced and nonexperienced practitioners (*LOE 2b*; *Grade B*). *Syringe feel is inaccurate for differentiating tissues*, *and higher pressures are generated unknowingly* (*LOE 5*; *Grade D*). *Injection pressure can be kept within safe limits reliably by using compressed air injection technique* (*CAIT*) *or pressure measurement devices* (*LOE 2b*; *Grade C*). *Opening pressure can detect needle nerve contact reliably in interscalene block* (*LOE 2b*; *Grade C*).

While intrafascicular injections require higher injection pressures, a low injection pressure has a good negative predictive value for neurologic dysfunction [21, 97]. Two important pressures to monitor when performing a PNB are the opening pressure (OP) and injection pressure (IP). The OP is the pressure in the needle–tubing–syringe assembly before the injectate begins to flow through the needle. A high OP (>20 psi) has been shown to correlate with nerve damage [75]. Once flow has begun, IP at the needle tip depends on various factors, including needle size, length of tubing, and syringe volume. Avoiding high IP is as important as OP in preventing further damage from injectate flow into the perineurium. Simple "syringe feel" is inaccurate in determining what tissues the performer is injecting into, irrespective of operator experience as shown in an animal model where only 12 of 40 anesthesiologists (30 %) correctly identified intraneural injection using "syringe feel" [107]. Anesthesiologists also vary widely in their perception of injection pressure and the speed of injection. In a study of 30 anesthesiologists performing simulated injections in a lab model, a 20-fold variability in baseline injection pressure and speed of injection was noted. When resistance was increased gradually in a blinded fashion during injection, 70 % of anesthesiologists exceeded the recommended injection pressure of 20 psi [109, 114].

The inaccuracy of "syringe feel" and a wide variability in baseline perception of the performer has led to the use of objective methods and devices to monitor injection pressure during PNB performance. These include the compressed air injection technique (CAIT) [109, 121] and B.Braun's BSmart™ injection pressure monitor. When using CAIT, a set volume of air is drawn into the syringe containing the injectate, and the air is compressed to a certain percentage of its initial volume when injecting. In vitro evaluation of this technique has been shown to ensure injection pressures substantially below the threshold considered significant for nerve injury, irrespective of the needle or syringe type when the air compression was ≤50 % of the original volume. Currently, no animal or clinical studies have evaluated the technique, so its impact on clinical outcomes is unknown. Recently, the use of the BSmart™ device in patients ($n = 16$) undergoing ultrasound-guided interscalene brachial plexus block consistently (97 %) revealed an opening pressure of ≥15 psi at the time of needle–nerve contact [75]. Nevertheless, the specificity of using injection pressure monitoring to avoid intraneural needle placement is still suspect. High injection pressures can be caused by contact with fascia, tendon, or bones. Moreover, needle tip pressure may be dependent on the needle–syringe combination [179].

Ultrasound

Ultrasound guidance can detect intraneural injection and is dependent on operator experience (*LOE 2*; *Grade B*). *Use of ultrasonography does not prevent intraneural injection* (*LOE 2*; *Grade B*). *Long-term neurologic complications following PNB have not declined as a result* (*LOE 2b*; *Grade B*).

Ultrasound can be a useful tool for avoiding and detecting intraneural needle placement and injection but is not foolproof in preventing intraneural injection. Currently available ultrasound technology cannot differentiate between the different layers of the nerve and therefore cannot distinguish between inter- and intrafascicular injection. Possible ultrasonographic indicators of intraneural injections include visualization of the needle tip within the nerve, increase in the nerve cross-sectional area by at least 15 %, spread of local anesthetic within the epineurium upon proximal-to-distal scanning, and real-time visualization of fascicle separation on injection. It is important to note that, if any of these signs is observed on ultrasound, intraneural injection has already occurred.

When performing PNB, the needle tip is often not visualized on ultrasound, and needle advancement without proper needle tip visualization is a common error that persists even after adequate experience. Surrogate markers, such as increase in cross-sectional surface area or local anesthetic solution found between the fascicles, are therefore used to monitor for intraneural injection. The occurrence of unintentional intraneural injections during ultrasound-guided PNB has been noted frequently in cadaveric studies [117] and the clinical setting [63, 78, 91, 98] and is most likely due to dependence on the practitioner's expertise in detecting intraneural needle placement or injection. In a study of assessment of intraneural injection by novices and experts, the sensitivity of detecting a low volume (0.5 mL) intraneural injection was 65 % in novices and 84 % in experts, but the specificity of assessment was 98 % irrespective of the level of expertise [86]. Although Bigeliesen et al. [63] showed that intraneural needle tip placement was detected reliably in only 69 % of cases, surrogate markers of intraneural injection (e.g., increase in cross-sectional area of nerve) can detect intraneural injections reliably (94 %) [93, 100]. Ruiz et al. [98] evaluated whether an in-plane (IP) approach to femoral nerve block was better than an out-of-plane (OOP) approach for avoiding needle–nerve contact and intraneural injection. Although they noted a higher incidence of intraneural injec-

tions with an OOP approach (64 % vs. 9 % IP), their definition of intraneural injection was the presence of local anesthetic below the nerve, rather than visualization of intraneural needle tip or injectate placement on ultrasound. This, combined with the lack of evidence from other types of PNBs, suggests that further study is needed to conclude with certainty that OOP approaches increase the chances of needle–nerve contact and intraneural injection.

Orebaugh et al. [4, 5] investigated whether the use of ultrasound has led to a decrease in neurologic complications. In both retrospective reviews, no differences in long-term neurologic complications were found between blocks performed under nerve stimulation or ultrasound guidance. Electromyography detected nerve injury following nerve stimulation-guided block in 3/3290 cases, but no long-term neurologic injuries were detected following ultrasound-guided blocks (0/2146). An update in 2012 showed the incidence of nerve injury lasting 6–12 months was significantly higher with nerve stimulation alone (4/5436) compared to ultrasound guidance (1/9069), but no significant difference in the incidence of long-term injuries (>1 year) was observed between the two groups (3/5436 nerve stimulation vs. 0/9069 ultrasound). This has also been supported by a prospective study by Liu et al. [92]. Although the underlying reason(s) for not seeing a reduction in complications despite the increasing use of ultrasound in regional anesthesia practice is unclear, it may explained in part by the old adage, "A tool is only as good as the person using it," which is highly applicable when it comes to using imaging technologies such as ultrasound.

Monitoring neurologic outcomes following regional anesthesia.

To monitor and manage patients effectively with possible peripheral nerve injury following regional anesthesia, it is important to have a basic understanding about classification and the pathophysiology of neurologic injuries.

Pathophysiology

The overall clinical course of pathophysiology of peripheral nerve injury usually takes 2–4 weeks to manifest and progress [180, 181] for most nerves. However, there is a primary histological change involving physical fragmentation of both axons and myelin, a process that begins within hours of injury (Wallerian degeneration) occurring at the axon distal to the site of injury [181]. For the portion of the nerve proximal to the injury, it also undergoes a retrograde degeneration. Eventually, the axons in the endoneurial network undergo chromatolysis and are replaced by Schwann cells. The process of recovery begins after 4–6 weeks, and the integrity of endoneurial network is crucial at this recovery phase and correlates with clinical recovery (see the section on practical aspects below). If the endoneurium is intact, the regenerating axons grow into them and are subsequently myelinized by the Schwann cells. If there is a disruption of endoneurial network, the regenerating axons grow aimlessly in all directions, resulting in a neuroma. The classification of nerve injury and its subsequent course is described in Table 5.7. For practical purposes, Sunderland's classification is used to classify and predict outcomes.

As presented in Table 5.7, nerve injury is not necessarily synonymous with clinical complications and at times may not lead to any detectable clinical symptoms or signs. In other words, the injury may lead to subclinical complications with no overt clinical manifestations. Individuals who present with neurologic symptoms and sequelae may therefore only represent the tip of the iceberg (Fig. 5.3). Thus, it is important to consider and interpret carefully the evidence regarding the incidence of clinical neurologic complications.

Practical Points in Mechanism of Nerve Injury

A neuronal injury is more likely to arise when a negative interaction between a susceptible host (inadequately protected nerve), an injurious agent (local anesthetic, needle, or injection pressure), and a hazardous working environment (poor supervision/guidance for locating needle, unsafe practices, unintended exposure) occurs. Risk stratification by minimizing one of the triangle's components should, in theory, preclude the manifestation of the event. Hence it is vital to choose a technique tailored to each patient's existing physiology (nonmodifiable risks) as delineated earlier. The clinician should attempt to minimize all modifiable risks

Table 5.7 Classification of nerve injury

Sunderland	Seddon	Description of injury	Recovery
First degree	Neuropraxia	Nerve is intact. Conduction block and demyelination noted	Complete recovery within days–weeks
Second degree	Axonotmesis	Wallerian degeneration noted from this stage onward. Nerve structure is intact but with axonal disruption	Recovery within weeks to months following axonal regeneration
Third degree	Axonotmesis	Disruption of endoneurium	Partial recovery may occur but not complete recovery
Fourth degree	Axonotmesis	Disruption of perineurium. Cell body loss from this stage onward	Permanent deficits. Recovery unlikely
Fifth degree	Neurotmesis	Disruption of epineurium	Permanent deficits. Recovery unlikely even with surgery

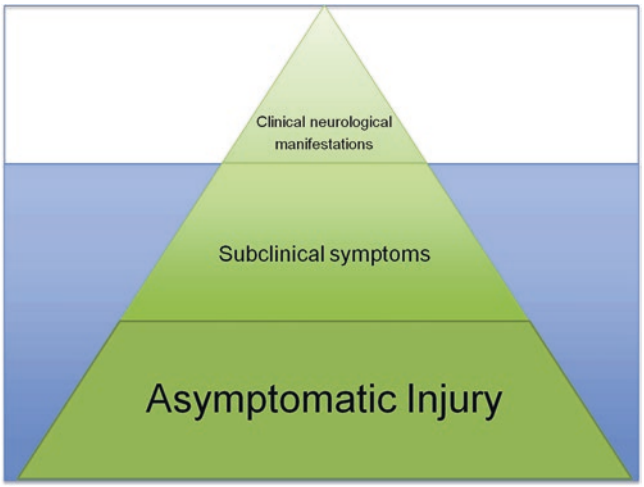

Fig. 5.3 Schematic diagram of relationship of injury and clinical symptoms

such as needle trauma, pressure injury, and LA neurotoxicity using appropriate monitoring techniques and safe practices. A clear understanding of the procedure by the patient and good communication between the clinician and the patient is vital to detect iatrogenic injury either during performance of the block or in the recovery period. Hence we recommend the following practice points which may help in early identification of neurologic outcomes:

- Preoperative assessment and documentation of neurologic function (Identify at-risk patient)
- Clear communication with the patient regarding the block procedures and postoperative recovery of sensory and motor function
- Minimal sedation during the performance of PNB to permit patient–clinician communication.
- Use of all available monitoring technique during the performance of PNB. We routinely use US + NS guidance (0.2 mA) for needle placement and employ CAIT for injection pressure monitoring.
- Close monitoring and adequate follow-up in the event of procedural paresthesia/signs of intraneural injection to ensure recovery of neurologic function
- Use dilute LA solutions in high risk patients (i.e., preexisting neuropathy and presence of surgical risk for compartment syndrome).
- Early neurology referral in those patients with red flags for iatrogenic nerve injury.

Classifying and managing patients with neurologic injury can be challenging given that a widely accepted algorithm is lacking for monitoring neurologic recovery following PNB. We present a simplified algorithmic approach for follow-up of peripheral nerve blocks (Fig. 5.4). Most common symptoms following neurologic injury are sensory changes such as persistent numbness, pain, or persistent paresthesia/dysesthesia in the distribution of the nerve block. The presence of motor weakness out of proportion to that from PNB or after the discontinuation of the block should prompt early referral after ruling out mechanical causes such as tight surgical dressing/tourniquet injury. Evolving sensory/motor lesions also mandate early referral since neurologic deficits arising within the first 24 postoperative hours likely represent acute injury. The routine practice in the majority of institutions includes a follow-up visit or phone call on POD-1 to ensure the resolution of block following discontinuation but, many of the sensory-motor disturbances arise several days to a couple of weeks following PNB and such cases need to be referred to neurology for evaluation if it does not resolve within 4–6 postoperative weeks. Neurologists commonly perform nerve conduction studies, evoked potentials, and electromyography which identifies the site of lesion and the timing of injury thereby helping in the diagnosis and prognosis of injury. These tests are invasive procedures and are not without limitations. Nerve conduction studies are useful in evaluating large sensory-motor nerve fibers while unmyelinated fibers may be missed. EMG requires several weeks of denervation before changes can be detected. Hence cases wherein an evolving/nonresolving lesion is suspected or motor weakness is present are referred to neurology and the majority of cases with mild sensory disturbances are managed conservatively with follow-up.

Conclusion

In summary, long term neurologic complications following regional anesthesia are rare and are usually a result of an interplay between the host (patient) factors, causative agents (mechanical and chemical), and environment (regional anesthesia tools and methods). Many of the factors responsible for the neurologic complications are nonmodifiable and hence screening for at-risk patients is necessary. Unintentional intraneural injections are thought to occur frequently during PNB and intraneural injections may not necessarily result in neurologic complications as long as they are extrafascicular. Most of the evidence for neurologic injury following PNB such as needle design, pressure monitoring, and local anesthetic neurotoxicity arises from animal models and their findings are being extrapolated to clinical practice. Evidence from animal experiments indicates that intrafascicular injections used with higher injection pressures are more likely to result in nerve injury. While technological improvements in regional anesthesia practice continue to improve our ability to detect and prevent nerve damage, preparation, vigilance, and careful observation remain a regional anesthesiologist's most important tools in ensuring patient safety.

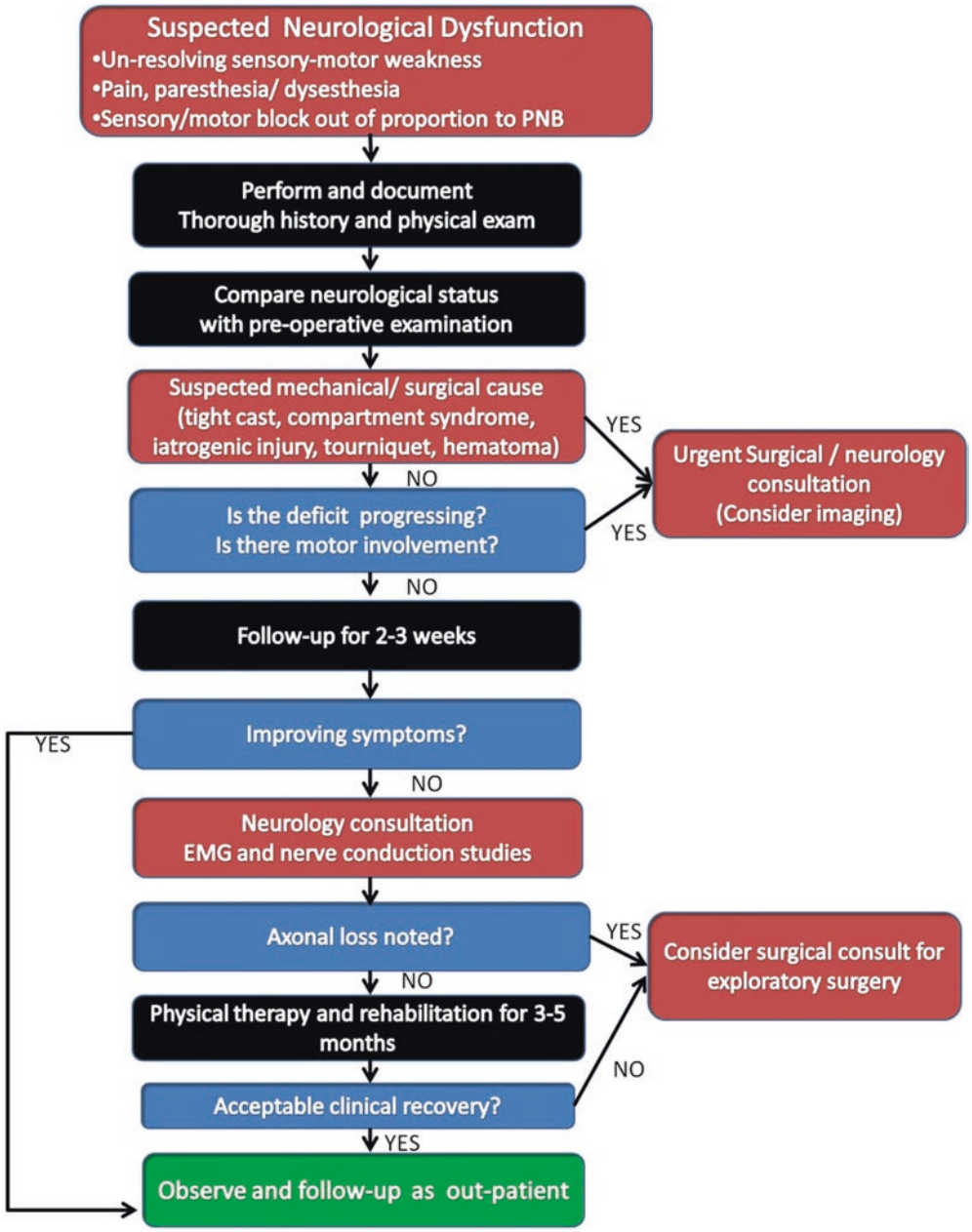

Fig. 5.4 Pathway to classify and manage neurological injury following peripheral nerve blocks

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