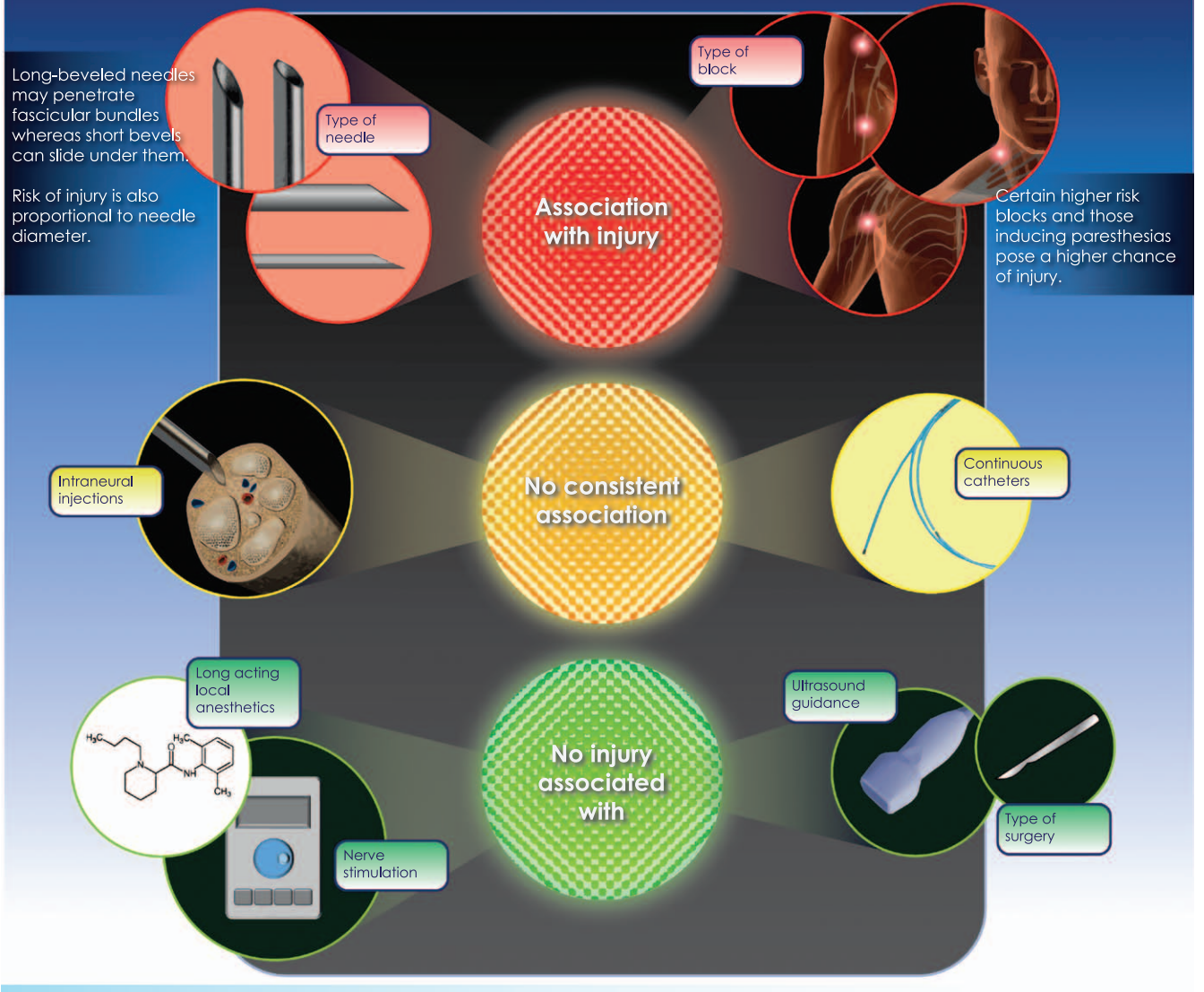
ANESTHESIA & ANALGESIA® Infographic

Threading the Needle With Peripheral Nerve Blocks: *Achieving Analgesia, Avoiding Neurological Injury*

A recent review identified risk factors for long term neurological injury, which occurs in 2.4-4 / 10,000 nerve blocks.[1]



Differences in complication definitions and complication categorization impeded analysis. More high quality data are needed.

One of the possible long termcomplications of a peripheral nerve block is neurological injury. In this infographic, we describe risk factors that have been demonstrated to be associated with increased risk of long term neurological complications, and review risk factors that have not been associated with these complications.[1]

REFERENCE

1. Sondekoppam RV, Tsui BCH. Factors associated with risk of neurologic complications after peripheral nerve blocks: a systematic review. *Anesth Analg*. 2017;124:645–660.

IARS International Anesthesia Research Society

Section Editor: **Honorio T. Benzon**

SYSTEMATIC REVIEW ARTICLE

CME

Factors Associated With Risk of Neurologic Complications After Peripheral Nerve Blocks: A Systematic Review

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The onset of neurologic complications after regional anesthesia is a complex process and may result from an interaction of host, agent, and environmental risk factors. The purpose of this systematic review was examine the qualitative evidence relating to various risk factors implicated in neurologic dysfunction after peripheral nerve block (PNB). The MEDLINE, OVID, and EMBASE databases were primary sources for literature. Cochrane, LILACS, DARE, IndMed, ERIC, NHS, and HTA via Centre for Reviews and Dissemination (CRD; York University) databases were searched for additional unique results. Randomized controlled studies, case–control studies, cohort studies, retrospective reviews, and case reports/case series reporting neurologic outcomes after PNB were included. Relevant, good-quality systematic reviews were also eligible. Human and animal studies evaluating factors important for neurologic outcomes were assessed separately. Information on study design, outcomes, and quality was extracted and reviewed independently by the 2 review authors. An overall rating of the quality of evidence was assigned using GRADE (Grading of Recommendations Assessment, Development and Evaluation) criteria. Relevant full-text articles were separated based on type (prospective, retrospective, and nonhuman studies). Strengths of association were defined as high, moderate, inconclusive, or inadequate based on study quality and direction of association. The evidence from 77 human studies was reviewed to assess various host, agent, and environmental factors that have been implicated as possible risks. Most of the available evidence regarding the injurious effects of the 3 cardinal agents of mechanical insult, pressure, and neurotoxicity was extracted from animal studies (42 studies). Among the risk factors investigated in humans, block type had a strong association with neurologic outcome. Intraneural injection, which seems to occur commonly with PNBs, showed an inconsistent direction of association. Measures meant to increase precision and ostensibly reduce the occurrence of complications such as currently available guidance techniques showed little effect on the incidence of neurologic complications. Recovery from neurologic injury appears to be worse in patients with pre-existing risk factors. Categorization and definition of neurologic complication varied among studies, making synthesis of evidence difficult. Also, a significant portion of the evidence surrounding neurologic injury associated with PNB comes from animal or laboratory studies, the results of which are difficult to translate to clinical scenarios. Of the human studies, few had an a priori design to test associations between a specific risk factor exposure and resultant neurologic sequelae. A few risk factor associations were identified in human studies, but overall quality of evidence was low. Much of the evidence for risk factors comes from animal models and case reports. The final neurologic outcome seems to represent the complex interaction of the host, agent, and the environment. (Anesth Analg 2017;124:645–60)

Long-term neurologic injury is a feared complication after peripheral nerve blocks (PNBs) with a risk of debilitating and, at times, devastating consequences. Such events are relatively rare with an incidence ranging between 2.4 to 4 per 10,000 blocks, but are concerning because of the potential for patient morbidity.[1–6] Neurological function after a PNB can be thought to lie along a spectrum ranging from normal function to complete neural damage and is the net result of the interplay between associated risk factors.

Findings from numerous human and animal studies suggest that multiple factors contribute to the risk of neurologic injury.[7–9] Risk factors important for neurologic outcomes after PNB are commonly thought to include type of nerve block, presence of pre-existing neuropathy, occurrence of intraneural injection, mechanical trauma (needle trauma), pressure injury,

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Accepted for publication November 8, 2016.

DOI: 10.1213/ANE.0000000000001804

Funding: Dr Tsui is supported by a Clinical Scholar Award from the Alberta Heritage Foundation for Medical Research (AHFMR). Dr Tsui's research is supported by the Canadian Anesthesia Research Foundation.

The authors declare no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.anesthesia-analgesia.org).

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local anesthetic (LA) neurotoxicity, neuronal ischemia, and iatrogenic injury from surgery, among others.[7,8,10–18] Although many systematic reviews and database studies have extensively evaluated the incidence rates of neurologic complications associated with these individual risk factors,[19] the interactions and associations between them have rarely been examined.

Ever since John Snow, the pioneer anesthesiologist and father of modern epidemiology, first attempted to explain patterns in cholera outbreaks in 1850s London, the principles he described have been invoked to investigate and control disease.[20] The epidemiologic triangle, which describes the division of the causes of disease into agent-, host-, and environment-specific categories, still has relevance today.[21] Classically, the epidemiologic triangle was used to investigate the causes of infectious diseases such as cholera, but has since been proved useful as a framework for categorizing and understanding noninfectious pathology as well. When considering the incidence of neurologic injury occurring after regional anesthesia, the same rationale can also be used as a framework to classify the complexity of the possible interactions among the various risk factors involved (Figure 1). Using this triad model, complex neurologic risk factors can be readily and broadly classified into host (anatomic and comorbidity factors), agent (mechanical, pressure, and chemical neurotoxic insults), and environmental (guidance techniques, supervision, safe practice culture) categories. The neurologic injury may then subsequently represent the final outcome of the interaction among these risk factors. Minimization or elimination of any of the triangle's components may potentially, in theory, interrupt the interaction and reduce the likelihood of the injury or possibly prevent it entirely. We have, therefore, performed a systematic review from the perspective of the epidemiologic triangle evaluating the pertinent clinical and pathophysiological aspects surrounding regional anesthesia that have bearing on neurologic complications after PNB.

METHODS

Search Strategy and Selection of Studies

A systematic review of the medical literature was performed between November and December 2015 using the search strategy described subsequently. Search terms and details of the complete search strategy are described in Supplemental Appendix A (Supplemental Digital Content 1, http://links.lww.com/AA/B598). We chose 1975 as the starting year because the first systematic investigations of factors important to causation of nerve injury after regional anesthesia were published in the late 1970s.[22]

Both human and animal studies were included for the review. Primary searches were performed in the MEDLINE, OVID, and EMBASE databases. Additional database searches including Cochrane, LILACS, DARE, IndMed, ERIC, NHS, and HTA via Centre for Reviews and Dissemination (CRD; York University) 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.

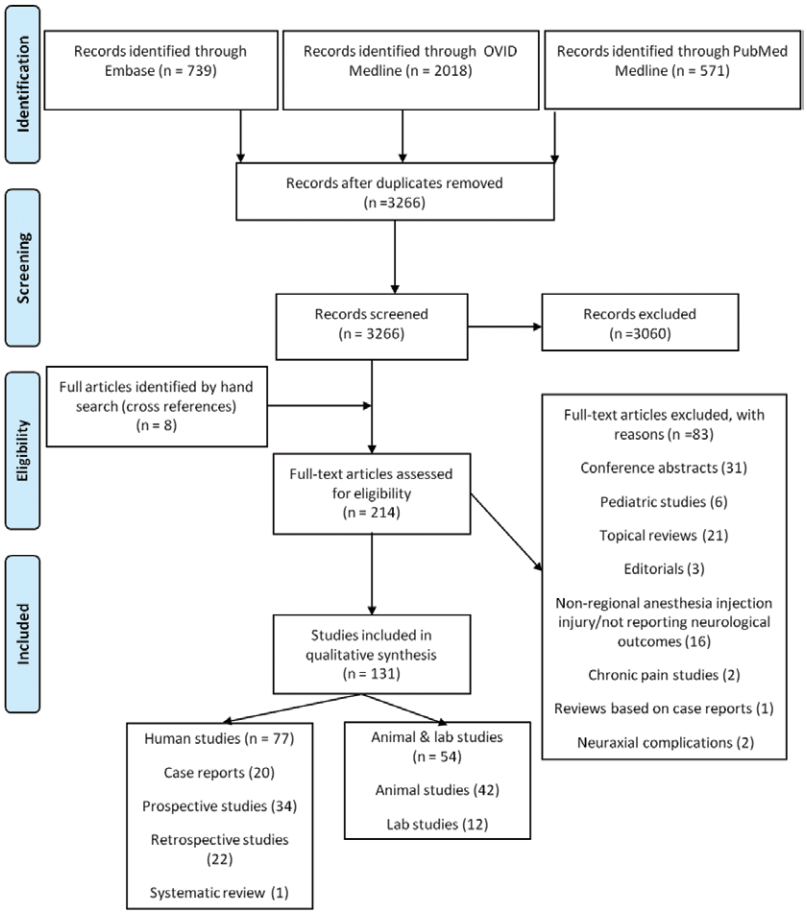

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Literature Selection

The full text of all articles obtained from the searches was retrieved for critical appraisal. Bibliographies of reviews and primary studies were examined to supplement the electronic search to ensure that no original research studies were missed. We included closed claims analyses, meta-analyses, systematic reviews, randomized controlled trials (RCTs), controlled studies without randomization, observational studies, retrospective studies, and comparative studies. Given the rarity of long-term neurologic dysfunction, case reports and case series reporting neurologic complications were also included for this review. Correspondence not reporting cases, pediatric studies, and conference abstracts with incomplete data sets was excluded.

Evidence Evaluation

Relevant full-text articles evaluating the risk factors of neurologic complications and the techniques intended to prevent them were separated based on literature type (human and animal studies) and subsequently reviewed independently in duplicate. The present review was limited to risk factors previously thought to be important for neurologic outcomes after regional anesthesia.[7–9] We followed the principles used by similar reviews based on observational studies and adapted a basic set of criteria for evaluating studies similar to those of the Agency for Healthcare Research and Quality (AHRQ) evidence reports.[23,24]

Data were extracted and entered into a database (MS Excel; Microsoft Corp., Redmond, WA). Methodological quality among the human studies short-listed for full manuscript review was summarized in an Excel spreadsheet listing the study design (observational, RCT, etc), study size, type(s) of blocks, outcome measures, definition and time point of neurologic assessment, selection and measurement bias, duration of follow-up, and any associated risks or confounding factors. The principles of the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) working group were used to summarize the quality of evidence for each factor (Table 1). According to GRADE recommendations, RCTs are given a "high" rating, whereas observational studies are given a "low" rating. Among non-RCT studies, we gave a "low" rating for prospective cohort studies, whereas retrospective cohort studies were downgraded along with case reports to a "very low" rating.

Ratings were further modified based on study design, internal and external validity of results, directness of evidence (ie, whether the study population was representative of the general population), and whether confounders were accounted for. One investigator (R.V.S.) assigned the ratings, which were reviewed by the other investigator (B.C.H.T.); any disagreement was discussed and resolved once a consensus was reached. For the purposes of classification, short-term neurologic assessment was defined as the point within 3 months after PNB when a neurologic evaluation was performed. Long-term neurologic assessment was defined as deliberate assessment performed more than 6 months after the PNB. Intraneural injection was defined for the purpose of the review as any injection performed beneath the outer epineurium[25] and any data relating to it were summarized separately.

Data Synthesis and Analysis

Many of the outcomes related to risk factor exposure and subsequent neurologic injury cannot be tested in a randomized fashion in humans as they can in animals because of obvious ethical concerns. For the purposes of this review, results from human and animal studies were summarized separately for each risk factor. Synthesizing study results was particularly challenging because reporting of neurologic injury was inconsistent. Neurologic injury can be inferred in a variety of ways in studies and may be simply based on the symptoms of persistent weakness, paresthesia, dysesthesia, or pain in the distribution of the nerve block or by objective measures such as electromyography and other nerve conduction studies.

Another issue in summarizing the data is the timing of assessment of neurologic function. It is well known that neurologic dysfunction can occur as early as the immediate postoperative period or may be delayed as much as 3 weeks after PNB.[26,27] However, reporting of such complications may not be rigorous enough to detect them at different time points in all studies. Given the large scope of the review and the methodological heterogeneity of the studies included for analysis, we did not summarize the data quantitatively but instead summarized the type of association indicated by the evidence as increased/decreased risk, inadequate evidence, or no consistent direction of association.

RESULTS

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. Eight additional articles identified from a manual search of references from relevant articles were included. Eighty-three studies were

Table 1. Levels of Quality of a Body of Evidence in the GRADE Approach

Underlying Methodology	Quality Rating
• Randomized trials or double-upgraded observational studies	High
• Downgraded randomized trials or upgraded observational studies	Moderate
• Double-downgraded randomized trials or observational studies	Low
• Triple-downgraded randomized trials; or downgraded observational studies; or case series/case reports	Very low
Factors that may decrease the quality level of a body of evidence	
• Limitations in the design and implementation of available studies suggesting high likelihood of bias	
• Indirectness of evidence (indirect population, intervention, control, and outcomes)	
• Unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses)	
• Imprecision of results (wide confidence intervals)	
• High probability of publication bias	

Abbreviation: GRADE, Grading of Recommendations Assessment, Development and Evaluation.

excluded based on the previous criteria, leaving 131 full-text articles for review (Figure 1).[1–6,10–12,14–19,22,26–143] We grouped the factors implicated in neurologic injury after PNB into 3 categories: patient/host factors, agent/injurious factors, and environmental/guidance-related factors. Table 2 summarizes the evidence of association between risk factors and neurologic outcomes based on human studies, whereas Table 3 summarizes the evidence from animal studies. To synthesize the evidence for each factor, we reviewed the combined observational, RCT, and case report evidence in humans and assigned an overall GRADE quality rating for each factor (Table 4). Because the majority of evidence for the risk factors was based on observational studies, the quality of the evidence for most factors was rated as low or very low. In the following section, we have summarized the key findings from human and animal studies; the sections following these summaries contain the results for each risk factor.

Evidence From Human Studies

There was inadequate evidence to associate most evaluated risk factors with neurologic injury (Table 1). The most consistent risk association was found for nerve block type, as confirmed by previous prospective cohort studies, retrospective database reviews, and 1 systematic review on the incidence of neurologic complications after regional anesthesia. Neurologic complications attributable to PNB were not further influenced by either the type of surgery or the use of particular guidance techniques (ultrasound [US] and nerve stimulation [NS]). Two cohort studies confirmed increased postblock neuropathy with long-bevel needles compared with short-bevel needles, as also noted in animal models. Evidence of association between neurologic complications and the use of continuous catheter blocks or intraneural injection was inadequate.

Six studies investigating unintentional intraneural injections, 4 using US and 2 using NS to guide block placements, reported that the incidence varied depending on the guidance technique and the type of block.[12,14–16,51,104] Among US studies, proximal sciatic nerve blocks had an incidence of unintentional intraneural injection of 16.3%,[12] which was comparable with the proximal brachial plexus block (15.5% for interscalene and 17.7% for supraclavicular approaches).[14] Femoral nerve block (9%–64%),[104] popliteal sciatic nerve block (76% with NS and 39% with US),[15,16] and median nerve block (43%)[51] all showed a high incidence of intraneural injection.

Evidence From Animal Studies

Animal studies evaluated the risk factors of needle design, bevel orientation, pressure injury, and LA/adjuvant-related neurotoxicity in a controlled fashion (Table 2). One study evaluated diabetic neuropathy and revealed slower nerve conduction velocity and longer block duration in affected animals. The inaccuracy of NS in differentiating intraneural from extraneural needle location was initially evaluated in animal models and subsequently in human trials. With regard to the accuracy of US, only 1 study compared the accuracy of US, NS, and a combined guidance technique.

RISK FACTORS FOR NEUROLOGIC INJURY AFTER PNB

Patient/Host Factors

Early regional anesthesiologists acknowledged the paradox of potential neurologic complications after PNB[13,152] and the lack of complications after deliberate needle–nerve contact.[153] Various anatomic, surgical, and patient factors may affect the incidence of postoperative nerve injury and include type of nerve block, type of surgery, associated comorbidities, presence of pre-existing neuropathy, and nonmodifiable risk factors.

Neural Architecture (Human Studies). Three studies assessed neural anatomy with relevance to PNB.[93,94,118] 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 (Figure 2). The epineurium—the outer covering of the nerve—encases the fascicular bundles within a connective tissue network known as interfascicular epineurium and provides cushioning for the fascicles. The fascicular bundle is 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 insults.[154] 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 perineurium maintains an intrafascicular pressure that is reflected in the intracellular pressure of the axons[155,156]; thus, injection deep to the perineurium generally requires greater injection pressure (IP) compared with injection within the epineurium.

The content of individual components was found to vary among different nerve types and also along a given nerve every 0.25 to 0.5 mm, and the branching pattern at any given site was inconsistent.[117] It was also noted from 2 cadaveric studies that, although individual fascicle size is inversely related to the number of fascicles at a given location along the nerve,[117] the connective tissue content and cross-sectional area of a nerve are directly proportional to it.[93,94] Although Moayeri et al[93] and Moayeri and Groen[94] noted a proximal oligofascicular pattern progressing to a polyfascicular pattern in the brachial plexus and sciatic nerve, Sunderland and Ray[118] noted a wide variation in the fascicular pattern of the sciatic and forearm nerves with no consistent pattern in any part of the nerve.

Nerve Block Type (Human Studies). The varied fascicular topography may place some blocks at a higher risk than others as evidenced by different incidences of neurologic complications associated with different nerve blocks. Prospective studies estimate the incidence of long-term neurologic injury after PNB in the range of 2.4 to 4 per 10 000 blocks,[1,19,26,27,42,44] whereas transient neurologic deficits lasting up to 2 weeks occur more frequently with an incidence varying between 8.2% and 15%.[3,86] The differential incidence for both short-term and long-term neurologic dysfunction was reported by 6 prospective and 5 retrospective cohort studies. Although the exact incidences differed for each block, some nerve blocks such as axillary brachial plexus, interscalene, femoral, and sciatic nerve blocks were

Table 2. Human Studies: Evidence and Grading

Factor (References)	Studies, n	Participants, n	Summary of Findings	Association With Neurologic Dysfunction (GRADE Eating)
Biologic/host factors				
Nerve anatomy[93,94,118]	3 cadaveric studies	…	• Intraneural fascicular topography has wide variability • Connective tissue content of a peripheral nerve varies depending on the number of fascicles at a given site • Neural connective tissue and number of fascicles increase proximally to distally	Inadequate evidence (very low)
Type of nerve block[1–6,19,26,27,42,44,110]	12 studies (1 systematic review, 6 prospective, and 5 retrospective cohort studies)	85,479	• Certain types of nerve blocks (axillary, interscalene, femoral, sciatic, and popliteal sciatic) have higher incidence of neurologic dysfunction compared with others • Procedure-induced paresthesia may increase the incidence of neurologic dysfunction • Transient neurological dysfunction after PNB is more common than long-term dysfunction and usually resolves with time	Increased risk with certain blocks (moderate) (The impact of US guidance from prospective studies in the future may impact our confidence in the estimate of the effect.)
Pre-existing neuropathy[18,33,39,41,57,61,79]	1 retrospective cohort study, 6 case reports	100 + 6 case reports	• Pre-existing neuropathy may not be worsened by PNB, but outcomes tend to be worse when neurologic dysfunction occurs in the presence of pre-existing neuropathy	Inadequate evidence (very low)
Age[144]	1 cadaveric study	1	• Connective tissue content increases with age, which may influence block onset and recovery	Inadequate evidence (very low)
Sex	…	…	…	…
Diabetes[37]	1 cohort study	39	• Diabetic patients require higher stimulation thresholds both outside and inside the nerve to elicit a motor response	Inadequate evidence (low)
Agent factors				
Type of surgery[26,27,42,66,67,119,136]	7 studies (3 prospective and 4 retrospective studies)	16 063	• PNB does not increase the risk of iatrogenic injury across a wide spectrum of surgeries	No association (moderate)
Needle design[36,99]	2 cohort studies	46	• No postoperative neurologic dysfunction was noted on injection with short-bevel needles (22 patients); with long-bevel needles, 4 of 20 patients had neurologic dysfunction lasting 3–12 months	Possibly increased risk with long-bevel needles (low)
Needle size	…	…	…	…
Bevel orientation	…	…	…	…
Intraneural injections (incidence of unintentional injections:[12,14–16,51,104] (deliberate intraneural injections:[37,103,105,123]) (case reports:[10,11,17,18])	12 studies (2 RCTs, 9 cohort studies, 1 cadaveric study); 4 case reports	1130 + 4 case reports	• Unintentional intraneural injections occur more often than previously expected • Deliberate or unintentional intraneural injection does not always result in neurologic dysfunction • Intraneural injections have a rapid block onset	Inadequate evidence of association (moderate)
Long-acting local anesthetics[78]	1 cohort study	2382	• No increased risk of neurologic complications with the use of long-acting local anesthetics in a variety of nerve blocks	No association (low)
Continuous catheter[3,6,18,28,33,39,44,50,60,96,97]	7 studies (4 cohort, 3 retrospective); 4 case reports	18 955	• Continuous catheters have been used safely with a low incidence of long-term nerve damage noted in some studies; other studies and case reports suggest a fairly high incidence of temporary nerve dysfunction	Inadequate evidence of association (low)
Adjuvants	…	…	…	…
Performance factors				
Neurostimulation[37,47,69]	3 studies (1 RCT; 2 cohort studies)	127	• Low-current nerve stimulation-guided blocks do not necessarily result in postoperative neurologic dysfunction	No association (low)

(*Continued*)

Table 2. Continued

Factor (References)	Studies, n	Participants, n	Summary of Findings	Association with Neurologic Dysfunction (GRADE eating)
Electrical impedance[32]	1 cohort study	140	• Nerves in diabetic patients require higher stimulating currents for both intra- and extraneural needle placement • An increase in electrical impedance (>4.3%) may indicate accidental nerve puncture during PNB	Inadequate evidence (low)
Ultrasound guidance[4,5,12,14,37,80,88,92,98,104,108]	11 studies (2 RCT; 9 cohort studies)	9900 + 3 studies evaluating human performance	• Ultrasound guidance can detect intraneural injection but is dependent on operator experience • Use of ultrasonography does not prevent intraneural injection • Neurologic complications after PNB have not declined as a result of ultrasound guidance	No association (moderate)
Pressure measurement[48,55,122,125,126]	5 cohort studies (only 1 cohort study for measurement of OP in clinical scenario)	16 + 3 studies evaluating human performance	• Syringe feel is inaccurate for differentiating tissues; high injection pressures are often generated unknowingly by both experienced and nonexperienced practitioners • Injection pressure can be kept within safe limits reliably by using compressed air injection technique or pressure measurement devices • Opening injection pressure can detect needle–nerve contact reliably in interscalene block	Inadequate evidence for prevention of neurologic injury (low)
General anesthesia[40]	1 retrospective review	548	• Long-term neurologic complications were not noted in this review of interscalene blocks performed under general anesthesia	Inadequate evidence of association (very low)

Abbreviations: GRADE, Grading of Recommendations Assessment, Development and Evaluation; OP, opening pressure; PNB, peripheral nerve block; RCT, randomized controlled trial.

deemed to be at a higher risk than others. This differential incidence was also confirmed by a meta-analysis of the incidence of neurologic complications after PNB.[19] Three prospective cohort studies also suggested that procedure-induced paresthesia may increase the likelihood of transient neurologic symptoms after PNB.[3,27,110] None of the selected studies reported association of neurologic dysfunction with age, sex, or body mass index, although 1 study noted an increase in the connective tissue content with age.[144]

Surgery Type (Human Studies). Several retrospective studies note that certain types of surgery[157–159] carry a higher risk of nerve injury, especially those involving excessive neural stretch,[160] trauma,[161] inflammation,[63] ischemia,[35] or prolonged tourniquet time.[67,162] This has also been acknowledged in the second American Society of Regional Anesthesia and Pain Medicine (ASRA) practice advisory on the neurologic complications associated with regional anesthesia.[163] The issue of whether or not PNBs increase the incidence of iatrogenic nerve injury was investigated in 4 retrospective[66,67,119,136] and 3 prospective studies.[26,27,42] In a retrospective review of 380,680 cases during a 10-year period, Welch et al[136] found a 0.3% incidence of iatrogenic injuries. There was significant association between iatrogenic injuries and certain types of surgery, general anesthesia, and epidural anesthesia, but not PNB. Borgeat et al[26] and Candido et al[27] noted the incidence of neurologic sequelae unrelated to surgery being 7.9% and 3.3%, respectively, 1 month after NS-guided interscalene block, although most of these problems were thought to be unrelated to the block. Retrospective reviews of total shoulder arthroplasty,[119] knee,[67] and hip[66] surgeries also noted no such association.

Neuropathy.

Evidence From Animal Studies: In diabetic rats, conduction velocity is slower, and LAs produce a longer mean duration of sensory nerve block.[70,81] Although some animal models suggest neuronal damage from extraneurally placed LA,[70] others suggest no increased susceptibility.[81]

Clinical Evidence: Most regional anesthesiologists tend to avoid performing PNB in patients with neuropathic pain, although a retrospective cohort study[61] failed to demonstrate worsening of neurologic outcomes after axillary brachial plexus block in patients with pre-existing neuropathy. However, data from case reports[18,33,39,41,57,79] suggest that either subclinical or overt pre-existing neuropathy may render these patients susceptible to long-term nerve damage. Expert opinion regarding regional anesthesia in patients with neurologic disease therefore tends to err toward caution.[7,8] The degree of neural dysfunction in a chronically compromised nerve may be clinical or subclinical, and any secondary insults such as hypoxia or ischemia, LA neurotoxicity, or direct mechanical trauma is thought to exacerbate it.[7] Importantly, the secondary insult need not be at the site of the neural compromise itself, a phenomenon known as "double-crush syndrome."[164] In fact, a double-crush injury in the form of 2 distinct low-

Table 3. Evidence From Nonhuman Studies

Factor (Reference)	Studies, n	Key Findings
Mechanical injury		
Needle design[22,36,62,90,91,99,101,106,114]	8 animal and 1 cadaveric study	• Nerve trunks usually slide under an advancing short-bevel needle compared with long-bevel needles • Long-bevel needles cause more functional or histologic damage compared with short-bevel, pencil-tip, or Tuohy needles, but superiority among the latter 3 types is currently unknown • When short-bevel needles penetrate the perineurium, the resulting nerve damage is greater than that caused by long-bevel needles
Needle size[113]	1 animal study	• Needle gauge may influence the degree of damage irrespective of needle type
Bevel orientation[22,62,90]	3 animal studies	• The amount of damage is greater when the needle bevel is perpendicular to nerve fibers than when it is parallel
Pressure injury[22,34,59,75,111,132,133]	7 animal studies	• Perineural, followed by extrafascicular, injection requires the lowest injection pressure; intrafascicular injections generate high injection pressure • Although high injection pressures result in functional and histologic nerve damage, intraneural injection with low injection pressures may not necessarily result in nerve damage.
Peripheral neuropathy[70,81]	2 animal studies	• Animal models have shown that conduction velocity is slower, and local anesthetics produce a longer mean duration of sensory nerve block in diabetic versus nondiabetic rats • Although some animal models suggest neuronal damage from extraneurally placed local anesthetic, others suggest no increased susceptibility
Local anesthetic neurotoxicity[38,43,53,56,65,70–74,81,89,95,109,128,137,140–142,145–151]	21 studies	• Both extra- and intrafascicular injection of local anesthetic can result in histologic damage, but it is far greater after intrafascicular injection • All local anesthetics are neurotoxic in increasing concentrations, and individual local anesthetics differ in their neurotoxic potential • Both epinephrine and local anesthetics decrease neural blood flow, and their combination has synergistic effects • Local anesthetics are more neurotoxic than adjuvants; although some adjuvants may have neurotoxic potential, others may be neuroprotective
Accuracy of guidance techniques		
Nerve stimulation[29,45,102,124,131,139]	6 studies	• When used at low currents, nerve stimulation has low sensitivity but high specificity for detecting proximity of the needle tip to the target nerve • Nerve stimulation cannot differentiate between intraneural needle placement and needle–nerve contact • Higher stimulating currents are required in diabetic individuals for detecting intra- and extraneural needle placement
Ultrasound[130]	1 study	• Combined technique has better accuracy and lower incidence of intraneural injections compared with individual techniques alone

grade insults has been shown to be more damaging to the nerve compared with an insult at a single site.[165]

Causative Agents

Nerve injury can result from mechanical trauma (direct needle trauma, pressure injury) or chemical insults (LA and adjuvant neurotoxicity). Because of logistic and ethical reasons, most of the direct evidence regarding causative factors for neurologic dysfunction emanates from research on animals and human cadavers. Evidence on intraneural injections is probably the most relevant clinical evidence from human trials regarding the impact of noxious agents on subsequent nerve function.

Mechanical Agents

Needle Trauma.

Evidence From Nonhuman Studies: Eight animal studies and 1 cadaveric study evaluated the impact of needle design on nerve injury (Table 3), which was further confirmed in 2 human studies.[36,99] Using cadaver tissue, Sala-Blanch et al[106] showed that, although fascicular contact is fairly common with intraneural needle entry, injury to the fascicles rarely occurs. The degree of nerve damage from needle trauma depends on bevel type, angle of needle insertion, and needle size (gauge).

Long-bevel (14° angle) needles have a tendency to penetrate fascicular bundles through the perineurium and

therefore have a greater chance to cause nerve injury, but fascicles slide under or away from short-bevel (45° angle) needles.[22] Of 134 fascicles contacted by the needle in the study by Sala-Blanch et al,[106] only 4 were damaged and all by long-bevel needles. The amount of nerve damage after intraneural needle placement is also higher when the bevel is inserted transversely to the nerve fiber compared with insertion along the long axis of the nerve.[22,62,90]

When neural damage from other needle designs is considered, animal studies have shown that needles with tapered ends such as Whitacre and Sprotte needles are comparable with each other[90] and with Tuohy needles.[90,113,114] These tapered-tip needles have also shown to be comparable with short-bevel needles in terms of neural damage.[62,90,115] 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 22-G needles (3%) and 17- and 18-G needles (40%).[113]

In general, short-bevel needles have become preferred for PNB because they have trouble penetrating the perineurium and result in a lower incidence of related neural injury; however, when they do penetrate the perineurium, the amount of mechanical trauma far exceeds that from a long-bevel needle.[101]

Clinical Evidence: In humans, the evidence for greater nerve damage from long-bevel needles comes from 2 studies on axillary brachial plexus blocks. When deliberate intraneural injections were performed using short-bevel needles, no immediate postoperative neurologic dysfunction was noted,[36] whereas 4 of 20 patients had neurologic dysfunction lasting 3 to 12 months.[99]

Pressure Injury.

Evidence From Nonhuman Studies: Two important pressures to monitor when performing a PNB are the opening pressure (OP) and IP. The OP is the pressure in the needle-tubing-syringe assembly before the injectate begins to flow through the needle, whereas the IP is the pressure required to maintain the flow of injectate after it is initiated. Seven animal studies evaluated IP during PNB.[22,34,59,75,111,132,133] In 1 rat model, low IPs (<25.1–27.9 kPa) were noted for injections performed around the nerve without penetration of the outer epineurium, whereas IPs increased slightly (69.8–86.5 kPa) on entering the epineurium.[132,133] In another rabbit model, the subepineurial IP (3.3–7.9 kPa) was then shown to drastically increase once the needle entered the fascicles (39.9–99.7 kPa).[111] It was also shown in rabbit sciatic nerves that intrafascicular injections resulted in rapid spread of injectate over long distances within the fascicle.

Corollary to this finding, a study by Hadzic et al,[59] looking at intraneural injections in the canine sciatic nerve, showed that 4 of 7 intraneural injections performed with high IP (>25 psi) displayed axonolysis, demyelination, and cellular infiltration indicative of intrafascicular injection, whereas those with low IP (<4 psi) were confirmed as being extraneural. The neurologic consequences of pressure injury were also studied by Kapur et al[75] who showed that intraneural injections with high OP (8/20) commonly resulted in clinical deficits, whereas the remaining low-pressure

Table 4. Summary of Findings for Risk Factors and Neurologic Injury After Peripheral Nerve Blockade

Direction of Association of Factors	Quality of Evidence
Increased risk	
Type of nerve block	Moderate
Procedure-induced paresthesia	Moderate
Needle design	Low
Decreased risk	
None found	…
No association	
Type of surgery	Moderate
Ultrasound guidance	Low
Neurostimulation guidance	Low
Long-acting local anesthetics	Low
No consistent association	
Intraneural injections	Low
Continuous catheters	Low
Inadequate evidence	
Anatomical factors	…
Age	…
Sex	…
Diabetes	…
Pre-existing neuropathy	…
Needle size	…
Bevel orientation	…
Injection pressure monitoring	…
Electrical impedance	…
Performance under general anesthesia	…

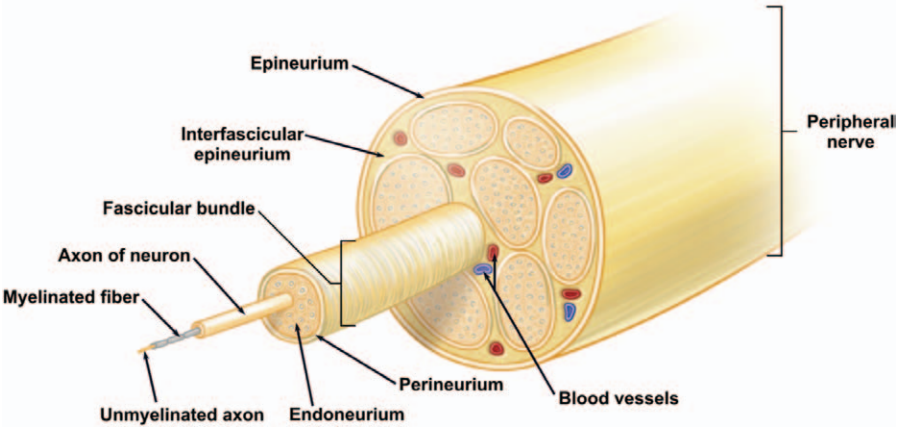

Figure 2. Schematic cross-section of a peripheral nerve (Adapted and reproduced with permission from Springer).

intraneural injections (12/20) did not result in any neural dysfunction beyond 24 hours. However, whether the high IP resulted from intrafascicular injections was not confirmed by the study. A separate porcine study also found a lack of functional deficits with low-pressure intraneural injections (<15 psi) all confirmed to be extrafascicular; however, it did note that the nerves showed signs of inflammation for up to 2 days postinjection and changes in nerve architecture under US for up to 4 days.[34]

Pressure injury can result even in the absence of direct neural trauma, as shown in an animal study in which the presence of perineural hematoma itself resulted in inflammation and structural injury to the nearby nerves.[116]

Clinical Evidence: There is some evidence from a human study showing that low IP during deliberate intraneural popliteal sciatic nerve block does not necessarily lead to early postoperative neurologic dysfunction.[103] Nonetheless, further studies of IP and perineural pressure in clinical practice are needed. The utility of pressure measurement techniques is covered in the discussion of guidance techniques.

Neurotoxicity.

Evidence From Animal Studies: Using different animal models, 21 studies evaluated LA neurotoxicity, and 4 studies evaluated adjuvant toxicity. Broadly, the studies looked at the comparative neurotoxicity of different LA solutions with or without adjuvants[53,56,109,137,141,142] and the impact of topical application[38,43,70–74,95,128,140,166] or intraneural injection of LA.[53,56,65,81,89,109] Intraneurally injected LA may result in histologic changes without any functional neuropathy.[65,81,89] Although there is evidence regarding an increased amount of nerve damage after intrafascicular LA compared with topical application,[109] whether this damage is because of mechanical injury or LA neurotoxicity is currently unknown because intrafascicularly injected saline and LA produced comparable neuronal damage in an animal model.[53,109]

All LAs exhibit neurotoxic potential,[167] but some may be more neurotoxic than others.[53,56] The neurotoxicity of LAs 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.[145–147] Transient neurologic symptoms after spinal anesthesia are thought to represent a mild consequence of LA neurotoxicity[148]; and possibly transient neurologic symptoms after PNB represent a similar situation, in which small-diameter axons (carrying pain and temperature sensation) are more susceptible to the toxic effects of LAs than large-diameter axons (carrying motor and proprioception impulses). Another important consequence of LA administration is its effect on neuronal blood vessels. This differs depending on the animal model and study methodology, but in general most LAs have vasoconstrictive properties (excluding bupivacaine).

In summary, LAs are thought to cause nerve dysfunction through a combination of direct neurotoxicity and vasoconstriction of vessels responsible for neuronal blood flow. The neurotoxic potential of LAs far exceeds that of any adjuvants used in regional anesthesia,[140,141] and the isolated effects of the adjuvants on nerve tissue depend on the individual agent.[128,149] Although adjuvants such as opioids, clonidine, dexamethasone, and neostigmine do not influence the neurotoxic potential of LAs in vitro, drugs such as ketamine and midazolam may themselves be neurotoxic at higher doses. Dexmedetomidine was shown to be neuroprotective in rats after intraneural sciatic nerve injection, possibly by decreasing the neurotoxic potential of bupivacaine at the site of injury.[128]

Clinical Evidence: Animal and in vitro models suggest that the neurotoxic effect of LAs is time- and concentration-dependent,[142] but whether this holds true in human subjects is unknown. Although long-acting LAs[78] and catheters for continuous nerve blocks[6,44,50] have been used safely with a low incidence of long-term nerve damage, some catheter studies[3,60,96,97] (reported incidences of 0.2%–1.9% for symptoms lasting >6 months) and case reports[18,28,33,39] suggest a higher incidence of temporary nerve dysfunction after continuous PNB. As noted by Capdevila et al,[44] use of bupivacaine infusion, intensive care unit stay, and age <40 years were all associated with long-term neuropathy, whereas continuous catheter technique was associated with a low overall incidence of long-term neuropathy. Further prospective studies are needed to clarify the safety profile of prolonged exposure of nerves to different concentrations of LA.

Intraneural Injections in Clinical Practice. Intraneural injection probably represents the best clinical evidence for the combined impact of the 3 injurious agents of needle trauma, pressure injury, and LA neurotoxicity. The results from 6 clinical studies[12,14–16,51,104] and 1 cadaveric study[98] showed that unintentional intraneural injection occurs frequently in both upper and lower limb blocks. Only 5 studies investigated the effects of deliberate intraneural injection.[37,103,105,123] In each, US was used to identify intraneural injection, and 1 study used NS in addition to US.[103] A 10% incidence of transient neurologic deficit was observed in one study,[37] whereas another study evaluating deliberate intraneural injections performed under US versus NS showed an increased success rate with US but a higher incidence of paresthesia.[108] None of the studies except the 1 utilizing long-bevel needles revealed any increase in neurologic complications during follow-up (1–4 weeks after the procedure), highlighting the impact of needle design on neurologic outcomes.

Intraneural injections were also shown to hasten block onset,[12,15,16] improve block success,[123] and in animal models prolong the block duration.[75] Irrespective of unintentional or targeted intraneural injections using either low current NS or US guidance, none of the trials except 1 reported long-term postoperative neurologic dysfunction related to PNB.[12,15,16,36,37,103–105,123] It is also to be noted that the follow-up period in some of these studies was not long enough to allow symptoms to develop, and many of the studies were not sufficiently powered to assess the incidence of neurologic dysfunction or nerve injury. However, evidence of injury as a result of intraneural injections that comes from case reports indicates that such injections are not without risks.[10,11,17,18] Hence, it cannot be recommended as safe practice to perform deliberate intraneural injections until data

from larger studies are available. Although the reviewed literature showed a decreased incidence of intraneural injections with US guidance studies, whether this is true in clinical practice needs to be confirmed with well-designed prospective studies.

Environmental Influences

Guidance techniques for performing PNB have evolved over time from landmark-based techniques to NS and US guidance. Most of these techniques aim at improving the accuracy and success rate of PNBs, but few studies have evaluated their ability to improve block safety. The decrease in LA systemic toxicity with use of US guidance is well known,[2] but neither prospective database studies nor retrospective reviews have been able to demonstrate a decrease in the incidence of long-term neurologic dysfunction after PNB.[2,4–6]

Nerve Stimulation.

Evidence From Animal Studies: In animal studies, low stimulating current requirements (<0.2 mA) have been suggested to correlate with histologic evidence of nerve injury (50% incidence), whereas current intensity >0.5 mA implied extraneural placement.[131] This has led to the popular practice, whenever a motor response is elicited at a stimulating current <0.2 mA, of deliberately withdrawing the needle until stimulation is obtained at currents between 0.2 and 0.5 mA. Despite this, it is important to point out that several subsequent studies have shown the inaccuracies of NS in predicting needle tip location at both low and high current stimulation.[29,45,124,131] A minimum stimulating current of <0.2 mA was a specific, but not sensitive, indicator of intraneural needle placement, given that extraneural injection occurred even with low current stimulation (50% incidence).[131] However, higher stimulating currents are sometimes needed to elicit a motor response after intraneural needle placement.

Recently, Wiesmann et al[139] showed that a low stimulating current may indicate either needle–nerve contact or intraneural placement, suggesting that low currents cannot differentiate between the 2 locations. The noncorrelation of needle tip location and NS is because of a variety of factors influencing motor response after stimulation. The stimulating current is influenced by pulse width, interaction of the needle tip with the fascicles, and the degree to which depolarization or hyperpolarization occurs as a result of the stimulating current.[150,151] The minimal stimulating current for each nerve is therefore different,[107] and a single value cannot be extrapolated for all nerves.

A demyelinating neuropathy because of any systemic or local cause may increase the minimum stimulating current for the nerve. This implies that, unlike nonneuropathic nerves, a current higher than 0.2 mA will be required to differentiate intraneural from extraneural needle location. The supporting evidence regarding this concept was seen in a diabetic neuropathy model where higher stimulating currents were required to differentiate intraneural from extraneural needle location. When a low stimulation threshold was used to guide a needle in hyperglycemic animals, all injections were intraneural, whereas none of the low current stimulation injections in normoglycemic animals had the same pattern of injectate dispersion.[102]

Clinical Evidence: Specificity of intraneural needle location with low current stimulation was confirmed in a human study using noninsulated needles. A median (range) stimulating current of 0.17 (0.03–3.3) mA was used when a paresthesia was obtained deliberately.[47] Other clinical studies documenting the inaccuracy of NS in differentiating intraneural from extraneural injections were reported when insulated block needles were used.[47,103] Low stimulation currents have been used for sciatic nerve blocks[69] and infraclavicular blocks[76] without evidence of nerve damage. This is similar to findings in studies on deliberate intraneural injections.

One human study has shown agreement with the diabetic animal model tested for NS. A significant number of diabetic patients undergoing supraclavicular brachial plexus block required a higher stimulation current when the needle was placed perineurally (57% required currents >1.0 mA vs 9% nondiabetic) and intraneurally (29% required currents of 0.5–1.0 mA vs 2% nondiabetic).[37]

IP Monitoring (Human Studies Only). Simple "syringe feel" is inaccurate in determining what tissues the performer is injecting into, irrespective of operator experience.[122] In an animal model, only 12 of 40 anesthesiologists (30%) identified intraneural injection correctly using "syringe feel."[122] Anesthesiologists vary widely in their perception of IP and the speed of injection. In a study of 30 anesthesiologists performing simulated injections in a laboratory model, a 20-fold variability in baseline IP and speed of injection was noted. When resistance was increased gradually in a blinded fashion during injection, 70% of anesthesiologists exceeded the recommended IP of 20 psi.[48,126]

The inaccuracy of "syringe feel" and a wide variability in baseline perception of the performer have led to the development of objective methods and devices to monitor IP during PNB performance. These include the compressed air injection technique (CAIT)[125,126] and B.Braun's BSmart IP monitor (B. Braun Melsungen AG, Hessen, Germany). 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 on injection. In vitro evaluation of this technique has been shown to ensure IPs substantially below the threshold considered significant for nerve injury when the air compression was ≤50% of the original volume, irrespective of the needle or syringe type. Currently, the impact of CAIT on clinical outcomes is unknown. Recently, the use of the BSmart device in patients (n = 16) undergoing US-guided interscalene brachial plexus block consistently (97%) showed an OP of ≥15 psi at the time of needle–nerve contact.[55] Overall, the value of using IP monitoring to avoid intraneural needle placement is contentious because it may not readily differentiate between extrafascicular and extraneural injections, whereas high IPs can be caused by contact with fascia, tendon, or bones. Furthermore, needle tip pressure may be dependent on the needle–syringe combination.[151]

Ultrasound. US can be useful for detecting and avoiding intraneural needle placement but is not foolproof in preventing intraneural injection. Currently available US 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 LA within the epineurium on proximal-to-distal scanning, and real-time visualization of fascicle separation on injection. It is important to note that if any of these signs are observed on US, intraneural injection has already occurred.

Evidence From Animal Studies: Needle guidance methods were evaluated for accuracy in placing a needle tip close to a nerve using an animal model.[130] The needling and subsequent injections were performed using NS (0.3–0.5 mA), US (placing the needle tip as close to the target nerve as possible), or combined US + NS guidance. With a combined technique, the accuracy of needle tip placement at the desired point was 98.5%, whereas the incidence of intraneural injection was 0.5%. The respective percentages with US alone were 81.6% and 4%, and NS alone was 90.1% and 2.5%, respectively.

Clinical Evidence. The occurrence of unintentional intraneural injections during US-guided PNB has been noted frequently in both cadaveric studies[98] and the clinical setting[12,14,36,104] and is most likely because of the lack of practitioner's expertise in detecting needle tip location and at times because of patient body habitus or needle trajectory. In a study of intraneural injection by novices and experts and using nerve cryosections as the reference standard, 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.[80] Although Bigeleisen et al[37] showed that intraneural needle tip placement was detected reliably in only 69% of cases, surrogate markers of intraneural injection (eg, increase in cross-sectional area of nerve) can detect intraneural injections reliably (94%) with experience.[92,105] Ruiz et al[104] evaluated whether an in-plane (INP) approach to femoral nerve block was better than an out-of-plane (OOP) approach for avoiding needle–nerve contact and intraneural injection. The investigators noted a higher incidence of intraneural injections with an OOP approach (64% vs 9% IP); however, these results may be inconsistent with other studies because the definition of intraneural injection used in this study was the presence of LA below the nerve rather than visualization of intraneural needle tip or injectate placement on US. Combined with the lack of evidence from other types of PNBs, these results suggest that further study is needed to conclude with certainty that OOP approaches increase the chance of intraneural injection.

Orebaugh et al[4,5] investigated whether the use of US has led to a decrease in PNB-related neurologic complications. In both retrospective reviews, no differences in long-term neurologic complications were found between blocks performed under NS or US guidance. An update in 2012 showed that the incidence of nerve injury lasting 6 to 12 months was significantly higher with NS alone (4/5436) compared with US guidance (1/9069), but no significant difference in the incidence of long-term injuries (>1 year) was reconfirmed. These findings are supported by a prospective study by Liu et al.[88] Although the underlying reason(s) for failing to observe a reduction in complications despite the increasing use of US in regional anesthesia practice is unclear, it may be 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 US.

Lessons From Case Reports. Case reports identified by our search help to shine a light on factors related to neurologic complications after PNB (Supplemental Digital Content 2, Appendix B, http://links.lww.com/AA/B599). Twenty-one case reports/series reported the occurrence of neurologic complications in 24 patients. Most patients were middle-aged (median 50.5 years) and included 12 males and 12 females. The most common presentation was usually either a combination of persistent sensory and motor deficits (9 cases) or pure motor weakness (9 cases), whereas pure sensory deficits were rare (3 cases). Four patients had catheters placed, whereas the rest received single-injection blocks. Recovery of normal nerve function failed to occur in 12 patients, whereas the remainder experienced recovery ranging anywhere from 1 week to 2 years. In 11 cases, NS was used, 5 used US guidance, 5 used a landmark/paresthesia technique, 1 used a combined US + NS technique, and 1 case did not document the guidance method used. Signs of intraneural injection were observed in 4 of the reports. The collective results show that both healthy patients and those with some form of subclinical or overt neuropathy (5/24 patients) are susceptible to neurologic complications. Presence of risk factors may be a prognostic sign because only 2 of the 5 patients with pre-existing neuropathy had recovery of some nerve function after a prolonged period of time.

DISCUSSION

This is the first systematic review to summarize the evidence regarding factors associated with neurologic injury after PNB using an epidemiologic approach. Among the many risk factors and guidance techniques reviewed, few human studies possessed sufficient evidence from which firm conclusions could be drawn about their association with neurologic outcomes. The evidence for many of the risk factors was drawn mainly from animal studies. Like other systematic reviews of diseases arising from complex interactions between multiple risk factors,[23,168] neurologic injury after PNB may be best appreciated in the context of an epidemiologic triangle consisting of patient factors, causative agents, and environmental influences.

The epidemiological triangle (Figure 3) is a common injury model used to describe the relationship between an agent, a host, and the environment.[169,170] In this review, a complex interaction was noted to exist among the patient, injury (causative agent), and practice conditions (environment). The final event, the development of disease in conditions with multiple risk factors, is the result of a chain of interactions. The individual risk factors present in this chain are themselves either contributory or necessary for the outcome to occur.[21] Although we have classified the relevant risk factors for neurologic complications as being specific to the host, agent, or environment, whether each individual risk factor is just contributory or is necessary for event

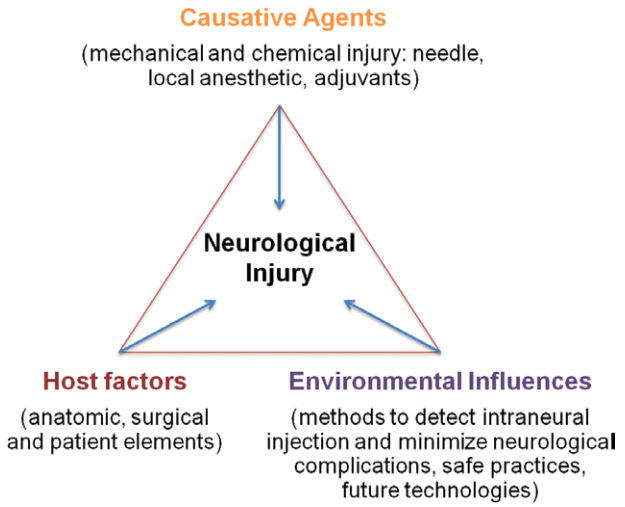

Figure 3. Epidemiologic triangle demonstrating relationship among causative agents, host factors, and environmental influences on neurologic injury.

causation needs to be determined in the future. Hence, the safest approach appears to be identification and prevention of all potential risk factors.

Risk factors we evaluated in humans included biologic and comorbidity factors (neural anatomy, pre-existing neuropathy, type of nerve block, age, and diabetes), agent factors (needle design, type of surgery, intraneural injections, long-acting LAs, and continuous catheter blocks), and environmental factors (NS, US, electrical impedance, and IP measurement). The impact of the cardinal agents of injury such as mechanical trauma, LA neurotoxicity, and pressure injury were assessed directly in animal studies, but their impact could only be inferred from human studies. It is important to point out that this model is not without limitations; it can be argued as oversimplifying a complex interaction. Indeed, in certain contexts, host and agent may not be totally isolated entities but can both be considered part of the environment. However, despite these limitations, the epidemiologic triangle model, in this context, may help the reader appreciate the complexity of interacting factors that determine how clinical or subclinical outcomes relate to PNBs.

Among the 35 prospective studies reporting short-term assessment, a wide variability in the time of assessment was found, ranging from 24 hours to 6 weeks postblock, whereas 2 studies failed to mention the assessment period entirely (Supplemental Digital Content 2, Appendix B, http://links.lww.com/AA/B599). Few studies aimed to examine long-term neurologic sequelae.[3,26,27,36,37,42] More commonly, patients who had persistent symptoms were referred to neurology for assessment and management either by the investigators or by the surgical team. Retrospective studies identified neurologic complications based on neurology referral or by documentation in medical records. Unsurprisingly, we found wide variability in the reported incidences of neurologic dysfunction irrespective of the study design or nerve block, likely because of variability in the definition of the reported outcomes. In general, retrospective studies reported lower incidences compared with prospective studies. Methods to detect neurologic dysfunction varied across studies, but typically included symptomatology such as pain, persistent paresthesia, dysesthesia, motor weakness, and/or definitive tests such as electrophysiological studies.

Limitations and Future Directions

The most apparent limitation that impacted our analysis was the lack of prospective, controlled studies using live humans to assess such risk factors as pressure injury and deliberate subepineural injection. However, obvious ethical concerns preclude carrying out these studies and limit them to animal or laboratory models. As such, we may never be able to obtain high-quality, clinically useful evidence regarding the interplay between intraneural injection and nerve injury, instead relying on retrospective studies and the occasional case report to provide information about this association.

Another major limitation of our review is the inherent inconsistency among the studies included in our analysis. An a priori hypothesis for risk factor exposure and neurologic injury was not present in many studies, and most were not adequately powered to look for this outcome measure. In the studies we reviewed, nonstandardized definitions and time periods for the assessment of neurologic function made comparisons across studies difficult. Another issue was that the type and degree of exposure was not validated for many of the risk factors. We therefore chose to perform a qualitative review, given the clinical diversity and methodological heterogeneity among the studies recovered by our search. As such, our review was not designed to compare effect size estimates for each risk factor.

By excluding gray literature such as conference abstracts with incomplete data sets, we may have missed some important evidence on these risk factor associations. Systematic reviews evaluating complex diseases, including observational studies, often unknowingly evaluate the association between overall exposure and outcome rather than between a single risk factor and neurologic recovery. The best example for this is intraneural injection, in which analysis in an individual study is not specific to 1 or 2 risk factors but to global neurologic outcome. Most retrospective studies failed to comment on temporary injury; such recall bias, which is inherent to retrospective studies, might have influenced our conclusions. Finally, although our search strategy is similar to that used for other systematic reviews of neurologic complications, we may have overlooked relevant studies unknowingly, given the complexity of the topic and the nature of disease causation.

CONCLUSIONS

In conclusion, improvements are needed in the reporting of neurologic complications after regional anesthesia. Standardized definition and time points for identifying these outcomes will help to identify incidence rates and quantify the problem more accurately for different PNBs. Well-designed observational studies and RCTs evaluating neurologic outcomes are needed. The association between PNB and neurologic complications is difficult to analyze in the context of various confounding factors inherent to the patient population, surgical technique, and PNB approaches.

Neurologic injury seems to result from a complex interplay among host (patient) factors, environmental factors (regional anesthesia tools and methods), and causative agents (mechanical and chemical). Many of the factors responsible for neurologic complications are nonmodifiable, meaning that screening for at-risk patients is necessary. Although the ideal goal is to place a needle outside the epineurium but as close to the nerve as possible, unintentional intraneural injections occur frequently during NS- and US-guided PNB yet may not necessarily lead to nerve injury. Previous animal and human research has shed light on potential risk factors, but future research should adapt rigorous scientific methodologies to identify and stratify the various risk factors important for neurologic outcomes. Study designs and statistical methods addressing the multiplicity of sources, difficulties in data collection, and variation in statistical analyses may improve the evidence regarding important risk factors for neurologic complications after PNB.

DISCLOSURES

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Contribution: This author helped analyze the data and prepare the manuscript.
This manuscript was handled by: Honorio T. Benzon, MD.

ACKNOWLEDGMENTS

The authors thank Dr. Gareth Corry for assistance with manuscript preparation and Ms. Brianne McConnell for the help with the literature search.

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