Local anesthetics: New insights into risks and benefits

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Introduction

Regional anesthetic (RA) techniques are increasingly advocated in the perioperative management of ambulatory surgery. Promising evidence shows that RA (i) leads to a reduction in the amount of opioid consumption, thus decreasing post-operative nausea / vomiting (PONV), and (ii) improves pain relief. Considering that pain and PONV are the top two reasons for prolonged hospitalization or re-hospitalization after ambulatory surgery, the use of regional techniques is likely to continue to rise for the foreseeable future. Moreover, recent evidence has widened the spectrum of use of RA blocks into the post-discharge period. As the indications for regional anesthesia and analgesia procedures in ambulatory surgery increase, and the contemporary boundaries of patient selection are pushed further outward, an increasing number of ambulatory surgery patients will present for RA with substantial comorbidities, including neurologic disease.

Neuropathies are a heterogeneous group of neurological conditions secondary to genetic, inflammatory, metabolic, or mechanical injury of nervous tissue. Their relevance in the perioperative management for ambulatory surgery lies, to a large extent, in the deliberation of whether to include a regional technique in the anesthesia plan. This becomes especially important in the case of patients suffering from long-standing diabetes mellitus (DM), whose occurrence in daily practice is projected to rise steadily, and who are often affected by diabetic peripheral neuropathy (DPN). Intuitively, it would seem logical that preexisting metabolic or structural neural defects increase the risk of nerve damage after RA. For decades, anesthesiologists have cautioned against RA in patients with preexisting neural disease. The widely accepted notion by Selander et al. that every nerve block entails a certain degree of (reversible) neuronal injury would lend support to this theory. However, current literature does not give definitive answers.
The aim of this review is to review the pathogenesis and incidence of nerve injury, to discuss implications of preexisting neurological disease upon the occurrence of nerve injury in the context of RA, and to describe strategies that may minimize the risk of iatrogenic aggravation of a preexisting neuropathy.

Nerve Injury during RA

Nerves are exposed to multiple risks during RA from the converging effects of local anesthetic (LA) pharmacology, technical aspects of nerve block, patient factors, and surgical factors (e.g., tourniquet). Only a minority of nerve injuries are caused by direct solitary mechanical trauma sufficient to damage a nerve permanently (e.g. intraneural injection).

Often, the toxicity of LAs and adjuvants is directly implicated in nerve injury, and a large body of literature supports the notion that LAs are directly neurotoxic. In cell cultures, dose- and time-dependent elicitation of cell death from LAs is observed, while in animal models, signs of nerve damage are evident even at clinically relevant doses. In patients, application of LA during nerve block results in very high concentrations of these drugs in target tissues, resulting in disruption of calcium signaling, triggering a cascade of events leading to programmed cell death. A plethora of contributing events has been investigated, some providing a potential link to preexisting neuropathy. For example, lidocaine selectively activates the pro-apoptotic p38 mitogen activated protein kinase in primary sensory neurons, causing neurotoxic effects. The same pro-apoptotic pathway is activated in neurons during DPN, while its inhibition diminishes the functional impact of neuropathy. It is thus conceivable that lidocaine is more toxic in nerves that are already prone to apoptosis owing to activation of the same deleterious pathway by both neuropathy and LA. This concept would, on a molecular level, be in analogy with the “double-crush hypothesis”, which states that preexisting injury of a
neuron leads to a supra-additive effect of a second injury harming the same nerve.\textsuperscript{18}

LAs can also damage nerves by interrupting blood flow, owing to vasoconstrictive properties of anesthetics such as lidocaine and bupivacaine.\textsuperscript{14} Direct mechanical damage by laceration of the perineurium leads to a disruption of the blood-nerve barrier and nerve edema.\textsuperscript{14} However, it is thought that permanent nerve damage is unlikely unless needle penetration is followed by intraneural injection of LA. Structural examinations show that injection of saline produces no long-lasting pathologic changes.\textsuperscript{19} Recently, it has been suggested that intraneural injection may not be necessarily harmful,\textsuperscript{20} and it would seem that nerve anatomy is supportive of this notion. Peripheral nerves are composed of nerve fibers as well as abundant amounts of connective tissue, especially at regions where nerves are exposed to mechanical and shear stress, such as across joints, so, a needle may pierce a nerve without damaging neural structures.\textsuperscript{14, 21} Nevertheless, it must be recognized that for commonly used LAs, toxicity is most likely influenced by the time and concentration of exposure of the peripheral nerve to the LA.\textsuperscript{14} Intraneural injection prolongs the exposure and increases the concentration of LA, and may reduce intraneural blood flow. Because of the potential risk of injuring nerve fibers upon intraneural needle placement and subsequent injection of LA, we believe the safest option is to avoid intraneural needle placement during anesthetic injection procedures. This concern particularly applies to neuropathic nerves.

Nerve injury can also be a consequence of general anesthesia (GA),\textsuperscript{22, 23} sedation,\textsuperscript{24} or surgery \textit{per se}.\textsuperscript{25} For example, after shoulder surgery, interscalene block is a less frequent cause of postoperative neuropathy than surgical factors.\textsuperscript{25} The term “coincident injury” describes an injury occurring during nerve block which is unrelated or only indirectly related to RA.\textsuperscript{26} One example is neuropathy caused by tourniquet inflation during total knee arthroplasty.\textsuperscript{27} RA is perhaps
more conspicuous than surgical events as a risk factor for nerve injury in the perception of patients and surgical colleagues, such that any injury evident after surgery during which RA was used is often, perhaps incorrectly, first attributed to the nerve block technique. This has the potential to mask the true cause of neurological injury and to delay appropriate therapy. At times, surgical risk factors may overlap with anesthesia-related factors to elicit nerve irritation or injury. For example, the association of toxicity (spinal lidocaine) and surgical positioning (lithotomy) in the pathogenesis of transient neurological syndrome has been demonstrated.

**Incidence of Nerve Injury after RA**

The incidence of nerve injury after RA has been reported with widely diverging results. RA procedures feature prominently in closed claims databases, with most complications, and all fatalities, occurring after neuraxial blocks, and a smaller number of injuries being reported after peripheral nerve blocks. Data of outcome studies shows that the risk for neuropathy following epidural and spinal anesthesia is 3.78 : 10,000 and 2.19 : 10,000, respectively. After peripheral nerve block, the incidence of transient neuropathy is less than 3 : 100, whereas permanent nerve damage is very rare. Recently, Watts et al. investigated outcomes after 1065 peripheral nerve blocks, and found one transient and one permanent case of nerve injury, amounting to an overall incidence of block-related nerve injuries of 0.22%. The Australasian Regional Anesthesia Collaboration investigated 7156 blocks in 6069 patients, and found thirty patients with potential nerve damage (0.5%), but at analysis, only 3 had neuropathy attributable to RA, giving an incidence of 0.04%. Another investigation reported two cases of neuropathy following continuous popliteal sciatic nerve block in 400 patients, resulting in a risk of 0.5%. 34
Evidence for elevated risk in patients with preexisting neurological disease

For several decades, there has been a growing consensus that preexisting nerve injury increases the risk of neuropathy in patients undergoing surgery. Originating from the first recommendations to avoid neuraxial anesthesia in patients with preexisting neuropathy, it was later hypothesized that preexisting neuropathies may predispose peripheral and central nerves to subsequent injury during RA. Today, a more nuanced view has been adopted. While in some preexisting conditions, we are now more ready to administer RA and analgesia after a careful weighing of risks and benefits (e.g., obstetric epidural analgesia in patients suffering from multiple sclerosis), other neuropathies such as diabetic neuropathy are increasingly recognized as serious risk factors for postoperative neuropathy that may warrant a change of current practice.

In many patients, preexisting neurologic disease may represent an important risk factor, most notably in diabetic peripheral neuropathy, multiple sclerosis, Guillain-Barre syndrome and Post-polio syndrome.

Specific disease patterns

Diabetic peripheral neuropathy

Diabetes mellitus is a disease increasing in prevalence in most high-income countries, leading in turn to an increasing prevalence of DPN. It is estimated that about 10% of diabetic patients present with DPN at the time of diagnosis, while this number rises to more than 50% of diabetic patients 5 years later, probably even faster in poorly controlled DM type 1. Diabetic neuropathy is the most common neuropathy worldwide, and can be subdivided into distal symmetric, autonomic, and focal/multifocal forms. Most patients suffer from a chronic distal symmetric nerve injury involving both sensory and motor fibers. Symptoms include hypesthesia and dysesthesia. Due to the
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development of symptoms in long fibers of the lower extremity, and the gradual spread to shorter axons, this variant has been designated length-dependent diabetic polyneuropathy.\textsuperscript{38} Whereas the traditional distal symmetric neuropathy is predominantly driven by metabolic factors, focal neuropathies seem to be caused by a combination of ischemic and inflammatory processes.\textsuperscript{38} Progression of DPN is difficult to predict in the individual patient, but poor glycemic control seems to be the main risk factor.\textsuperscript{39} Recently, genetic polymorphisms in the aldose reductase gene \textit{AKR1B1} have been reported to influence the severity and progression of the disease.\textsuperscript{40} Current evidence suggests that once structural damage has occurred, damage to end organs is irreversible.\textsuperscript{38,39} This is relevant to daily anaesthetic practice because on the one hand, cardiovascular and renal complications of this disease lead to many surgical procedures for which RA may be highly suitable. On the other hand, limited epidemiological \textsuperscript{41} and experimental \textsuperscript{42} evidence suggests an increased risk of local anaesthetic-induced neurotoxicity in this growing patient population. It should be kept in mind, however, that up to 30\% of neuropathies in diabetics may be unrelated to diabetes.\textsuperscript{43}

Concern regarding the performance of RA in diabetic patients has been promoted by epidemiological, experimental, and anecdotal observations. Retrospective data compiled by Hebl et al. indicate that preexisting DPN may be a risk factor for nerve injury after neuraxial anesthesia.\textsuperscript{41} Even though direct extrapolation of the results from this study is difficult owing to the small number of complications observed (n=2), it is worth noting that these iatrogenic injuries occurred in diabetic patients using full doses of 0.5 or 0.75\% of neuraxial bupivacaine.\textsuperscript{41} The risk of nerve damage was described as 10-fold higher in DPN than the estimated 0.04\% reported for the general patient population.\textsuperscript{31}

Experimental evidence supports increased toxicity of LA in diabetic test animals.\textsuperscript{42,44} In a landmark study, Kalichman and Calcutt found that 2\% lidocaine
used for sciatic nerve block in rats produced moderate nerve injury in healthy animals, but induced severe degeneration in diabetic animals.\(^{42}\) Recently, Kroin et al. showed that lidocaine 1% was safe in a comparable setting for peripheral nerve blockade, whereas there was slight evidence of nerve injury when lidocaine was used with additives (clonidine, epinephrine), or ropivacaine 0.5% was used.\(^{44}\) Anecdotal evidence lists several patients who experienced worsening of neurologic function after peripheral\(^ {45,46}\) or neuraxial\(^ {47-49}\) anesthesia. The extent of preexisting DPN in these patients ranged from subclinical\(^ {45}\) to severe,\(^ {49}\) and included the combination of both diabetic and alcoholic neuropathies.\(^ {48}\)

Other concerns in diabetic patients pertain to pharmacology of LA on diabetic nerves, and the extent to which diabetic nerves are amenable to peripheral nerve stimulation. While Kalichman and Calcutt did not find prolonged block in test animals,\(^ {42}\) the recent study by Kroin et al. showed prolongation of block duration in diabetic animals as compared to healthy controls.\(^ {44}\) It seems, therefore, that diabetic nerves are more sensitive to LA. In fact, regional blockade may be paradoxically efficient in diabetic nerves\(^ {50}\) owing to three reasons. First, nerves may be more sensitive to the LA itself;\(^ {42,44,50}\) second, the sensory area of a nerve may be partly anesthetized by neuropathy itself;\(^ {50}\) and third, microangiopathy may contribute to delayed absorption of LA. The possibility of altered responsiveness of diabetic nerves to electric stimulation was first raised in case reports demonstrating difficult stimulation of peripheral nerves in diabetic patients.\(^ {51-53}\) It would seem logical that a nerve that does not transmit usual impulses properly might be relatively resistant to nerve stimulation, itself a variable undertaking.\(^ {54}\) We have reported that the risk of intraneural needle placement is increased in diabetic dogs compared to controls when using a nerve stimulator to guide needle placement.\(^ {55}\) A more recent report combining ultrasound and nerve stimulation showed that for successful supraclavicular block, higher thresholds are necessary in diabetic versus non-
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DPN may thus complicate nerve stimulation, possibly resulting in increased incidence of unsuccessful nerve stimulation, or even intraneural needle placement, which may predispose to nerve injury.\textsuperscript{20} It may be appropriate in patients with severe DPN to adapt the stimulating patterns to longer pulses, as has been suggested in diabetic / ischemic neuropathy (i.e., from 0.1 msec to 1 msec),\textsuperscript{57} or employ ultrasound imaging to improve the accuracy of needle placement.

Whether for central or peripheral blockade, the degree of risk from the use of RA in diabetic patients cannot be exactly defined on the basis of current knowledge. Nonetheless, nerves in DPN are probably more sensitive to LA effects, including toxicity,\textsuperscript{50} we recommend reduction of the LA concentration for neural blockade in such patients. Retro-fitting of data from animal experiments using US FDA guidelines allows for estimation of safest doses in patients on the basis of current knowledge (Table 1). Dose reduction may be aided by the employment of ultrasound-guided RA in peripheral nerve blocks.\textsuperscript{58}

The addition of adjuvants without a corresponding decrease in LA concentration is, in general, not recommended.\textsuperscript{44,59} Diabetic nerves may already be at risk of neuronal ischemia and infarction owing to changes in endoneurial small vessels.\textsuperscript{59} Since lidocaine is vasoconstrictive itself,\textsuperscript{60} we recommend avoiding epinephrine during nerve blocks in DPN patients.

\textit{Multiple Sclerosis}

Multiple sclerosis (MS) is a chronic demyelinating neuroinflammatory disease. Its etiology is still debated, but a crucial issue is the interplay between polygenetic risk factors (HLA haplotypes) and environmental factors (viral infections, vitamin D deficiency, smoking).\textsuperscript{61} Manifestations typically appear in early adulthood, and as in many autoimmune diseases, women are predominantly affected. MS is the most common debilitating disease in young adults.\textsuperscript{62}
Diagnosis is primarily based upon the triad of neurologic symptoms, positive findings on magnetic resonance imaging, and the presence of oligoclonal bands on cerebrospinal fluid (CSF) examination. The evidence concerning RA risks in MS patients is limited. Data on peripheral nerve blocks are scarce, and most data on neuraxial techniques are from the obstetric population.

Traditionally, the use of peripheral blocks in patients with MS has been regarded as safe, since blocks are performed far from the main pathogenic demyelination and scarring processes occurring within the central nervous system (e.g., 63). However, there is evidence for involvement of the peripheral nervous system in MS, with peripheral nerves showing demyelination.64 Anecdotal 65 (albeit equivocal 66 67) reports of brachial plexopathy after peripheral nerve block have heightened awareness of the fact that a substantial share of MS patients may suffer from subclinical peripheral neuropathy, the incidence of which is reported inconsistently,68 and the clinical relevance of which remains unclear.69 Based upon circumstantial evidence, the notion that peripheral nerve blocks are most probably safe in MS patients still holds true, and peripheral RA continues to be a valid alternative to GA or central blocks.

The possibility that RA may worsen neurological status is a particular concern in spinal anesthesia. Despite the theoretical consideration that LA may have increased neurotoxic effects on demyelinated and thus pre-damaged neurons, there are no clinical studies to support this notion.70 Anecdotal evidence reports de novo exacerbation of previously undiagnosed MS through spinal anesthesia,71 but this could also be explained by transient and reversible worsening of negative symptoms through exposure to LA (see below).72 Initial reports demonstrating a higher risk of MS exacerbation after spinal anesthesia 73 have not been replicated in recent literature. A recent retrospective study found no evidence of relapse after epidural or spinal anesthesia in series of 18 and 17 patients, respectively.74
Research pertaining to neuraxial techniques in MS has been performed mostly in obstetric patients. Even though this patient population is not directly comparable to day-surgery patients, insights may be derived from these investigations. First, large-scale controlled studies have not linked any form of obstetric RA to worsening of symptoms of multiple sclerosis.\textsuperscript{70} Epidural anesthesia and analgesia, according to large-scale studies, appear safe.\textsuperscript{75, 76} Confavreux et al. reported that epidural labor analgesia was not a risk factor for disease relapse in parturients with multiple sclerosis in a trial involving 241 patients, of whom 42 had received epidural analgesia,\textsuperscript{75} confirming earlier results by Nelson and colleagues.\textsuperscript{77} This is reflected by the results of a recent survey among obstetric anesthesiologists in which the risk of epidural anesthesia / analgesia was judged to be low based on clinical experience.\textsuperscript{78} Furthermore, transient worsening of symptoms or \textit{de novo} relapse after childbirth may be mistakenly attributed to RA. After delivery, intrinsic nerve injury,\textsuperscript{79} fatigue,\textsuperscript{80} or pyrexia may exacerbate MS symptoms.\textsuperscript{78} Moreover, in patients with a relapsing form of MS, although pregnancy is associated with a decreased risk of flare-ups, the postpartum period is characterized by an increased risk of relapse. Pregnancy induces a transition from cellular immunity towards humoral immune responses, driven by the secretion of IL-10 from the feto-placental unit, thereby promoting immunological tolerance of the fetus. This cellular immunosuppression rebounds after delivery, causing increased relapse rate.\textsuperscript{75}

The limited evidence that exists is not sufficient to provide a definitive answer to the question of whether neuraxial blocks are safe in MS patients. Should symptoms arise in the perioperative period, there is an abundance of patient- and procedure-related risk factors potentially contributing to worsening of neurologic function. Moreover, the case of obstetrics illustrates that the neurological condition of the patient is not the only factor determining whether or not to perform RA. In obstetric patient, the risks of neuraxial anesthesia must
be weighed against the risks of GA in a parturient, which may explain why 90% of responders in a recent survey among obstetric anesthesiologists stated that after weighing risks and benefits, they would still perform spinal anesthesia for emergency caesarean section in MS patients.\(^7\)

Recommendations have been made to limit neuraxial doses to the lowest possible level,\(^8\) although this may increase the risk of insufficient analgesia. One argument in favor of limiting doses comes from a case-control study of 20 MS parturients, in which bupivacaine administered in doses above 0.25% was associated with what seemed to be a higher incidence of relapse.\(^2\) In general, definitive studies on pharmacological properties of LA in MS are lacking.\(^7\) Whether LA act longer on nerves from MS patients has been debated, with case reports describing normal \(^3\) versus prolonged \(^4\) block duration, and there is as yet no answer as to whether dynamics of nerve block are altered in MS. Although not tested in clinical or experimental MS settings, non-neurotoxic adjuvants such as clonidine and buprenorphine may hold promise for the future.\(^5\)

Finally, LA may directly interact with MS lesions. In patients, lidocaine can reversibly worsen symptoms of MS,\(^6\) presumably by blocking sodium channels in demyelinated areas just enough to produce symptoms, while healthy areas are not affected. These changes were noted at doses also observed systemically after epidural anesthesia in other investigations (low micromolar range).\(^7\) Paradoxically, lidocaine can worsen negative symptoms (i.e. paresis and hypesthesia resulting from demyelination), but can be used to effectively treat positive symptoms (i.e. spasticity, dysesthesia resulting from ectopic impulses) of MS, although the therapeutic range is very narrow.\(^8\) Interestingly, endogenous extracellular pentapeptides are observed in the CSF of patients with Guillain-Barre Syndrome and MS, and these pentapeptides share many electrophysiological properties with LA.\(^9\)
In summary, peripheral nerve blocks have not been proved to be harmful to MS patients, and MS should not be considered to be an absolute contraindication for neuraxial blockade. Since LA toxicity may be more pronounced in demyelinated fibers, epidural anesthesia appears safer than spinal. Overall, it seems justifiable to perform peripheral nerve blocks and epidural anesthesia in patients with MS, with due attention to restricting LA concentration. Use of spinal anesthesia in MS patients in the presence of safe and feasible alternatives should be avoided. MS patients need to be informed about potential symptom aggravation irrespective of whether RA is employed.

Post-polio syndrome

Post-polio syndrome (PPS) is the most prevalent motor neuron disease in North America. A recent review contradicted the notion that PPS affects only the aged. Indeed, many patients with PPS are of working age, and through new infections in the developing world, PPS will remain an anesthetic challenge for decades to come. PPS is characterized by central fatigue, pain and muscle weakness, frequently associated with sleep-disordered breathing (hypoventilation). Although the exact pathogenic mechanism remains obscure, current avenues of investigation implicate overuse of the enlarged motor units formed during recovery from polio, accelerated aging of motor units, persistent viral infection, and chronic inflammation.

Patients with PPS are not well suited to undergo day-case surgery because of postoperative monitoring necessities, but the sheer number of patients suffering from this disease will necessitate discussion on the perioperative use of RA, especially since these patients frequently have to undergo orthopaedic procedures. Risks of RA must be balanced against the dangers of GA, such as controversies regarding use of depolarizing and nondepolarizing muscle relaxants, sensitivity to sedative or analgesic
medication, and risk of hypoventilation and aspiration.\textsuperscript{91} Concerns with regard to regional anesthetic techniques include temporary deactivation of muscles that contribute to respiration during neuraxial anesthesia,\textsuperscript{95} difficulty in puncture during neuraxial blockade in patients with secondary abnormal spinal anatomy,\textsuperscript{96}\textsuperscript{97} and the potential of iatrogenic worsening of symptoms.\textsuperscript{91} Two case reports have described spinal anesthesia using normal doses of tetracaine \textsuperscript{98} and bupivacaine \textsuperscript{96} without post-procedural worsening of symptoms. Similarly, no complications were reported in a small PPS group of three patients undergoing seven surgeries.\textsuperscript{92} In the largest series of patients with PPS, 79 patients undergoing neuraxial anesthesia or analgesia showed no worsening of neurological symptoms.\textsuperscript{74}

The data provided in current literature allows no clear recommendation to choose or avoid neuraxial techniques or peripheral nerve blocks in PPS. However, there is no evidence that the performance of spinal or epidural anesthesia increases the risk of disease progression, and it seems unlikely that peripheral nerve blocks are associated with an increased risk of morbidity. Considering the unusual sensitivity towards sedative and analgesic agents, it is recommended to avoid the use of opioid or sedative adjuvants to both central and peripheral blocks.

\textit{Guillain Barre Syndrome}

Guillain-Barre syndrome (GBS) is a heterogeneous cluster of conditions characterized by acute neuromuscular paralysis, probably due to post-infectious inflammation.\textsuperscript{99} In many patients, antibodies against neuronal membrane gangliosides are detectable.\textsuperscript{100} The disease develops weeks after the initial trigger. Paralysis is variable in extent and involvement of sensory, cranial, or autonomic nerves. The initial symptoms peak between 2 and 4 weeks after onset is followed by a much slower recovery. Diagnosis is not always straightforward,
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and is based upon clinical signs, electrophysiological and CSF diagnostics. The incidence is about 2 cases per 100,000 annually, increasing linearly with age, and predominantly affecting men.\textsuperscript{101} GBS is not typically associated with autoimmune or systemic diseases.\textsuperscript{99} Any individual’s prognosis is difficult to predict, and many patients continue to have moderate to severe impairment of neurologic function years after the initial onset of disease. Risk factors for prolonged neurologic deficit include older age at onset (>50 years), severe initial disease, and antecedent infection with campylobacter jejuni or cytomegalovirus.\textsuperscript{100} The disease is usually differentiated into acute inflammatory demyelinating polyneuropathy, which features demyelinating conduction block, and acute motor axonal neuropathy, in which modifications at neuronal sodium channels are thought to play a pathogenic role. In the latter form, antibodies that act as functional blockers of sodium channels and channel phosphorylation have been implicated.\textsuperscript{100, 102} As in MS, endogenous extracellular pentapeptides are observed in CSF (see above).\textsuperscript{89}

Reports of RA in GBS are few. The performance of peripheral nerve blocks has not been described in enough detail to allow definitive recommendations. However, in the setting of acute neuronal inflammation, peripheral blockade at these very nerves should probably be avoided. Most experience with neuraxial techniques has been gathered in obstetric patients. General comments are that the use of neuraxial anesthesia may be associated with exaggerated hypotension and bradycardia,\textsuperscript{103} but many patients with GBS respond normally to neuraxial anesthesia.\textsuperscript{104} Pharmacologically, both normal\textsuperscript{105} and higher-than-normal\textsuperscript{106} spread of LA administered using an epidural technique have been reported, but most case reports describe usual block properties.

Anecdotal evidence suggests that epidural anesthesia may activate the onset or recrudescence of GBS\textsuperscript{107, 108} hours\textsuperscript{109} or weeks\textsuperscript{110} after surgery under
epidural anesthesia. The hypothetical link between RA and GBS is interaction of LA with peripheral myelin, or nerve trauma due to epidural block, with subsequent inflammation as the precipitating factor. However, definitive attribution of GBS to RA beyond a temporal association is difficult. Occurrence or recurrence of GBS has been described for surgery without RA, and often the time-lag between initiating trigger and onset of GBS symptoms is unclear.

Case reports have described successful use of epidural anesthesia at high doses, and even spinal anesthesia, in parturients with residual symptoms of GBS. Recently the use of combined spinal and epidural anesthesia in a parturient with GBS was reported without unusual hemodynamic effects or exaggerated effects of LA.

Weighing of risks and benefits of RA in patients with GBS needs to take into account the alternative risks of GA in this patient population, and the status of the disease. It has been suggested that acute neuronal inflammation should be a relative contraindication for RA and the possibility of a postoperative diagnostic dilemma from the combined effects of RA and GBS argue for caution.

In patients with residual symptoms of GBS, the safe use of neuraxial blockade has been described using both high and low volumes and doses of LA. The few case reports describing a temporal relationship between RA and the development of GBS do not suffice to classify RA as a risk factor for GBS.

Strategies to minimize risk in peripheral nerve blocks

Preoperative Assessment

Preoperative assessment should always include a review of medical conditions that would predispose a patient to peripheral neuropathy. Subclinical peripheral neuropathy and increased vulnerability to LA toxicity may already be present in these patients. Next, documentation of existing neurologic deficits, both by history and physical examination, should be performed. Any decision to
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proceed with RA must include a risk-benefit analysis that considers the possible increased risk of peripheral nerve blockade in patients with a peripheral neuropathy compared with the risks of GA in the same patient. Importantly, the risks and benefits of RA should be discussed with the patient and documented in the medical record. Recent surveys of regional anesthesiologists both in academic and community settings have suggested that this practice is not consistently performed.117

Technique of Regional Anesthetic

Choice of nerve localization technique and its relation, if any, to the risk of peripheral neuropathy has long been a topic of controversy. The goal of nerve and needle localization has traditionally been to deposit the LA around the epineurium without penetration or laceration, using nerve stimulation. One limitation of stimulator techniques is the lack of a predictable relationship between the threshold for nerve stimulation and needle-to-nerve distance. Significant variability exists between patients and for different nerve localization sites. This relationship may even further be complicated in patients with underlying neuropathies, such as DPN.55 Ultrasound guidance may improve needle placement accuracy and reduce LA dose,58 which are both desirable in neuropathic patients. While this seems plausible and of particular interest in patients with neuropathy, superior safety by using ultrasound imaging has yet to be confirmed.118

Choice of Local Anesthetic

A second area of controversy is type and concentration of LAs. All LAs are neurotoxic at high concentrations,119 and potentially toxic even at clinical concentrations.85 Neurotoxic effects are comparable between LAs at equipotent doses. Diabetic nerves in animal studies have demonstrated an increased
sensitivity to LAs. Diabetic nerves require a lower concentration of LA for successful nerve block and have a longer duration of block. Concentration of LA and duration of nerve block correlate with histological fiber damage. It is noteworthy that in Kalichman’s study of sciatic nerves of diabetic rats, significantly increased nerve fiber damage was noted at 4% lidocaine versus 2% lidocaine. In the study by Kroin et al, 1% lidocaine caused no significant nerve fiber injury in diabetic rats. Thus, use of the lowest effective concentration and amount of LA may reduce the risk of nerve fiber damage. This raises the question of what concentration of LA is necessary for adequate surgical anesthesia for, e.g., DPN patients. A recent study by Kocum and colleagues showed that 0.25 % bupivacaine may be employed to produce effective femoral and sciatic blocks in patients with diabetic foot syndrome. Further investigations are needed to determine the optimal concentration of LA that achieves successful surgical anesthesia while minimizing risk.

Role of Adjuvants

Epinephrine reduces blood flow in the peripheral nerve. Although the temporary reduction in blood flow is well tolerated by most peripheral nerves, the nerves of patients with compromised vascular integrity due to diabetes, arteriosclerosis, or other injury may not tolerate severe reductions in blood flow. Furthermore, by reducing neural blood flow, epinephrine decreases the washout of LA and prolongs the duration of LA exposure. These properties prolong the LA block for intermediate acting LA and may potentiate toxicity. In diabetic nerves, epinephrine 5 mcg/ml prolongs the block by lidocaine 1%, causing histologic evidence of axonal degeneration, which is absent with lidocaine or epinephrine alone. In another study, epinephrine 5 mcg/ml caused significant reduction in blood flow of healthy nerves, whereas epinephrine 2.5 mcg/ml did not. On this basis, some have advocated using reduced doses of epinephrine in
patients with peripheral neuropathy to reduce the risk of nerve damage.\textsuperscript{118,123} We advocate a more conservative stance of avoiding epinephrine in DPN patients altogether. The absence of this marker for intravascular injection, we also recommend slow, incremental administration of the LA dose, and use of lidocaine in preference to agents capable of producing malignant ventricular dysrhythmias such as bupivacaine and ropivacaine.\textsuperscript{124,125} Similarly, clonidine has been advocated as a useful adjuvant for peripheral nerve blockade.\textsuperscript{123} In doses as low as 0.1 mcg/kg, clonidine has been shown to significantly increase the duration of anesthesia for intermediate acting LA.\textsuperscript{126} The effect of clonidine is peripherally mediated and is likely the result of activity dependent hyperpolarization of the peripheral nerve fibers.\textsuperscript{127} In diabetic sciatic nerves, the addition of clonidine 7.5 mcg/ml to 1% lidocaine significantly prolonged block duration compared with lidocaine 1% plain but also produced histologic evidence of axonal degeneration.\textsuperscript{44} Of note, this represents a higher dose of clonidine than would be used clinically. Further investigations using lower concentrations of clonidine may reveal a dose where anesthesia may be augmented without augmenting axonal toxicity.\textsuperscript{128} Clonidine and buprenorphine \textsuperscript{85} may prove to be useful adjuvants or replacements \textsuperscript{129} for LA.

Summary

Based on limited data, mostly from animal studies, the risk of axonal injury to peripheral nerves compromised by peripheral neuropathy may be reduced by limiting the concentration and duration of LA exposure. Strategies to accomplish this may include reducing the concentration of the selected LA, reducing or avoiding added epinephrine, and utilizing a nerve localization technique that minimizes the incidence of intraneural injections. Further investigations should clarify the safe and effective concentrations of LA and adjuvants in patients with peripheral neuropathy, and whether the potential for
combined adjuvants reduces or eliminates the need for LA. Similarly, the safety of different nerve localization techniques and nerve block selection should be explored to optimize safety in this vulnerable, and growing patient population.

**Strategies to minimize risk in neuraxial blocks**

*Evaluation of Risk*

Several authors have speculated that patients with peripheral neuropathy may be more vulnerable to symptomatic complications after neuraxial block. First, due to the “double-crush” phenomenon, otherwise asymptomatic lesions along a conduction pathway may produce symptoms following even a mild degree of anesthetic-induced neurotoxicity. Second, “peripheral neuropathies” such as diabetic polyneuropathy, may also produce changes in the spinal cord.

*Choice of Local Anesthetic*

Similarly to effects on the peripheral nervous system, all LA can cause dose dependent neurotoxicity. Some studies have raised concern that lidocaine in clinically used concentrations may have a propensity for increased neurotoxicity compared with similarly potent doses of bupivacaine. The presence of peripheral neuropathy has not been associated with transient neurologic symptoms in ambulatory patients. Limiting the dose and concentration of LA in neuraxial blocks has been advocated to minimize the risk of neurotoxicity. In ambulatory patients, the use of the lowest effective dose of LA may also enable rapid return of sensory and motor function.

*Use of Adjuvants*

Hydrophobic opioids such as fentanyl have been added to both low dose bupivacaine and lidocaine spinal anesthetics to augment sensory blockade. A relative paucity of animal data exists regarding the toxicity of spinal fentanyl.
In clinical practice, few concerns about neurotoxicity have been raised regarding low dose fentanyl or sufentanil used for ambulatory anesthesia. The limited animal studies which have been done have not revealed significant histologic or physiologic evidence of neurotoxicity. Therefore the addition of lipophilic opioids to low doses of LA appears to be a useful adjunct of to decrease the total dose of LA needed for successful surgical anesthesia in ambulatory patients, but with the concomitant undesirable side-effects such as pruritus, nausea, and somnolence in the elderly.

Epinephrine is rarely used in ambulatory patients as the resulting delayed resolution of neuraxial anesthesia is usually not desirable for ambulatory patients undergoing relatively short procedures. Epinephrine in most clinically used doses does not significantly affect spinal cord blood flow. However, epinephrine does worsen spinal cord injury when given with 5 % lidocaine or 1 to 2 % tetracaine in rats. It is likely that this effect is due to reduced clearance and therefore prolongs exposure to the LA than to any direct effect of the epinephrine. Also, when used with chloroprocaine, epinephrine can cause flu-like symptoms. Because of its undesirable prolongation of anesthesia and possible enhancement of toxicity, neuraxial epinephrine is best avoided in patients with peripheral neuropathy presenting for ambulatory anesthesia.

Summary

Neuraxial anesthesia can be provided to patients with preexisting neuropathy on the basis of thorough risk-benefit-analysis. Strategies to minimize the risk of nerve toxicity include the use of the lowest effective dose of LA, avoidance of epinephrine, and possible use of adjuncts such as lipophilic opioids. Careful selection of agents can provide optimal surgical anesthesia and time to discharge readiness as well as maximizing safety.
Conclusion

RA is a reasonably safe and at the same time highly effective method of providing pain relief to day-surgery patients. There is no universal answer to the question of whether a regional anesthetic technique is the best choice for patients with preexisting neuropathy. In most patients, the decision is complex and requires a careful and individual weighing of risks and benefits of both general anesthesia and regional anesthesia. In patients with preexisting neurological disease, function can deteriorate perioperatively irrespective of whether RA is employed. In diseases such as DPN and MS, reducing local anesthetic concentration is appropriate. Focused informed consent regarding RA versus GA with these patients should be followed by close observation for potential sequelae.

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Table 1
Proposal for concentration and maximum single dose of local anesthetics in patients with DPN based upon equipotency.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration</th>
<th>DPN-adjusted</th>
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<tbody>
<tr>
<td>Lidocaine</td>
<td>2 %</td>
<td>1 %</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>1.5 %</td>
<td>0.75 %</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>0.75 %</td>
<td>0.375 %</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>0.5 %</td>
<td>0.25 %</td>
</tr>
</tbody>
</table>

Equipotency values based on Hadzic A (ed.) Textbook of Regional Anesthesia and Acute Pain Management, 2006, The McGraw-Hill Companies. We are indebted to Brian Williams MD, MBA, for his kind permission to use his calculations in this manuscript.