Regional Anesthesia in Anesthetized or Heavily Sedated Patients

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The American Society of Regional Anesthesia and Pain Medicine (ASRA) Practice Advisory on Neurologic Complications in Regional Anesthesia and Pain Medicine includes an evidence- and expert opinion-based section on performing procedures on anesthetized or heavily sedated patients. This practice advisory is based on existing scientific literature, pathophysiological principles, and expert opinion. The advisory panel examined the ability of anesthetized or heavily sedated patients to recognize and report intravascular injection of local anesthetic or impending neurologic injury. The advisory panel also considered whether or not the ability to recognize and report symptoms could actually affect the occurrence of nerve injury or local anesthetic systemic toxicity. The advisory contains recommendations pertaining to both adult and pediatric patients. *Reg Anesth Pain Med 2008;33:449-460.*

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When properly performed, regional anesthesia is a safe clinical practice with a risk of serious complication that is not significantly different than that of general anesthesia. This report focuses on an area of particular controversy—whether or not it is safe to perform regional anesthesia or pain medicine procedures on patients who are anesthetized or heavily sedated. We define the *anesthetized patient* as one who is under general anesthesia. A *heavily sedated patient* is one who is sedated to the point of being unable to recognize and/or report any sensation that the physician would interpret as atypical during block placement. Given the variability in response to sedative/hypnotics and analgesics that might be used for sedation, it is impossible to provide dosage guidelines or drug recommendations that clearly draw a line between "light" and "heavy" sedation.

Those who routinely perform regional blocks in anesthetized or heavily sedated patients argue that this practice increases safety by decreasing the chance that the patient will move suddenly and cause the block needle to impale a vital structure. In addition, they point out that anesthesia or heavy sedation increases patient acceptance and therefore increases the number of patients who will potentially benefit from regional anesthesia/analgesia. Many clinicians who perform regional anesthesia in infants and children often invoke this latter reasoning, noting that regional blocks would be impractical in the pediatric patient population without anesthesia or heavy sedation.

Those who eschew the practice of performing blocks in anesthetized or heavily sedated patients assert that doing so removes important early warning signs that help prevent both local anesthetic systemic toxicity and neurological injury. Their basic assumption is that the awake or minimally sedated patient will be able to report developing symptoms of systemic local anesthetic toxicity before a toxic dose is injected or will be able to recognize and report pain or other atypical symptoms from an errant needle before neurological injury occurs. While this reasoning seems logical, it is as unproven as are the assertions of those who advocate performing blocks in anesthetized or heavily sedated patients.

In this article, we review the available literature in

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an effort to come to a consensus as to whether the risk of complications from regional anesthesia procedures is increased or decreased by anesthesia or heavy sedation. The data reviewed necessarily consist of case reports, large and small observational human studies, and experimental animal studies, because there are no prospective, randomized, controlled clinical trials aimed at evaluating the impact of anesthesia or heavy sedation on the risk of complications from regional anesthesia or pain medicine procedures. Indeed, such studies may never be conducted because of logistical difficulties associated with performing a properly controlled study that examines an event as rare as anesthesia-related nerve injury. Consequently, we are left to draw conclusions from indirect sources.

Systemic Local Anesthetic Toxicity

Systemic toxicity from local anesthetics is manifest either within the central nervous system (CNS) or the cardiovascular system, with CNS toxicity occurring at significantly lower plasma concentrations than cardiovascular toxicity.

Central Nervous System Toxicity

The reported incidence of seizures during regional anesthesia varies between approximately 0.1 and 1 per thousand, with the lower incidence reported by the French SOS Regional Anesthesia Hotline Service,[1] which used a voluntary reporting methodology, and the higher incidence obtained from a retrospective chart review from the Mayo Clinic.[2] Local anesthetic plasma concentrations high enough to cause seizures can be reached either by unintentional intravascular (venous or arterial) injection, systemic absorption from the perineural or epidural injection site, or a combination of both.

Human studies of local anesthetic CNS toxicity demonstrate that if plasma concentrations rise slowly, subjects will progress through a fairly stereotypic series of CNS symptoms prior to developing seizures.[3,4] The early CNS symptoms of rising local anesthetic plasma concentration include tongue or circumoral numbness followed by "lightheadedness" and then visual or auditory disturbances. Consequently, one could reasonably argue that an awake patient attuned to the symptoms of early local anesthetic CNS toxicity would be able to warn a clinician of developing CNS toxicity prior to seizures and that if the local anesthetic is being injected slowly enough, the injection could be aborted before a dose large enough to cause seizures (or worse) is administered. Consistent with this argument are studies demonstrating that an unpremedicated subject can detect an intravenous bolus of lidocaine (1.5 mg/kg), 2-chloroprocaine (90 mg), or bupivacaine (25 mg) with 100% sensitivity, but that the sensitivity decreases to between 60% and 80% with even small doses of sedatives or opioid analgesics (e.g., 1.5-2.8 mg midazolam and 60-96 μg fentanyl).[5,6]

The argument that aware patients could meaningfully detect an intravascular injection of local anesthetic is appealing, but is not universally applicable. For example, seizures that result from systemic absorption of local anesthetic generally occur after most or all of the local anesthetic has been injected; thus premonitory symptoms typically occur too late to prevent a toxic dose from being administered. Moreover, seizures that occur as a result of unintentional local anesthetic injection into the carotid or vertebral arteries during stellate ganglion or interscalene blocks have occurred after as little as 1.5 mL of local anesthetic were injected.[7] Similarly, patients in whom local anesthetic is unintentionally and rapidly injected intravenously may develop seizures before they have time to recognize and report CNS symptoms and prevent the administration of a toxic dose. In all of these groups of patients, the fact that they may be unanesthetized and unsedated provides no discernable benefit and in some cases may actually increase the risk of CNS and potentially cardiovascular toxicity (see below).

Several studies have demonstrated that the use of an appropriate local anesthetic "test-dose" (e.g., epinephrine, isoproterenol) can help identify unintentional intravascular local anesthetic injection.[8] Importantly, the dose of epinephrine or isoproterenol and the diagnostic criteria for considering a cardiovascular response to be positive may be different in anesthetized versus awake patients (and in "elderly" patients[9]) but the sensitivity is still high if the appropriate test dose and criteria are used.[10-15] In contrast, patient report of CNS symptoms can never be 100% sensitive because of the large number of patients incapable of either sensing or adequately communicating their symptoms (e.g., young children, demented patients, patients with a language barrier).

Therefore, although experimental reports indicate that unsedated/unanesthetized patients who are verbal and fully cognizant can detect and report symptoms of intravascular injection of local anesthetics, this situation is not universally applicable in clinical practice. Because an appropriate test dose that is properly applied and monitored is virtually 100% effective at detecting intravascular injection in patients regardless of their premedication, the test dose, and not patient report, should be considered a more reliable method to detect or prevent intravascular injections that might lead to systemic toxicity.

Moreover, appropriate sedation can actually decrease the risk of seizures.[16-18] Sedative hypnotics

(e.g., benzodiazepines, barbiturates, propofol) and volatile anesthetics significantly raise the threshold for local anesthetic-induced seizures and may increase the safety margin for local anesthetic CNS toxicity. This assumes that anesthesia or heavy sedation are not accompanied by significant respiratory depression, which can in fact lower local anesthetic-induced seizure threshold because increased P_aCO_2 displaces local anesthetics from plasma protein binding sites.[19,20]

Cardiovascular Local Anesthetic Toxicity

Unlike CNS toxicity, which can occur from absorption of local anesthetic properly deposited at the intended block site, the local anesthetic concentrations required to produce severe cardiovascular toxicity can probably be reached only by intravascular injection. Consequently, prevention of cardiovascular toxicity probably rests entirely on the ability to prevent significant intravascular injection of local anesthetic. Indeed, the available data suggest that the most effective method to prevent intravascular injection is by slow, incremental injection of a local anesthetic solution containing a marker of intravascular injection (e.g., epinephrine, isoproterenol) while simultaneously monitoring for the objective cardiovascular response. Therefore, in terms of preventing cardiovascular toxicity by preventing intravascular injection there is no reason to believe that there is any advantage in avoiding blocks in anesthetized or heavily sedated patients.

Of note, anesthesia or heavy sedation may modulate the manifestation of cardiovascular toxicity. For example, Ohmura et al.[21] showed that volatile anesthetics (sevoflurane) and propofol raise the threshold for early (dysrhythmias) but not late (asystole) manifestations of bupivacaine cardiovascular toxicity in rats. Similarly, Bernards et al. showed that benzodiazepine premedication increased the dose of bupivacaine required to produce cardiac dysrhythmias and prevented the early hypertension and tachycardia experienced by control animals.[22] However, consistent with the study by Ohmura et al.,[21] benzodiazepines did not alter the bupivacaine dose or plasma concentration at which cardiovascular collapse occurred.

The mechanism by which general anesthesia or sedation alter the early hemodynamic manifestations of bupivacaine toxicity is not well understood. Bernards and Artru have shown that isolated CNS administration of local anesthetics causes hypertension, tachycardia, and dysrhythmias by increasing sympathetic outflow and that this can be blocked by GABA agonists.[23,24] Thus, the early sympathetically mediated cardiovascular effects of intravenous local anesthetics may be centrally mediated and thus decreased by drugs that depress the CNS. However, terminal manifestations of local anesthetic cardiovascular toxicity, such as pulseless electrical activity, are likely mediated by direct effects on the myocardium and therefore unaltered by sedative/hypnotics or general anesthetics.

In summary, anesthesia or heavy sedation may mask signs of developing CNS toxicity and therefore potentially increase the risk of administering a cardiotoxic dose before intravascular injection is recognized. However, intravascular injection is more reliably detected with an appropriate intravenous test dose, thus obviating the need to rely on the patient report of symptoms to detect an intravascular injection. Consequently, our recommendation is that the potential ability of general anesthesia or heavy sedation to obscure early signs of *systemic local anesthetic toxicity* is not a valid reason to forgo performing peripheral nerve or epidural blocks in anesthetized or heavily sedated patients. Our recommendation is based on human and animal data and general agreement of expert opinion; as such, this is a class I recommendation (Appendix 1). The recent introduction of ultrasound-guided regional anesthesia may change these recommendations in the future. Ultrasound guidance allows for the use of significantly lower local anesthetic volumes[26] and may facilitate avoidance of intravascular injection. However, seizures have been reported despite the use of ultrasound guidance.[27]

Neural Injury

Although nerve block is commonly blamed for the nerve injuries that are associated with surgery performed under regional anesthesia, nerve injury can also be caused by pneumatic tourniquet pressure, surgical disruption of a nerve, nerve stretch, etc. As an example, Borgeat et al.[28] followed 74 patients (of 520 studied) who developed neurological "symptoms" after interscalene block performed for shoulder surgery. After 1 month, 41 patients still had symptoms and 30 of these underwent electroneuromyography because of worsening symptoms (paresthesia, dysesthesia, pain not related to surgery). Of these 30, 8 had sulcus ulnaris syndrome (thought related to how the arm was splinted postoperatively), 2 had carpal tunnel syndrome, and 1 had complex regional pain syndrome. The remaining 19 had normal studies. At 3 months, 20 patients remained symptomatic and again underwent electroneuromyography, which demonstrated carpal tunnel syndrome in 2, complex regional pain syndrome in 4 and plexus injury in 2. The remaining patient exams were normal. By 9 months, all patients were asymptomatic except 1 patient with a persistent brachial plexus injury (C6 root). Thus, of the pa-

tients whose symptoms were formally investigated by electromyoneurography only 2 had an identifiable injury that could have been caused by the nerve block, although it could just as easily have been caused by excessive stretch of the brachial plexus during the surgical procedure.[29,30]

Because most studies/case reports that present patients with neurological symptoms after peripheral nerve block fail to definitively establish the block as the source of the injury, it is difficult to draw any "scientifically valid" conclusions regarding the potential role of anesthesia or heavy sedation in the genesis of nerve injury during block placement. That said, we will attempt to cull some useful information from the available literature (Table 1).

Concern about the risk of nerve injury is probably the most often cited reason for not performing peripheral nerve blocks in anesthetized or heavily sedated patients. The assumption is that the awake/aware patient can recognize impending nerve injury before it occurs and thereby prevent it. Most clinicians are attuned to accept paresthesia or pain during local anesthetic injection as evidence of potential nerve injury. The crux of the issue with respect to performing blocks in anesthetized or heavily sedated patients is whether paresthesias/pain are sensitive and specific indicators of potential nerve damage. The related issue is whether the injury has already occurred by the time the patient reports the paresthesia/pain, or can injury still be prevented at that point by withdrawing the needle and not injecting any or additional local anesthetic.

Paresthesias are not a specific indicator of nerve injury. For example, Faryniarz et al. recently reported their prospectively collected data on 133 patients who had interscalene blocks placed for outpatient shoulder surgery.[56] The blocks were placed by eliciting a paresthesia and no patient developed permanent neurological injury (although 2 patients complained of transient neuropraxias that could not be demonstrated on formal sensorimotor testing, and which did not occur in the territory of the elicited paresthesia). Thus, available data indicate that a paresthesia, per se, is not an indication of incipient nerve injury, i.e., it has a very low specificity (Table 2).

There is some evidence that pain/paresthesia may have some sensitivity as an indicator of potential nerve injury. For example, Auroy et al. noted 4 peripheral nerve injuries in their series of 21,278 voluntarily reported peripheral nerve blocks.[32] All 4 patients were "awake" (degree of sedation, if any, not specified), all reported that, ". . . needle puncture was associated either with paresthesia during puncture or with pain on injection," and all neurological injury was in the same distribution as the paresthesia/pain. Although the numbers are very small, the 100% incidence of paresthesia/pain during the blocks that produced nerve injury suggests that these sensations may be clinically relevant as an indicator of *potential* nerve injury. Unfortunately, because the incidence of pain/paresthesia not associated with nerve injury was not reported, it is impossible to calculate the specificity of pain/paresthesia from these data. Moreover, all injections were halted when patients complained of pain/paresthesia. The fact that patients developed injury despite prompt termination of the injection could be interpreted as evidence that the patient's warning is insufficient to prevent injury and is, therefore, clinically useless. However, it is also possible that the injury might have been worse if injection had commenced/continued. Thus, this study suggests that awake patients sometimes notice pain/paresthesia with needle insertion/local anesthetic injection and that at least sometimes the pain/paresthesia may indicate nerve injury. Multiple other studies and case reports provide much the same general information contained in the Auroy et al. study,[32] namely, that nerve injuries occur, albeit rarely, that paresthesias and painful injections sometimes occur and are sometimes associated with nerve injury (associated, not proved causal), and that the large majority of nerve injuries are temporary (Table 1). The missing link that makes it impossible to draw useful conclusions is evidence that the reported neurological injuries were actually caused by the nerve block and not by tourniquet ischemia, surgical trauma, traction, casting, or some other nonblock-related event.

Ben-David et al. conducted a retrospective, nonrandomized study comparing the incidence of neurological injury in 336 patients receiving axillary block under general anesthesia or under sedation.[57] The incidence of postoperative neurological symptoms that were recorded in the patients' retrospectively reviewed charts was statistically significantly greater in the anesthetized group (7.5% of 106 patients) compared with the unanesthetized group (2.6% of 230 patients). Unfortunately, there were important demographic differences between the groups. In particular, the anesthetized group was dramatically younger than the sedated group (average 13.9 years vs. 48 years) because all patients under age 14 were anesthetized for their blocks. Thus, the difference in incidence of neurological injury could be the result of younger age and not the fact that the blocks were performed in anesthetized individuals. In fact, if one performs a subset analysis of their data and compares the 48 patients in the anesthetized group who were 14 years or older (age range 14-70) with the sedated group (age range 14-74) the incidence of neurological injury is 4.2% and 2.6%, respectively ($P > .05$ by χ^2 test). Thus, after correcting

for age, the risk of neurological injury does not appear to be statistically significantly increased by general anesthesia in this study.

With respect to the risks of nerve injury, the available data are insufficient to draw meaningful conclusions as to whether the risk is increased when performing peripheral nerve blocks in anesthetized or heavily sedated patients. Neither the position that peripheral nerve blocks can never, or that they can always, be performed safely in anesthetized/sedated patients is supported by the medical literature. Here a more nuanced recommendation may be appropriate. Recognizing that awake patients may not be able to sound a warning that prevents nerve injury, but that anesthetized or heavily sedated patients can never provide a useful warning, it is perhaps prudent, i.e., conservative, to suggest that blocks not be performed in anesthetized or heavily sedated patients as a routine. However, recognizing the lack of sufficient data, it may be reasonable, after specific consideration of risk-to-benefit, to place peripheral nerve or neuraxial blocks in anesthetized or heavily sedated patients if the particular clinical situation warrants it. Because this recommendation is based on incomplete and conflicting data and an absence of consensus among experts it is a class II recommendation (Table 2).

Of note, most but not all,[58] reports of nerve injury have been associated with placing blocks in anesthetized or heavily sedated patients undergoing upper extremity surgery. Whether this reflects a true difference in risk between upper and lower extremity blocks, relatively fewer lower extremity blocks placed, or both, is unknown. With regard to specific upper extremity blocks, case reports document spinal cord injury during the placement of interscalene blocks in patients under general anesthesia, which heightens concern associated with this practice. The Panel therefore recommends that interscalene blocks should not be performed in anesthetized or heavily sedated adult or pediatric patients (class I) (Table 2).

Nerve Localization—Peripheral Nerve Stimulation and Ultrasound

Concern that needle-to-nerve contact might increase the risk of neurological injury, coupled with experimental animal evidence supporting that concern,[59] led to the use of nerve stimulators with the expectation that they would ensure adequate proximity of the needle-to-nerve without necessitating nerve contact. In the context of performing blocks in anesthetized or heavily sedated patients it has been suggested that use of a nerve stimulator allows nerve identification without nerve contact. However, Choyce et al. intentionally elicited paresthesias during axillary brachial plexus block with a stimulating needle,[60] and noted that a motor response occurred at a current of 0.5 mA or less in only 41 of 53 blocks (77%). In 5 blocks, the necessary current ranged from 1.0 mA to 3.3 mA. Urmey and Stanton reported an even poorer correlation between paresthesia and motor response using a similar methodology in unsedated patients having interscalene brachial plexus block.[61] Only 30% of their patients had a motor response with stimulating currents up to 1 mA, even though they had experienced a paresthesia. Likewise, both Chan et al.[62] and Tsai et al.[63] reported the motor response to nerve stimulation in controlled animal models may be absent even when needles are inserted intraneurally and current intensity of $\geq$1 mA is used. Thus, these studies suggest that it is possible to contact a nerve (assuming paresthesia = needle-to-nerve contact) without eliciting a motor response using currents generally thought to indicate adequate nerve proximity ($\sim$0.5 mA). Therefore, the potential risk is that clinicians may repeatedly contact a nerve in an anesthetized patient because they do not elicit a motor response at typically used current intensity.

In recent years ultrasound has promised the ability to see needle-to-nerve interactions and thereby deposit drug sufficiently close to the nerve to ensure a block without the need to contact the nerve. The implication is that it should be possible to block nerves in patients without the need to elicit their help to prevent unintentional needle-to-nerve contact or intraneural injection; consequently the issue of anesthesia or heavy sedation would be moot. Unfortunately, the use of ultrasound for peripheral nerve blocks is too new to know if it will actually provide this degree of safety. One potential technical limitation of ultrasound that might impact its safety is the fact that it provides only a very limited plane of view. Thus, it is possible for the needle tip to be contacting or within a nerve outside of the plane of view, especially because it can be difficult to distinguish the needle tip from a cross section of the needle shaft passing obliquely through the plane of view. In addition, interpretation of ultrasound imaging is subjective and entirely dependent on the skill of the sonographer.[64] As an example, Sites et al.[65] identified 398 errors committed by novices during performance of 520 peripheral nerve blocks. Importantly, the most common errors were: (1) failure to visualize the needle tip; and (2) failure to recognize maldistribution of local anesthetic.

Nevertheless, a recent study by Perlas et al. shows the potential value of ultrasound and provides ad-

Table 1. Reports of Peripheral Nerve Injury With Major Conduction Blocks: 1980-2006

First Author, Date	Type of Study	Sample Size	Approach, Dose, Technique (Number of Patients)	Surgical Site	Sedation During Block (Number of Patients)	Paresthesia During Needle Placement or Injection	Neurologic Complications (Number of Patients)	Follow-Up, and Consequences (Number of Patients)
Al-Nasser, 2004[31]	Case report		Continuous psoas compartment, 45 mL, NS	Knee	Awake	None	Femoral nerve injury	6 months, recovery
Auroy, 2002[1]	Prospective survey	43,946	Peripheral nerve blocks, NS (9), P (3)	NA	NA	Paresthesia during needle placement reported by 2 patients with neuropathy	Peripheral neuropathy (12)	6 months, recovery (5); still present (7)
Auroy, 1997[32]	Prospective survey	21,278	Peripheral nerve blocks	NA	Awake	Paresthesia during needle placement reported by all 4 patients with neurologic injuries	Neurologic injuries (4)	48 hours to 3 months, recovery (4)
Barutell, 1980[33]	Case report		Interscalene, 8 mL, P	Thumb	Awake	Sharp paresthesia in arm when needle inserted; became worse during injection	Plexus lesion, C7-T1	5 months, permanent
Bashein, 1985[34]	Case report		Interscalene, 50 mL, P	Shoulder	Awake	Paresthesia during needle placement; generalized seizure after injecting LA	Phrenic nerve injury	3 years, permanent
Ben-David, 2006[35]	Retrospective study	336	Axillary, 0.4 to 0.6 mL/kg, P	Hand	Awake adult (230) GA adult (48) GA child (58)	NA	Nerve injury (6) Nerve injury (2) Nerve injury (6)	3 weeks to 4 months, recovery (6) 6 to 7 weeks, recovery (2) 4 weeks to 36 months, recovery (5), permanent (1)
Bogdanov, 2005[36]	Retrospective study	548	Interscalene, 20 to 30 mL, NS	Shoulder	GA	NA	No injuries	4 to 8 weeks
Bonner, 1997[37]	Case report		Sciatic, 25 mL, NS	Tibial	Awake	No paresthesia	Sciatic nerve palsy	12 months; recovery
Borgeat, 2001[28]	Prospective study	521	Interscalene, 40 to 50 mL, NS	Shoulder	Awake	NA	Plexus lesion (74) Plexus lesion (41) Plexus lesion (20) Plexus lesion (6) Plexus lesion (1)	≥10 days 1 month, recovery (33) 3 months, recovery (21) 6 months, recovery (14) 9 months, recovery (5); permanent (1)
Candido, 2005[38]	Prospective study	693	Interscalene, 30 to 40 mL, NS	Shoulder and upper arm	Awake	No paresthesia reported by 29 patients with neurologic injury	Neurologic injuries (29)	4 to 26 weeks, recovery (29)
Cheney, 1999[39]	Case series (closed claims)	NA	Axillary	NA	Awake (12); GA (1)	Paresthesia during needle placement in 4 patients with nerve injury; paresthesia with injection in 2 of 4 with injury	Brachial plexus injuries (13)	NA
Ediale, 2004[40]	Case report		Interscalene, 30 mL, NS	Shoulder	Awake	No paresthesia	Hemidiaphragmatic paresis	18 months, improvement

Fanelli, 1999[41]	Prospective cohort study	3,996	Axillary, 23 ± 5 mL; interscalene, 25 ± 5 mL; femoral/sciatic, 28 ± 4 mL, NS	Upper and lower extremities	Awake	Paresthesia during block placement (629) No paresthesia during block placement (3,367)	Neurologic dysfunction (14) Neurologic dysfunction (55)	4 to 12 weeks, recovery (68); injury still present in 1 patient at 25 weeks
Giaufre, 1996[42]	Prospective study	4,090 children	Peripheral nerve blocks	NA	GA or sedated or awake	NA	Neurologic injuries (0)	1 month
Gillespie, 1987[43]	Case report		Interscalene, 20 mL, P	Finger	Awake	Paresthesia during needle placement; none during injection	Reflex sympathetic dystrophy (1)	90% relief of symptoms at 10 weeks
Imran, 2004[44]	Case report		Axillary, 20 mL, transarterial	Hand	NA	Uneventful	Axillary nerve injury	8 months, permanent
Kaufman, 2000[45]	Case series	7	Supraclavicular (2); axillary (2); stellate ganglia (1); wrist (1); upper cervical region (1)	Upper extremity	Awake	Pain during injection (7)	Nerve injuries (7)	2 to 3 years, permanent
Lim, 1984[46]	Case report		Supraclavicular, 35 mL, P	Finger	Awake	Paresthesia during needle placement; none during injection	Brachial plexus injury (1)	8 weeks, recovery
Pearce, 1996[47]	Prospective study	200	Axillary, 50 mL, transarterial	Hand, forearm, elbow	Awake	No paresthesia reported in 8 patients with dysesthesia	Dysesthesia (8)	2 to 7 days, recovery (5); persisting symptoms (3)
Shah, 2005[48]	Case report		Sciatic, anterior approach, 30 mL, NS	Lower leg	Awake	High resistance at beginning of injection; no paresthesia	Common peroneal neuropathy (1)	3 years, permanent
Stan, 1995[49]	Prospective study	1,000	Axillary, 40 to 50 mL, transarterial	Upper limb	Awake	No paresthesia reported by 2 patients with injury	Ulnar nerve injury (1) Median nerve injury (1)	<1 month, recovery (2)
Stark, 1996[50]	Case series	3	Axillary, 40 to 45 mL	Hand	NA	No unusual issues	Ulnar nerve injury (2) Median nerve injury (1)	3 years, permanent
Sukhani, 1994[51]	Case report		Interscalene, 40 mL, NS	Shoulder	NA	No paresthesia during block	Horner's syndrome	1 month, steady resolution
Tsao, 2004[52]	Retrospective review	NA	Axillary, NA	Hand	NA	NA	Infraclavicular brachial plexopathy (13)	3 months to 2.5 years, recovery (2); permanent (9); lost to follow-up (2)
Walton, 2000[53]	Case report		Interscalene, 40 mL, NS	Shoulder	Awake	No paresthesia during block	Brachial plexopathy	26 weeks, recovery
Weber, 2002[54]	Retrospective study	218	Interscalene, 36 ± 6 mL, NS	Shoulder	Awake	NA	Neurologic injuries (2)	1 to 2 years, recovery (1); permanent (1)
Winchell, 1985[55]	Prospective study	854	Brachial plexus block, NA, P	Upper extremity	Awake	Paresthesia during needle placement in all injured patients	Neuropathy (3)	18 days to 7 months, recovery (3)

Abbreviations: GA, general anesthesia; LA, local anesthetic; NA, not available; NS, nerve stimulation technique; P, paresthesia-seeking technique.

Table 2. Recommendations: Performing Regional Anesthesia in Anesthetized or Heavily Sedated Patients*

Limiting local anesthetic systemic toxicity
- The potential ability of general anesthesia or heavy sedation to obscure early signs of *systemic local anesthetic toxicity* is not a valid reason to forgo performing peripheral or epidural nerve blocks in anesthetized or heavily sedated patients. (Class I)

Limiting neural injury

Monitoring and prevention
- There are no data to support the concept that peripheral nerve stimulation or ultrasound guidance, and/or injection pressure monitoring, reduce the risk of peripheral nerve injury in patients under general anesthesia or heavy sedation. (Class I) Because ultrasound-guided peripheral nerve block and pressure monitoring are relatively new technologies, this recommendation may change with the acquisition of more clinical experience and data.

Adult neuraxis
- Warning signs such as paresthesia or pain on injection of local anesthetic inconsistently herald needle contact with the spinal cord. Nevertheless, some patients do report warning signs of needle-to-neuraxis proximity. General anesthesia or heavy sedation removes any ability for the patient to recognize and report warning signs. This suggests that neuraxial regional anesthesia should be performed rarely in adult patients whose sensorium is compromised by general anesthesia or heavy sedation. (Class II)

Pediatric neuraxis
- The benefit of ensuring a cooperative and immobile infant or child may outweigh the risk of performing neuraxial regional anesthesia in pediatric patients undergoing general anesthesia or heavy sedation. The overall risk of neuraxial anesthesia should be weighed against its expected benefit. (Class II)

Interscalene blocks
- Case reports document spinal cord injury during the placement of interscalene blocks in patients under general anesthesia, which heightens concern associated with this practice. Interscalene blocks should not be performed in anesthetized or heavily sedated adult or pediatric patients. (Class I)

Adult peripheral nerve blocks
- Because general anesthesia or heavy sedation removes all opportunity for adults to communicate symptoms of potential nerve injury, peripheral nerve blockade should not be routinely performed in most adults during general anesthesia or heavy sedation. However, the risk-to-benefit ratio of performing peripheral nerve blockade under these conditions may improve in select patient populations (e.g., dementia, developmental delay, or when unintended movement could compromise vital structures). (Class II)

Pediatric peripheral nerve blocks
- Regardless of wakefulness, infants and children may be unable to communicate symptoms of potential peripheral nerve injury. However, uncontrolled movement may increase the risk of injury. Therefore, the placement of peripheral nerve blocks in children undergoing general anesthesia or heavy sedation may be appropriate after duly considering individual risk-to-benefit ratio. (Class II)

**Anesthetized* refers to patients under general anesthesia. *Heavy sedation* is defined as the patient being sedated to the point of being unable to recognize and/or report any sensation that the physician would interpret as atypical during block placement.

ditional insight into the role of paresthesias and nerve stimulators.[66] These investigators used ultrasound to visualize 22-gauge, insulated, short bevel needles as they were intentionally advanced toward nerves in the axillary brachial plexus with sufficient force to gently displace the nerve. Patients were then asked if they felt a paresthesia and the nerve stimulator was turned on and the current slowly increased until a motor response occurred. Interestingly, only 39 of 104 patients reported a paresthesia as the needle contacted the nerve (as directly visualized by ultrasound) and the likelihood of reporting a paresthesia was independent of the amount of midazolam the patients received (0-5 mg). A motor response was elicited in only 75% of patients at a current <0.5 mA, and in 100% at a current <1.0 mA. These observations suggest that ultrasound is a more sensitive indicator of needle proximity to peripheral nerves than either paresthesia or motor response to a nerve stimulator. Whether this will translate into greater safety with respect to nerve injury is yet to be seen. Importantly, there is reason to believe that use of ultrasound to prevent needle-to-nerve contact may not entirely avoid nerve injury or even intraneural injection.[67] Bigeleisen[68] reports observing nerve puncture and intentional intraneural local anesthetic injection in 21 patients undergoing ultrasound-guided axillary block. In total, 72 nerves were punctured and received an intraneural local anesthetic injection, although no patient developed neurological injury. This study suggests that needle-to-nerve contact may not be as important a cause of nerve injury as we previously assumed. Furthermore, it calls into question the relative importance of intraneural/subepineurium versus intraneural/subperineurium needle placement and/or injection. The latter may be relatively more important and potentially more injurious because it disrupts the protective coverings that surround the fascicles, thus exposing axons to local anesthetic and/or additives.

Available data suggest that in the hands of persons with the necessary expertise ultrasound can improve our ability to identify targeted nerve and therefore possibly reduce mechanical nerve injury. However, nerve injury caused by toxic effects of local anesthetic on the nerve will probably not be reduced by use of ultrasound. Because the relationship between mechanical trauma and nerve injury is not clear, it should not be concluded that ultra-

sound will necessarily reduce the incidence or severity of peripheral nerve injury.

In summary, there are no data to support the concept that peripheral nerve stimulation or ultrasound guidance reduces the risk of peripheral nerve injury in patients under general anesthesia or heavy sedation. Because ultrasound-guided peripheral nerve block is a relatively new technology, this recommendation may change with the acquisition of more clinical experience and data. Similar considerations apply to our emerging knowledge of injection pressure monitoring.[69,70] This recommendation is based on human clinical data and general agreement of expert opinion, as such, this is a class I recommendation (Table 2).

Pediatric Regional Anesthesia

Although the safety of performing regional anesthesia in anesthetized or heavily sedated adults is a subject of vigorous debate, there is substantially less debate among pediatric regional anesthesiologists. In fact, heavy sedation or general anesthesia prior to performing regional blocks is the standard practice of most pediatric anesthesiologists. The reason is that infants and young children are unlikely to accept the needles, nerve stimulators, or cold ultrasound transducers that are requisites of regional anesthesia practice. Thus, without heavy sedation or general anesthesia, regional blocks would be all but impossible in pediatric anesthesia.

Why should we accept this practice virtually without question in the child but not the adult? The answer derives from differences in risk-to-benefit balance between the adult and the child. For example, a valid argument for not performing regional blocks in anesthetized or heavily sedated adults is that the physician loses the ability to ask the patient about subjective signs of accidental intravascular injection. However, infants and young children are incapable of providing this information, regardless of the child's state of wakefulness. A similar argument for not anesthetizing adults prior to regional blocks is to prevent nerve injury by using the patient as a monitor of needle-to-nerve contact or intraneural injection. Again, even awake infants and young children are incapable of articulating that they felt a paresthesia, thus general anesthesia does not remove this potential, albeit unproved, safety monitor. In fact, anesthesia or heavy sedation makes the use of nerve stimulators and ultrasound easier, while removing the risk of sudden movement.

Thus, the basis for treating infants/children differently than adults lies in the fact that adults should be able to lie still in the absence of general anesthesia or heavy sedation and, through effective communication, can provide potentially valuable safety information. Children cannot do likewise, consequently no safety information is lost if they are anesthetized or heavily sedated during regional blocks. Importantly, there are adults who have the same limitations as do infants/children, but for different reasons. Severe dementia, profound developmental delay, incapacitating mental illness, etc., may prevent an adult from "participating" in regional blocks. In these situations, as with children, it is not unreasonable to consider performing regional blocks during heavy sedation or general anesthesia when the clinician believes the patient will derive benefit from the block (Table 2).

There are some observational data available regarding pediatric practice. Giaufre et al. performed a prospective study that relied on voluntary reporting to a central registry in France.[42] These investigators received data on 19,103 blocks in pediatric patients, 95% of whom were anesthetized or sedated. There were a total of 23 minor complications and no serious complications or nerve injury reported. Thus, the complication rate was 1.2 per 1,000 procedures. While this may seem reassuring one must keep the study's limitations in mind. First, infants and young children cannot complain of dysesthesias, persistent paresthesias, subclinical motor impairment, sexual dysfunction, or cannot detect bowel or bladder incontinence prior to toilet training. Second, reporting was voluntary, which can place into question whether all complications were reported. Finally, the absence of major morbidity does not mean it will not occur. Statistically, the true incidence of any unreported event can be as high as 3/n. Thus, although the authors reported 2,396 epidural blocks without spinal cord injury, the incidence of spinal cord injury could still be as high as 1.3/1,000 (3/2,396).

Based on the available literature, and the significant differences between children and adults with respect to self-control and the ability to communicate effectively, it is our recommendation that anesthesia or heavy sedation should not be considered an absolute contraindication to regional anesthesia in children. This recommendation is based on human data and general agreement of expert opinion; as such, this is a class II recommendation (Table 2).

Summary

The decision to perform regional anesthesia or pain medicine procedures in anesthetized or heavily sedated patients is controversial, complicated, and must be made in the absence of traditional forms of evidence-based medicine. Our recommendations, which

tend towards conservative interpretation of the literature and expert opinion, are summarized in Table 2. Regional anesthesia is undergoing significant changes in how regional blocks are administered. The introduction of ultrasound guidance, new modes of electrical nerve stimulation,[71] and injection pressure monitoring[69,70] hold the promise of increasing the effectiveness, and possibly safety, of peripheral and neuraxial blocks. Should future clinical trials prove that the new monitoring methods during peripheral nerve block are beneficial, the current recommendations would require updating.

Appendix 1

The classification system used is shown in Appendix 1.

References

1. Auroy Y, Benhamou D, Bargues L, Ecoffey C, Falissard B, Mercier F, Bouaziz H, Samii K. Major complications of regional anesthesia in France. The SOS regional anesthesia hotline service. *Anesthesiology* 2002;97:1274-1280.
2. Brown DL, Ransom DM, Hall JA, Leicht CH, Schroeder DR, Offord KP. Regional anesthesia and local anesthetic-induced systemic toxicity: seizure frequency and accompanying cardiovascular changes. *Anesth Analg* 1995;81:321-328.
3. Scott DB. Evaluation of the toxicity of local anaesthetic agents in man. *Br J Anaesth* 1975;47:56-61.
4. Scott DB, Lee A, Fagan D, Bowler GMR, Bloomfield P, Lundh R. Acute toxicity of ropivacaine compared with that of bupivacaine. *Anesth Analg* 1989;69:563-569.
5. Moore JM, Liu SS, Neal JM. Premedication with fentanyl and midazolam decreases the reliability of intravenous lidocaine test dose. *Anesth Analg* 1998;86:1015-1017.
6. Mulroy MF, Neal JM, Mackey DC, Harrington BE. 2-Chloroprocaine and bupivacaine are unreliable indicators of intravascular injection in the premedicated patient. *Reg Anesth Pain Med* 1998;23:9-13.
7. Korevaar WC, Burney RG, Moore PA. Convulsions during stellate ganglion block. *Anesth Analg* 1979;58:329-330.
8. Mulroy MF, Norris MC, Liu SS. Safety steps for epidural injection of local anesthetics: review of the literature and recommendations. *Anesth Analg* 1997;85:1346-1356.
9. Guinard JP, Mulroy MF, Carpenter RL. Aging reduces the reliability of epidural epinephrine test doses. *Reg Anesth* 1995;20:193-198.
10. Tanaka M, Goyagi T, Kimura T, Nishikawa T. The efficacy of hemodynamic and T wave criteria for detecting intravascular injection of epinephrine test doses in anesthetized adults: a dose-response study. *Anesth Analg* 2000;91:1196-1202.
11. Tanaka M, Nishikawa T. The combination of epinephrine and isoproterenol as a simulated epidural test dose in isoflurane-anesthetized adults. *Anesth Analg* 1998;86:1312-1317.
12. Tanaka M, Nishikawa T. A comparative study of hemodynamic and T-wave criteria for detecting intravascular injection of the test dose (epinephrine) in sevoflurane-anesthetized adults. *Anesth Analg* 1999;89:32-36.
13. Tanaka M, Nishikawa T. Efficacy of simulated intravenous test dose in the elderly during general anesthesia. *Reg Anesth Pain Med* 1999;24:393-398.
14. Tanaka M, Nishikawa T. T-wave amplitude as an indicator for detecting intravascular injection of epinephrine test dose in awake and anesthetized elderly patients. *Anesth Analg* 2001;93:1332-1337.
15. Tanaka M, Takahashi S, Kondo T, Matsumiya N. Efficacy of simulated epidural test doses in adult patients anesthetized with isoflurane: a dose-response study. *Anesth Analg* 1995;81:987-992.
16. Feinstein MB, Lenard W, Mathias J. The antagonism of local anesthetic induced convulsions by the benzodiazepine derivative diazepam. *Arch Int Pharmacodyn Ther* 1970;187:144-154.
17. Lee VC, Moscicki JC, DiFazio CA. Propofol sedation produces dose-dependent suppression of lidocaine-induced seizures in rats. *Anesth Analg* 1998;86:652-657.
18. Torbiner ML, Yagiela JA, Mito RS. Effect of midazolam pretreatment on the intravenous toxicity of lidocaine with and without epinephrine in rats. *Anesth Analg* 1989;68:744-749.
19. Burney RG, DiFazio CA, Foster JA. Effects of pH on protein binding of lidocaine. *Anesth Analg* 1978;57:478-480.
20. Englesson S. The influence of acid-base changes on central nervous system toxicity of local anaesthetic agents. I. An experimental study in cats. *Acta Anaesthesiol Scand* 1974;18:79-87.
21. Ohmura S, Ohta T, Yamamoto K, Kobayashi T. A comparison of the effects of propofol and sevoflurane on the systemic toxicity of intravenous bupivacaine in rats. *Anesth Analg* 1999;88:155-159.
22. Bernards CM, Carpenter RL, Rupp SM, Brown DL, Morse BV, Morell RC, Thompson GE. Effect of midazolam and diazepam premedication on central nervous system and cardiovascular toxicity of bupivacaine in pigs. *Anesthesiology* 1989;70:318-323.
23. Bernards CM, Artru AA. Effect of intracerebroventricular picrotoxin and muscimol on intravenous bupivacaine toxicity. Evidence supporting central nervous system involvement in bupivacaine cardiovascular toxicity. *Anesthesiology* 1993;78:902-910.
24. Bernards CM, Artu AA. Hexamethonium and midazolam terminate dysrhythmias and hypertension caused by intracerebroventricular bupivacaine in rabbits. *Anesthesiology* 1991;74:89-96.
25. Eagle KA, Berger PB, Calkins H, Chaitman BR, Ewy GA, Fleischmann KE, Fleisher LA, Froehlich JB, Gusberg RJ, Leppo JA, Ryan T, Schlant RC, Winters WL Jr, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Jacobs AK, Hiratzka LF, Russell RO,

Smith SC Jr, American College of Cardiology, American Heart Association. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery–executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *J Am Coll Cardiol* 2002;39:542-553.
26. Casati A, Baciarello M, Di Cianni S, Danelli G, De Marco G, Leone S, Rossi M, Fanelli G. Effects of ultrasound guidance on the minimum effective anaesthetic volume required to block the femoral nerve. *Br J Anaesth* 2007;98:823-827.
27. Zetlaoui PJ, Labbe JP, Benhamou D. Ultrasound guidance for axillary plexus block does not prevent intravascular injection. *Anesthesiology* 2008;108:761.
28. Borgeat A, Ekatodramis G, Kalberer F, Benz C. Acute and nonacute complications associated with interscalene block and shoulder surgery. A prospective study. *Anesth Analg* 2001;95:875-880.
29. Lynch NM, Cofield RH, Silbert PL, Hermann RC. Neurologic complications after total shoulder arthroplasty. *J Shoulder Elbow Surg* 1996;5:53-61.
30. McFarland EG, Caicedo JC, Guitterez MI, Sherbondy PS, Kim TK. The anatomic relationship of the brachial plexus and axillary artery to the glenoid. Implications for anterior shoulder surgery. *Am J Sports Med* 2001;29:729-733.
31. Al-Nasser B, Palacios JL. Femoral nerve injury complicating continuous psoas compartment block. *Reg Anesth Pain Med* 2004;29:361-363.
32. Auroy Y, Narchi P, Messiah A, Litt L, Rouvier B, Samii K. Serious complications related to regional anesthesia. Results of a prospective survey in France. *Anesthesiology* 1997;87:479-486.
33. Barutell C, Vidal F, Raich M, Montero A. A neurological complication following interscalene brachial plexus block *Anaesthesia* 1980;35:365-367.
34. Bashein G, Robertson HT, Kennedy WF. Persistent phrenic nerve paresis following interscalene brachial plexus block. *Anesthesiology* 1985;63:102-104.
35. Ben-David B. Retrospective study of the instance of neurological injury after axillary brachial plexus block. *Pain Pract* 2006;6:119-123.
36. Bogdanov A, Loveland R. Is there a place for interscalene block performed after induction of general anaesthesia? *Eur J Anaesth* 2005;22:107-110.
37. Bonner SM, Pridie AK. Sciatic nerve palsy following uneventful sciatic nerve block. *Anaesthesia* 1997;52: 1205-1207.
38. Candido KD, Sukhani R, Doty R, Nader A, Kendall MC, Yaghmour E, Kataria TC, McCarthy R. Neurologic sequelae after interscalene brachial plexus block for shoulder/upper arm surgery: the association of patient, anesthetic, and surgical factors to the incidence and clinical course. *Anesth Analg* 2005;100: 1489-1495.
39. Cheney FW, Domino KB, Caplan RA, Posner KL. Nerve injury associated with anesthesia: a closed claims analysis. *Anesthesiology* 1999;90:1062-1069.
40. Ediale KR, Myung CR, Neuman GG. Prolonged hemidiaphragmatic paralysis following interscalene brachial plexus block. *J Clin Anesth* 2004;16:573-575.
41. Fanelli G, Casati A, Garancini P, Torri G. Nerve stimulator and multiple injection technique for upper and lower limb blockade: failure rate, patient acceptance, and neurologic complications. Study Group on Regional Anesthesia. *Anesth Analg* 1999; 88:847-852.
42. Giaufre E, Dalens B, Gombert A. Epidemiology and morbidity of regional anesthesia in children: a one-year prospective survey of the French-Language Society of Pediatric Anesthesiologists. *Anesth Analg* 1996;83:904-912.
43. Gillespie JH, Menk EJ, Middaugh RE. Reflex sympathetic dystrophy: a complication of interscalene block. *Anesth Analg* 1987;66:1316-1317.
44. Imran D, Javaid M, Logan A. Axillary nerve injury in axillary block. *Plast Reconstr Surg* 2004;113:1084.
45. Kaufman BR, Nystrom E, Nath S, Foucher G, Nystrom A. Debilitating chronic pain syndromes after presumed intraneural injections. *Pain* 2000;85:283-286.
46. Lim EK, Pereira R. Brachial plexus injury following brachial plexus block. *Anaesthesia* 1984;39:691-694.
47. Pearce H, Lindsay D, Leslie K. Axillary brachial plexus block in two hundred consecutive patients. *Anaesth Intensive Care* 1996;24:453-458.
48. Shah S, Hadzic A, Vloka JD, Cafferty MS, Moucha CS, Santos AC. Neurologic complication after anterior sciatic nerve block. *Anesth Analg* 2005;100:1515-1517.
49. Stan TC, Krantz MA, Solomon DL, Poulos JG, Chaouki K. The incidence of neurovascular complications following axillary brachial plexus block using a transarterial approach. *Reg Anesth* 1995;20:486-492.
50. Stark RH. Neurologic injury from axillary block anesthesia. *J Hand Surg [Am]* 1996;21:391-396.
51. Sukhani R, Barclay J, Aasen M. Prolonged Horner's syndrome after interscalene block: a management dilemma. *Anesth Analg* 1994;79:601-603.
52. Tsao BE, Wilbourn AJ. Infraclavicular brachial plexus injury following axillary regional block. *Muscle Nerve* 2004;30:44-48.
53. Walton JS, Folk JW, Friedman RJ, Dorman GH. Complete brachial plexus palsy after total shoulder arthoplasty done with interscalene block anesthesia. *Reg Anesth Pain Med* 2000;25:318-321.
54. Weber SC, Jain R. Scalene regional anesthesia for shoulder surgery in a community setting: an assessment of risk. *J Bone Joint Surg Am* 2002;84-A:775-779.
55. Winchell SW, Wolfe R. The incidence of neuropathy following upper extremity nerve blocks. *Reg Anesth* 1985;10:12-15.
56. Faryniarz D, Morelli C, Coleman S, Holmes T, Allen A, Altchek D, Cordasco F, Warren RF, Urban MK, Gordon MA. Interscalene block anesthesia at an ambulatory surgery center performing predominantly

regional anesthesia: a prospective study of one hundred thirty-three patients undergoing shoulder surgery. *J Shoulder Elbow Surg* 2006;15:686-690.
57. Ben-David B, Barak M, Katz Y, Stahl S. A retrospective study of the incidence of neurological injury after axillary brachial plexus block. *Pain Pract* 2006;6:119-123.
58. Capdevila X, Pirat P, Bringuier S, Gaertner E, Singelyn FJ, Bernard N, Choquet O, Bouaziz H, Bonnet F. Continuous peripheral nerve blocks in hospital wards after orthopedic surgery. *Anesthesiology* 2005;103:1035-1045.
59. Selander D. Peripheral nerve injury caused by injection needles. *Br J Anaesth* 1993;71:323-325.
60. Choyce A, Chan VW, Middleton WJ, Knight PR, Peng P, McCartney CJ. What is the relationship between paresthesia and nerve stimulation for axillary brachial plexus block? *Reg Anesth Pain Med* 2001;26:100-104.
61. Urmey WF, Stanton J. Inability to consistently elicit a motor response following sensory paresthesia during interscalene block administration. *Anesthesiology* 2002;96:552-554.
62. Chan VW, Brull R, McCartney CJ, Xu D, Abbas S, Shannon P. An ultrasonic and histologic study of intraneural injection and electrical stimulation in pigs. *Anesth Analg* 2007;104:1281-1284.
63. Tsai TP, Vuckovic I, Dilberovic F, Obhodzas M, Kapur E, Divanovic KA, Hadzic A. Intensity of the stimulating current may not be a reliable indicator of intraneural needle placement. *Reg Anesth Pain Med* 2008;33:207-210.
64. Sites BD, Brull R, Chan VWS, Spence BC, Gallagher J, Beach ML, Sites VR, Hartman GS. Artifacts and pitfall errors associated with ultrasound-guided regional anesthesia. Part II: a pictorial approach to understanding and avoidance. *Reg Anesth Pain Med* 2007;32:419-433.
65. Sites BD, Spence BC, Gallagher J, Wiley CW, Bertrand ML, Blike GT. Characterizing novice behavior associated with learning ultrasound-guided peripheral regional anesthesia. *Reg Anesth Pain Med* 2007;32:107-115.
66. Perlas A, Niazi A, McCartney C, Chan V, Xu D, Abbas S. The sensitivity of motor response to nerve stimulation and paresthesia for nerve localization as evaluated by ultrasound. *Reg Anesth Pain Med* 2006;31:445-450.
67. Koff MD, Cohen JA, McIntyre JJ, Carr CF, Sites BD. Severe brachial plexopathy after an ultrasound-guided single-injection nerve block for total shoulder arthroplasty in a patient with multiple sclerosis. *Anesthesiology* 2008;108:325-328.
68. Bigeleisen PE. Nerve puncture and apparent intraneural injection during ultrasound-guided axillary block does not invariably result in neurologic injury. *Anesthesiology* 2006;105:779-783.
69. Hadzic A, Dilberovic F, Shah S, Kulenovic A, Kapur E, Zaciragic A, Cosovic E, Vuckovic I, Divanovic KA, Mornjakovic Z, Thys DM, Santos AC. Combination of intraneural injection and high injection pressure leads to fascicular injury and neurologic deficits in dogs. *Reg Anesth Pain Med* 2004;29:417-423.
70. Tsui BC, Knezevich MP, Pillay JJ. Reduced injection pressures using a compressed air injection technique (CAIT): an in vitro study. *Reg Anesth Pain Med* 2008;33:168-173.
71. Urmey WF, Grossi P. Use of sequential electrical nerve stimuli (SENS) for location of the sciatic nerve and lumbar plexus. *Reg Anesth Pain Med* 2006;31:463-469.

Appendix 1. Strength of Recommendations

Classification	
I	Animal and/or human evidence, and/or general agreement of expert opinion, support the effectiveness and usefulness of the recommendation.
II	The weight of conflicting evidence and/or the weight of expert opinion support the usefulness of the recommendation.
III	The usefulness of the recommendation is limited by absent or conflicting evidence and/or divergent expert opinion.

NOTE. This classification system is significantly modified from the American College of Cardiology/American Heart Association construct for classifying strength of evidence.[25]