Anatomy and Pathophysiology of Spinal Cord Injury Associated With Regional Anesthesia and Pain Medicine

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The American Society of Regional Anesthesia and Pain Medicine (ASRA) convened a panel in April 2005 to create a Practice Advisory on the Neurologic Complications of Regional Anesthesia and Pain Medicine. This review deals with the pathophysiology of spinal cord injury. The Practice Advisory recommendations are based on extensive review of existing animal and human studies, case reports, pathophysiology, and expert opinion.

The pathophysiology of spinal cord injury associated with anesthesia techniques is reviewed in depth, including mechanical trauma from direct needle injury or mass lesions, vascular injury from direct needle trauma or spinal cord infarction, and neurotoxicity from local anesthetics and adjuvants. Eight specific recommendations are offered that may reduce the likelihood of spinal cord injury associated with regional anesthetic or pain medicine techniques. Spinal cord injuries associated with regional anesthesia and pain medicine are exceedingly rare. The Practice Advisory's recommendations may, in selected cases, reduce the likelihood of injury, but the vast majority of these injuries are neither predictable nor preventable.

Injury to the neuraxis as a consequence of regional anesthesia or pain medicine procedures is ultimately linked to anatomic and/or physiologic damage to the spinal cord, the spinal nerve roots, or their blood supply. Mechanisms of injury are sometimes identifiable, as in the case of epidural hematoma, but can also be exceedingly difficult to pinpoint, as exemplified by most cases of presumed spinal vascular injury. This article will review the pathophysiology of spinal cord injury, including mechanical, vascular, and neurotoxic etiologies. Its goal is to provide an anatomic and pathophysiologic basis from which to build an understanding of neuraxial complications associated with regional anesthesia and pain medicine.

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Mechanical Injury

Many neuraxial anesthetic complications are secondary to mechanical injury of the spinal cord, spinal nerve roots, or the spinal nerves as they exit the intervertebral foramina. Injury to these structures may involve the vertebral column, space-occupying lesions within the vertebral canal, or direct trauma. These various mechanisms ultimately lead to loss of anatomic and/or physiologic neural integrity and often result in permanent injury.[1]

Direct Needle Trauma

The vertebral column acts as a protective barrier to the sensitive neural structures contained within. The anesthesiologist desires to gain access to these underlying spaces in a controlled, precise manner. Deposition of anesthetic agents into the subarachnoid space presumes that the needle is introduced caudad to the conus medullaris, thereby avoiding contact with the spinal cord. Case reports and medicolegal review suggest that direct spinal cord trauma has been associated with excessively caudad termination of the spinal cord and/or inaccurate determination of bony landmarks that overlie where the conus medullaris ends.[1,2] The spinal cord's termination typically coincides with the L1-2 vertebral interspace, but wide variation exists, with the terminus potentially occurring as high as T12 or as low as L4.[3] A line drawn between the iliac crests (Tuffier's line) usually corresponds to the L4-5 interspace or the L4 spinous process, but may instead cross the L3-4 or L5-S1 interspaces.[3] Furthermore, a practitioner's identification of a vertebral interspace is often inaccurate by 1 level cephalad or caudad, and up to 4 levels

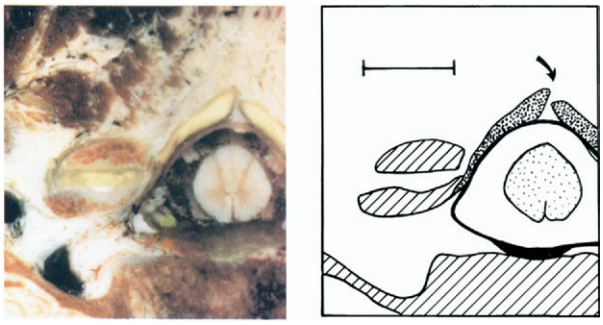

Fig 1. Cryomicrotome axial section of the C7-T1 spine. Note that the ligamentum flavum has failed to fuse in the midline (arrow), thereby permitting needle entry into the epidural space without the customary loss of resistance. Cryomicrotome from Quinn H. Hogan, M.D. Reprinted from Hogan.[5]

in patients whose surface landmarks are difficult to palpate.[2,4] These anatomic variations potentially lead to needle placement more cephalad than intended, exposing the spinal cord to direct trauma.

Two other anatomic occurrences contribute to unintentionally placing a needle too close to the spinal cord. Accurate placement of an epidural needle relies on the ligamentum flavum to signal proximity to the epidural space and to indicate entry into it when loss of resistance occurs. However, the ligamentum flavum does not always fuse in the midline,[5] potentially permitting needle passage directly into the epidural or subarachnoid space without benefit of the customary firmness followed by loss of resistance (Fig 1). This anatomic anomaly occurs throughout the neuraxis, but is particularly prevalent in the upper thoracic and cervical regions.[5,6] Similar failure to contact identifiable landmarks during needle passage can arise with congenital dysraphisms, such as spina bifida occulta. Second, the potential to unintentionally penetrate the meninges increases substantially as one moves cephalad along the neuraxis, because the posterior-to-anterior dimensions of the epidural space decrease from 5 mm to 8 mm in the lumbar spine to 1 mm to 2 mm in the upper thoracic and cervical spine.[5] Once a needle enters the spinal cord, damage occurs as a result of physical disruption of neural elements with accompanying edema or hematoma,[7,8] central syrinx creation from injected local anesthetic solution,[9,10] local anesthetic or adjuvant toxicity, or a combination of these mechanisms.[11] Permanent damage is more likely to accompany the injection of solutions into the spinal cord; the simple passage of a needle into the spinal cord or nerve roots without subsequent injection may not necessarily cause injury.

Trauma to spinal nerve roots or spinal nerves represents another cause of mechanical injury. Midline or paramedian approaches to the neuraxis should easily avoid contact with spinal nerves, which are partially protected by the vertebral laminae and transverse processes, and are sufficiently lateral to avoid contact with medially directed needles. Needles that unintentionally deviate lateral can contact the spinal nerve or the anterior or posterior ramus outside the foramen; or if medial to the facet within the lateral recess, can contact the dorsal nerve roots. Spinal nerves are also vulnerable to needle injury during perispinal techniques such as paravertebral block or from too medially directed needles during psoas compartment block (Fig 2). In

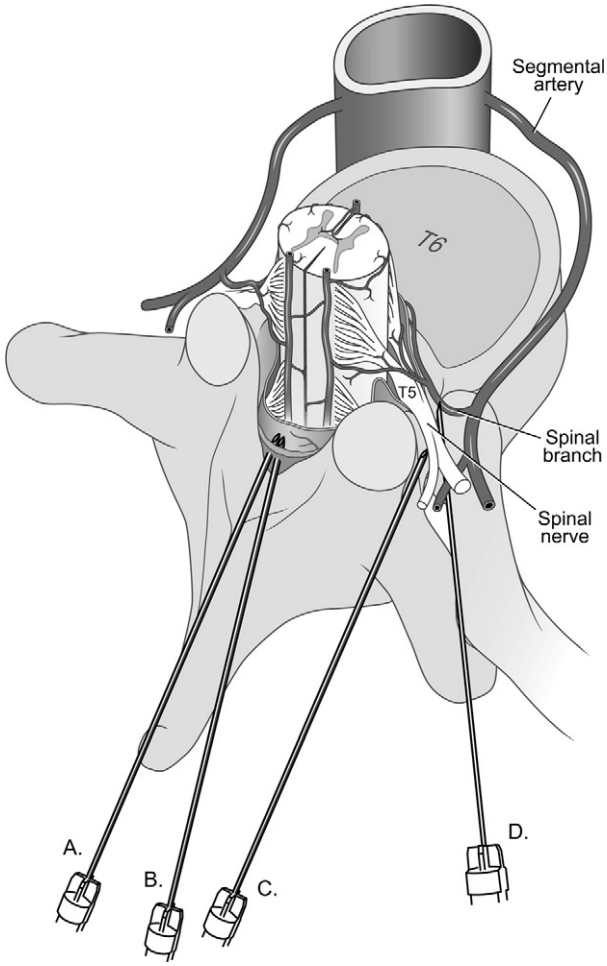

Fig 2. Midline or paramedian approaches to the thoracic neuraxis (needles A and B) are unlikely to encounter spinal nerves or major feeding arteries. However, unintentionally lateral approaches (needle C) are most likely to contact the spinal nerve or the anterior or posterior primary ramus outside of the foramen. A transforaminal approach (needle D) has the potential to come in close proximity to the spinal nerve or spinal artery branch. Note that transforaminal approaches are typically at the cervical or lumbar levels, not the T6 level as illustrated. Illustration by Gary J. Nelson. Reprinted from Neal and Rathmell.[12]

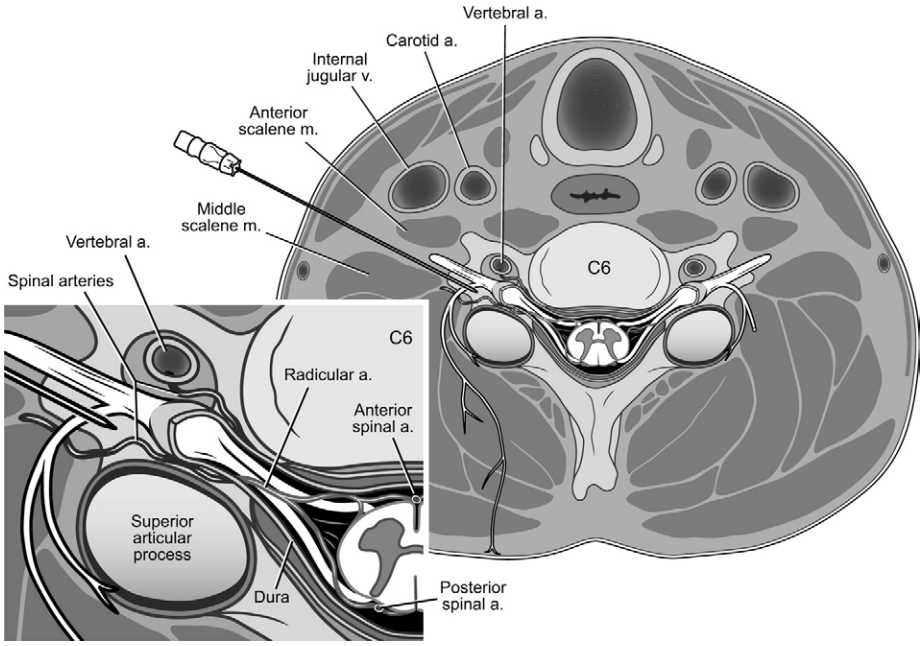

Fig 3. Transforaminal approach to the neuraxis. Note potential for the needle to contact either the spinal nerve or the spinal artery. a, artery; m, ; v, vein. Illustration by Gary J. Nelson. Reprinted from Neal and Rathmell.[12]

pain medicine, spinal nerves and nerve roots are especially vulnerable to needles directed towards the intervertebral foramen, as with cervical or lumbar transforaminal approaches (Fig 3).[13] A rare pathway to spinal cord injury can occur when a needle enters a peripheral nerve and subsequently injected substances travel retrograde along the perineurium to the spinal cord.[14]

Innervation of the meninges and spinal cord is an important component of neuraxial pathophysiology and the patient's recognition of needle trauma. A common misperception is that injury to the spinal cord is always heralded by intense pain or paresthesia, yet the spinal cord is devoid of sensory innervation. Needles or catheters can enter the spinal cord without warning.[2,15-18] Conversely, the actual injection of substances into the spinal cord is more commonly associated with intense sensation,[2,19,20] which has been postulated to result from rapidly increasing intramedullary pressure leading to the massive discharge of afferent neurons. Meningeal innervation is poorly understood.[21] Sensory neurons are variably present in meningeal tissue, as evidenced by the inconsistent awareness of pressure, pain, or paresthesia when needles puncture the meninges.[7,15,18,18a] Epidural local anesthetics do lessen the awareness of meningeal puncture,[22] which provides indirect evidence of clinically relevant sensory innervation. Nevertheless, the neuroanatomy of the spinal cord and its coverings cannot be consistently relied upon to provide warning or indication of needle or catheter-induced trauma.[16]

Clinical implications. When vertebral column protection is breached, whether by accident or intention, the neuraxis is susceptible to needle injury, yet large epidemiological surveys, case reports, and postinjury imaging suggest that direct neuraxis trauma is an exceedingly rare event. Indeed, <50% of academic anesthesiologists include the possibility of permanent neuraxial injury in their informed consent discussions.[22a,22b] Direct spinal cord injury was noted in 6 of 821 regional anesthesia neuraxial claims in the American Society of Anesthesiologists' Closed Claims database[1] and 9 of 127 neuraxial complications reported in over 1.7 million neuraxis anesthetics (0.0005%) performed over a 10-year period in Sweden.[2] Reports of injury and medicolegal databases provide valuable information, but are biased by the very presence of injury. Thus, the true incidence of neuraxis injury associated with anesthetic techniques is difficult to ascertain—arguably over emphasized by medicolegal databases, but under reported by anesthesiologists as a whole.

Pathophysiologically, the significance of a paresthesia is unclear. Paresthesia during spinal anesthesia can be common (6.3%),[23] while actual injury is exceedingly rare (0 to 8 per 10,000).[24] Descriptions of documented neuraxis injury present an inconsistent picture of nonanesthetized patients who either experience no warning signs during needle passage or alternatively, experience paresthesia only, pain with injection, or both.[1,2,19,23,25] There is some evidence to suggest that patients who experience pain on injection of an anesthetic agent are more likely to manifest injury (even when the injection is stopped and the needle repositioned); the injury often follows the same radicular pattern as its premonitory warning.[19]

Comparative outcome studies of performing neuraxial regional anesthesia in awake versus anesthetized patients do not exist and are unlikely to be performed because of the huge numbers of patients required to attain statistical significance of any results. Physicians must therefore rely on expert opinion, case reports, pathophysiology, and a few published series that have noteworthy limitations to their interpretation. For example, Horlocker et al.[26] reported placement of 4,298 lumbar epidural catheters in anesthetized adult patients without neurologic complications (95% CI, 0%-0.08%). Translation of these results to clinical practice must acknowledge their specific limitations: (1) all catheters were placed at lumbar levels, where unintentional contact with the easily moveable cauda equina may bear little relevance to the fixed thoracic spinal cord; (2) 99% of patients received neuraxial opioids alone, which do not possess the same neurotoxic potency as local anesthetics; and (3) the authors' 95% confidence interval suggests that major injury could occur in as many as 8 of 10,000 patients. Giaufre et al.[27] reported a similar experience with 15,013 pediatric patients undergoing neuraxial techniques, the majority of whom were lightly anesthetized (89%) or sedated (6%). Over half received caudal anesthesia and only 6% received thoracic epidural analgesia. By calculating the upper limit of the 95% confidence interval,[28] the results of Giaufre et al. suggest that neurologic injury could result from placing neuraxial blocks (mostly caudal and lumbar) in 2 per 10,000 anesthetized children. These results are arguably more reassuring than those reported in adult patients, because of the risk of an uncooperative infant or child sustaining injury during block placement. Although ultrasound can reliably predict skin-to-ligamentum flavum distance in infants and children, there is no evidence that doing so will affect the occurence of clinical injury.[28a]

Mass Lesions

The neuraxis is vulnerable to injury when masses within the central vertebral canal compete with the spinal cord for space. Intradural or extradural mass lesions effectively reduce available cross-sectional area within the canal and either directly compresses the spinal cord and/or increases cerebrospinal fluid (CSF) pressure. Injected and infused anesthetic solutions can further increase epidural space and CSF pressure.[29,30] Eventually, spinal cord compression or increased CSF pressure impairs blood flow by limiting arterial inflow, venous outflow, or by exceeding capillary pressure. Spinal cord ischemia or infarction then becomes the final common pathway to injury.

Reduction of vertebral canal cross-sectional area can be degenerative, acquired, or positional in nature. Degenerative changes include osteoporosis[2] and bony or soft tissue hypertrophy, including narrowed intervertebral foramina that impede the normal pressure-relieving egress of fluids from the epidural space.[5,31] The degree to which degenerative changes impact cross-sectional area is variable, ranging from mild bulging of disc material to severe encroachment of the vertebral canal by herniated nucleus pulposus or bony spurs (Fig 4). Collectively

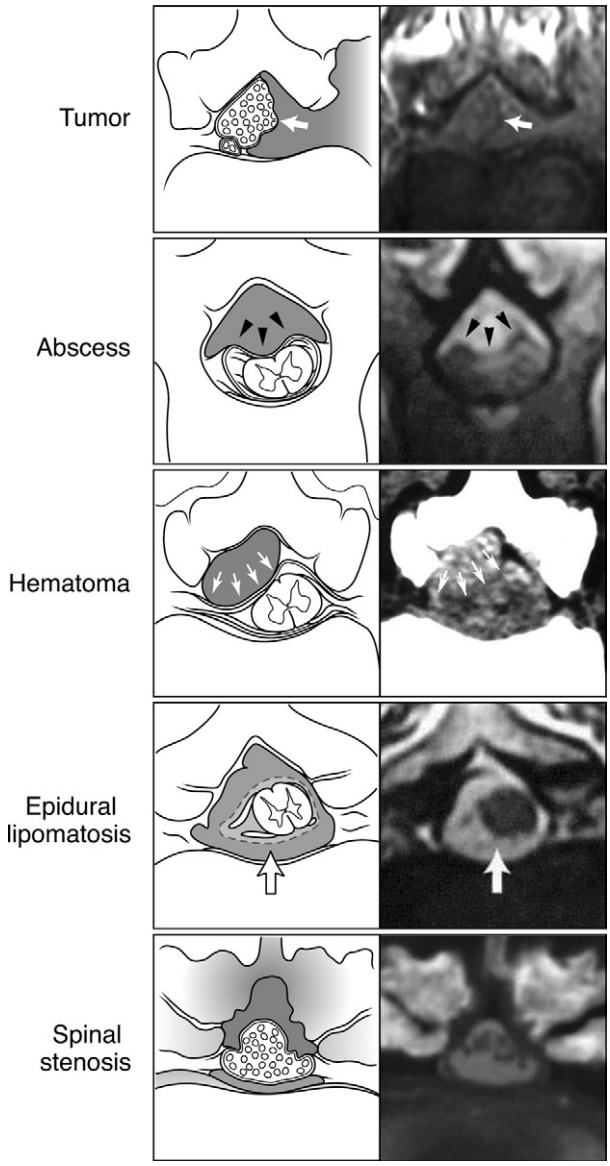

Fig 4. Extradural mass lesions. Note how various conditions can reduce spinal canal cross-sectional area and either directly compress the spinal cord or cauda equina (arrows), or increase epidural space or cerebrospinal fluid pressures through their mass effect. Illustration by Gary J. Nelson. Reprinted from Neal and Rathmell.[12]

termed spinal stenosis, these changes are postulated to contribute to neuraxis injury and may partially explain why clinically significant epidural hematoma happens more frequently in elderly patients.[2] The clinical variability of spinal stenosis implies that clinical decisions with respect to neuraxial block must be individually based. For instance, known lumbar spinal stenosis may have little if any impact on thoracic epidural space pressure-volume dynamics and would not be ipso facto a contraindication to thoracic epidural anesthesia. Further, despite injected epidural solutions temporarily raising epidural space pressure, there is no clear evidence that their administration has caused spinal cord injury in patients with spinal stenosis.

Acquired conditions affecting spinal canal cross-sectional area include intradural and extradural masses. Besides intramedullary tumors, intradural space-occupying lesions can result from morphinoid-induced catheter granulomas associated with chronic intrathecal infusions.[32,33] Extradural mass lesions include epidural hematoma and epidural abscess, in addition to rarer conditions such as ligamentum flavum hypertrophy or epidural tumor,[34] lipomatosis,[35-37] scleredema,[38] or ependymoma[39] (Fig 4).

Patient positioning can also affect spinal canal cross-sectional area. For example, available area decreases in the lithotomy position.[40] Case reports describe neuraxis injury associated with neuraxial blockade wherein it is speculated that the injury was at least exacerbated by extreme lordosis (in a patient under general anesthesia),[36] the lithotomy position in a patient with spinal stenosis and facet joint synovial cysts,[41] or the lateral thoracotomy position in a patient with stenosed spinal arteries and ankylosing spondylitis.[42]

In summary, mechanical injury to the neuraxis can arise consequent to direct needle trauma or to space-occupying lesions whose mass effect compromises spinal cord blood flow. Evidence to support contribution to injury varies with the mechanism of injury. In the case of epidural hematoma or abscess, extensive literature supports causation.[1,2,19,25,43-45] Conversely, neuraxis injury in the setting of rare extraspinal mass lesions, or relatively common surgical positions, spinal stenosis, or osteoporosis, only establishes association or chance occurrence.

Vascular Injury

Disruption of spinal cord blood flow (SCBF) with consequent spinal cord injury is a decidedly rare event in which a precise mechanism of injury is difficult to pinpoint. This impreciseness results from a multitude of factors, including inexact imaging of small spinal blood vessels, complex interactions of coexisting disease processes, and a probable overreliance on diagnosis of exclusion.

Anatomic and physiologic processes determine SCBF. Arterial blood supply originates from segmental arteries that derive from the vertebral artery or various primary and secondary branches from the aorta. Segmental arteries give rise to spinal branches, which enter an intervertebral foramen and continue as an anterior and/or posterior radicular artery. Medullary arteries are those radicular arteries that extend to the spinal cord to anastomose with the anterior spinal artery (ASA) and paired posterior spinal arteries. Most medullary arteries supply the posterior circulation; fewer than half significantly serve the anterior spinal cord[46] and these are disproportionately distributed in the cervical region.[46a,46b] Yet the cauda equina and spinal cord receive two thirds of their blood supply from the ASA system. The lower thoracic and lumbosacral spinal cord is typically supplied by a single major artery (the radicularis magna or artery of Adamkiewicz) that connects to the ASA. The radicularis magna artery arises from the left and enters the neuraxis between T9 and L1 in 80% of humans,[47,48] but may enter as high as T5 or as low as L5 in dogs and humans.[47,49-51] The radicularis magna provides 25% to 50% of total SCBF. There also exists a nonrobust collateral circulation between the anterior and posterior systems via the vasa coronae; moreover, the ASA is continuous throughout its course.[47] Nevertheless, regions of the innermost spinal cord are watershed areas at risk for inadequate circulation.[46-48] Disruption of a major reinforcing artery anywhere from the segmental arteries to the ASA could potentially cause spinal cord infarction (Fig 5).

Physiologically, SCBF is autoregulated within a range of 50 mmHg to 60 mmHg to 120 mmHg to 135 mmHg mean arterial pressure (MAP) in animal models.[52,53] Spinal cord circulation is thus analogous to cerebral circulation. SCBF varies in response to metabolic demand.[54,55] Indeed, neuraxial local anesthetic blockade is likely neuroprotective because these agents reduce spinal cord metabolic demand.[54-57] Only extreme degrees of hypotension should adversely affect SCBF in patients with intact spinal cord-blood barriers. In hemorrhaged dogs, SCBF only decreased when the MAP was less than 66 mmHg.[58] Clinical studies in humans undergoing spinal surgery have demonstrated absence of injury during prolonged periods of 60 mmHg MAP.[59]

Direct Needle Trauma

Mechanical- or drug-induced vasospasm, direct vascular trauma, or intravascular injection are frequently offered explanations for disruption of SCBF.

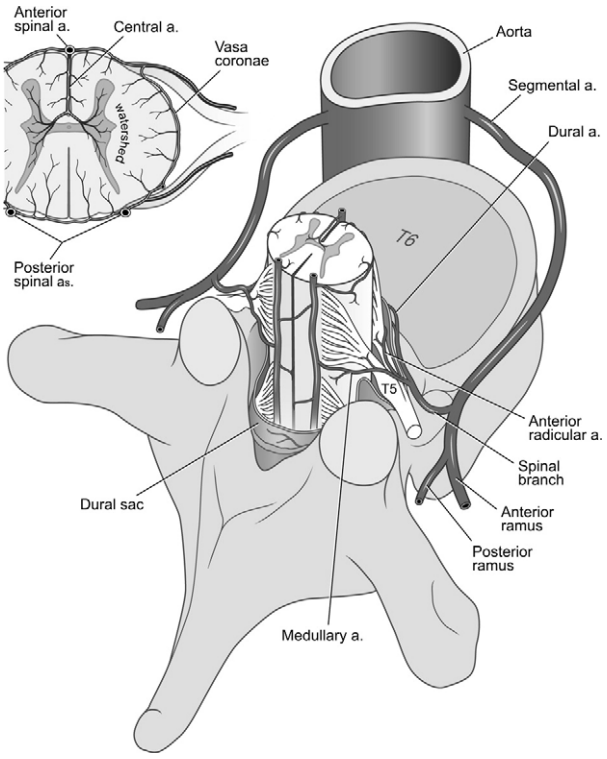

Fig 5. Arterial supply to the human spinal cord. Note that the segmental artery (a) gives rise to a spinal branch, which further divides into anterior and posterior radicular arteries (as). If the radicular artery extends to the spinal cord, it is termed a medullary artery. No more than 24 medullary arteries supply the spinal cord; less than half of them serve the more highly perfused anterior spinal cord and cauda equina. Illustration by Gary J. Nelson. Reprinted from Neal and Rathmell.[12]

Needle disruption of segmental arteries is conceivable with perispinal techniques such as celiac plexus block or paravertebral block. Deposition of phenol or alcohol near these vessels in animals causes vasospasm,[60] and some have postulated that these drugs or mechanically-induced vasospasm have led to paralysis after celiac plexus block.[61,62] Definitive evidence for either mechanism of injury is lacking (Fig 6). Cases of paralysis, cortical blindness, and death have been described following transforaminal blocks. The suggested mechanism of injury involves injection of particulate steroids into spinal branch or radicular arteries, with subsequent occlusion of blood flow to watershed areas[13,46a,62a] (Fig 3), but direct confirmatory evidence does not exist. Finally, unintentionally lateral needle placement during neuraxis block could injure segmental or spinal branch arteries, while near-midline needle contact with the spinal cord could disrupt the posterior spinal arteries and/or cause hematoma or edema (Fig 2). Either could lead to spinal cord ischemia or infarction, although the duality of the posterior spinal arteries makes complete disruption of blood flow to the posterior spinal cord unlikely.

Spinal Cord Infarction

Anterior spinal artery syndrome (ASAS) describes spinal cord ischemia or infarction that occurs within the territory of the ASA. This syndrome presents as painless, sudden or progressive, lower extremity flaccid paralysis with variable sensory deficit and maintenance of proprioception. The diagnosis of ASAS has been made in cases of unexplained injury associated with a neuraxial anesthetic technique, often invoking hypotension or the use of vasoactive spinal agents as the cause. Such speculation has little pathophysiological support. Because SCBF is autoregulated, hypotension would need to be extreme (<50 mmHg MAP) or in a setting of impaired autoregulation to cause ASAS. The duration of hypotension needed to cause spinal cord injury is uncertain, although many patients with ASAS develop symptoms over time rather than suddenly and completely.[63] Moreover, ASAS is not recog-

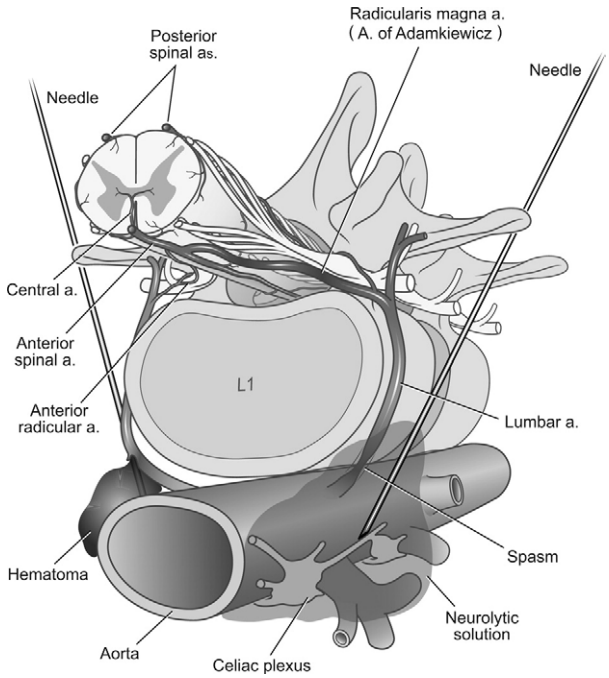

Fig 6. Proposed mechanisms of direct injury to reinforcing arteries (as) supplying the spinal cord. On the left, a needle can potentially disrupt a segmental artery (a) or precipitate a hematoma. On the right, needle irritation or injected phenol or alcohol can cause vasospasm. These proposed mechanisms have not been proven in humans. Illustration by Gary J. Nelson. Reprinted from Neal and Rathmell.[12]

nized as a complication commonly associated with prolonged low MAP conditions such as cardiac arrest, cardiopulmonary bypass, or induced hypotension of 60 mmHg or less for periods up to several hours.[59,64-66]

Local anesthetics have variable effects on SCBF depending on the specific local anesthetic and its combination with adjuvant drugs,[67] but their use does not contribute to reduction in SCBF out of proportion to reduced metabolic demand. Further, SCBF in animal models is maintained through wide ranges of MAP. Intravenous epinephrine or phenylephrine does not alter central nervous system blood flow.[68] Adjuvant epinephrine does not adversely affect SCBF.[67] Thus, there is no animal data or pathophysiologic explanation to support the contention that hypotension or vasoactive agents are probable causes of ASAS.

Like direct spinal cord trauma, ASAS and spinal cord infarct are rare complications—only 10 were reported in 821 medicolegal claims for neuraxial injuries.[1] In a series of 54 patients with ASAS, many cases occurred spontaneously and only 1 patient underwent a neuraxial anesthetic, which was not definitively identified as the cause of injury.[63] The comorbidity of ASAS is more typically that of spinal vascular atherosclerosis with subsequent embolic phenomena or postlesion hypoperfusion. Indeed, ASAS is most likely due to multiple insults including atherosclerosis,[42] aortic surgery, and/or severe hypotension. There are no reliable historical or diagnostic criteria to identify patients susceptible to ASAS.

In summary, direct vascular trauma from midline and paramedian approaches to the neuraxis is anatomically unlikely, but possible during lateral approaches or perispinal approaches such as psoas compartment or celiac plexus blocks. Injection of particulate matter into reinforcing arteries may explain injury after transforaminal steroid techniques. No human studies confirm or refute these theories of causation. In ASAS, underlying patient conditions such as atherosclerosis are more probable and reasonable pathophysiologic explanations than are hypotension or vasoactive agents.

Neurotoxicity

Neurotoxicity is another pathophysiologic mechanism for anesthesia-related neuraxis injury. Neurotoxicity can occur as an isolated event or in conjunction with physical injury to the spinal cord or spinal nerve roots.[19] When physical trauma breaches the blood-spinal cord barrier, the neuraxis is exposed to local anesthetics or vasoactive agents that are normally considered innocuous.

Even in the absence of physical damage, unique anatomic conditions contribute to the increased susceptibility of certain neuraxial tissues to neurotoxicity. For example, the cauda equina consists of nerves that are partially unmyelinated.[49] Its physical length increases surface area, making it particularly prone to contact with potentially neurotoxic agents. The spinal nerve roots (but not the dorsal root ganglia) reside within the blood-spinal cord barrier, but are theoretically at increased risk for neurotoxicity because they lack the mechanical and metabolic protection afforded to peripheral nerves or other structures within the central nervous system. High-dose local anesthetics can cause localized toxicity at the proximal portion of the posterior spinal nerve root in rats.[69] Further, spinal nerve roots have greater vascular permeability than other parts of the spinal cord and receive a significant portion of their nutrition from diffusion via the CSF and/or the radicular arteries. Thus, one can speculate that clearance of toxic substances away from spinal nerve roots may not be efficient compared with nerves with a more robust blood supply. Spinal nerve roots can be exposed to relatively concentrated local anesthetics if injection is made into a dural root sleeve, where small CSF volume impairs optimal dilution (Fig 3).[49] All of these conditions potentially place the spinal nerve roots at greater risk for local anesthetic neurotoxicity, although there are no animal or clinical studies to confirm or refute this theory.

Local anesthetic neurotoxicity is concentration-dependent and can occur at concentrations lower than those used clinically.[70,71] Local anesthetic neurotoxicity is therefore determined primarily by local anesthetic concentration within the CSF, which in turn is impacted by the total dose delivered. Clinically, drug maldistribution and excessive drug dose increase the CSF concentration of local anesthetics. Both of these conditions were believed contributory to cases of cauda equina syndrome reported after continuous spinal anesthesia with microcatheters,[72] although maldistribution can also occur with macrocatheters. Subsequent experimental models demonstrated that hyperbaric local anesthetics preferentially remain within the lumbosacral area of the subarachnoid space when they were injected slowly via small-bore catheters and when lumbar lordosis facilitated sacral residence of hyperbaric local anesthetic solutions.[73,74] Restricted pooling of concentrated local anesthetic can manifest clinically as inadequate sensory block level, which places the patient at risk for cauda equina syndrome if the practitioner responds to maldistribution by redosing local anesthetic and exceeding the maximum recommended dose.[72] Vasoconstrictors such as epi-

nephrine further worsen neurotoxicity in animal models, most likely by reducing local anesthetic clearance,[75] which is probably consequent to epinephrine decreasing dural blood flow.[76] Recognition of these conditions has resulted in expert opinion to limit initial and, in the case of redosing, total doses of local anesthetics and to avoid epinephrine in subarachnoid block.[77]

There are drug-specific examples of local anesthetic neurotoxicity. For instance, 2-chloroprocaine was implicated in neurotoxicity following subarachnoid injection of large doses intended for the epidural space. Previous experimental studies suggested that 2-chloroprocaine toxicity was related to its formulated acidity and bisulfite preservative.[78,79] Recent animal studies challenge this concept by demonstrating neurotoxicity from 2-chloroprocaine itself and a possible neuroprotective effect of bisulfite.[80] These issues take on increased importance with the contemporary revival of 2-chloroprocaine as a spinal anesthetic agent.[81] The relative potency of 2-chloroprocaine and lidocaine are similar; both drugs exhibit similar neurotoxicity in animal models.[80] This suggests that 2-chloroprocaine should have a safety profile similar to lidocaine, provided that both drugs are administered at or below their recommended maximum subarachnoid doses (60 mg to 100 mg for lidocaine,[77] 40 mg to 50 mg for 2-chloroprocaine[82,83]).

Spinal lidocaine is consistently more neurotoxic than bupivacaine in animal models.[70,84] Indirect clinical evidence suggests that this may also be true in humans. In the French SOS study, the incidence of neurologic complications associated with spinal anesthesia was over 6-fold higher with lidocaine than with bupivacaine. Consistent with the theory that mechanical damage increases the potential for neurotoxicity, those patients with longer duration symptoms were more likely to have experienced a paresthesia or pain on injection during the spinal anesthetic. Furthermore, persistent deficit was more often associated with high normal (75 mg to 100 mg) doses of lidocaine.[25]

In summary, neuraxial local anesthetics, opioids, adjuvants, and preservatives in clinically recommended doses are remarkably safe in the vast majority of patients.[85] Nevertheless, a patient may rarely be vulnerable to local anesthetic and adjuvant neurotoxicity even in "normal" clinical situations. Clinical evidence comes from case reports of neuraxis injury in patients who received standard doses of neuraxial local anesthetic with or without adjuvant,[86] or patients who sustained neuraxis injury following spinal or epidural anesthesia in whom neurotoxicity was the presumed mechanism of injury.[1,19,25] Neurotoxicity is more likely to occur in conjunction with physical disruption of the spinal cord-blood barrier by needle or catheter trauma, or from iatrogenic conditions leading to maldistribution and overdosing of neuraxial local anesthetics.

Summary

The pathophysiology of neuraxis injury associated with regional anesthesia and pain medicine procedures presumes that a mechanical, vascular, neurotoxic or a combination insult has occurred. With the exception of epidural hematoma or ab-

Table 1. Recommendations: Factors That May Limit Neuraxial Injury

Anatomic Factors

- Misidentification of vertebral level, unrecognized lateral needle placement or deviation, abnormal caudad termination of the spinal cord or failure of the ligamentum flavum to fuse in the midline may contribute to direct needle injury to the spinal cord. Clinicians are advised to be aware of these anatomic conditions, particularly in patients with challenging surface anatomy. (Class I)
- Surgical positioning and specific space-occupying extradural lesions (e.g., severe spinal stenosis, epidural lipomatosis, ligamentum flavum hypertrophy, or ependymoma) have been associated with temporary or permanent spinal cord injury in conjunction with neuraxial regional anesthetic techniques. These conditions are particularly relevant when they co-exist with an epidural hematoma or abscess. Awareness of these conditions should prompt consideration of risk-versus-benefit when contemplating neuraxial regional anesthetic techniques. (Class II)
- Patients with known tumor in the epidural space should undergo neuraxial imaging studies to define the extent of tumor mass. If the tumor is close to the planned site of epidural solution injection, alternative methods of anesthesia or analgesia should be considered. (Class II)
- For patients receiving neuraxial injection for treatment of pain (e.g., cervical epidural injection of steroids via an interlaminar route) radiologic imaging studies such as CT or MRI should be used to assess the dimensions of the spinal canal and this information should be considered in the overall risk-to-benefit analysis as well as guiding the selection of the safest level for entry. (Class II)

Physiologic Factors

- Clinicians are advised to be aware of and to avoid conditions that have been linked to the formation of epidural hematoma or epidural abscess, as noted in previous ASRA Practice Advisories. Such conditions include concurrent or imminent anticoagulation, the use of multiple anticoagulants, improper aseptic technique, and needle placement during untreated active infection. ([89-93]) (Class I)
- When neuraxial anesthesia is complicated by the development of mass lesions within the spinal canal (e.g., hematoma or abscess) resultant postoperative neurologic complications may be more likely or more severe in patients with preexisting severe spinal stenosis or other obstructive spinal canal pathology. (Class I)
- Warning signs such as paresthesia or pain on injection of local anesthetic inconsistently herald needle contact with the spinal cord. (Class I)
- Initial dosing or re-dosing of subarachnoid local anesthetic in excess of the maximum recommended dose may increase the risk of spinal cord or spinal nerve root neurotoxicity and should be avoided. (Class I)

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.

scess, the linkage of patient injury to a specific anesthetic procedure or perioperative event is mostly one of association rather than causation. Importantly, many of the factors that may contribute to neuraxis injury cannot be identified prospectively,[2] which suggests that a large portion of these injuries is unpreventable. Fortunately, after excluding relatively rare conditions such as hematoma or abscess, neuraxis injuries associated with regional anesthesia or pain medicine procedures are exceedingly rare.

Recommendations

The strength of scientific evidence that is used to arrive at these Practice Advisory recommendations is not easily measured by traditional stratification methodologies such as the United States Agency for Health Care Policy and Research scheme for ranking Statements of Evidence and Grades of Recommendation.[87] Because of the extreme rarity of the specific complications that are addressed in this manuscript, traditional methodologies such as randomized controlled trials, meta-analysis, or large human case series rarely exist and are unlikely to exist in the future. Our recommendations are therefore based on methodologies that are necessarily less robust, such as anatomic or pathophysiologic studies of human cadavers or animals, nonrandomized trials, retrospective series, case reports, or expert opinion. Recommendations from this Practice Advisory are based on a grading scheme that has been modified from an American College of Cardiology/American Heart Association construct that classifies the strength of guidelines for perioperative cardiac evaluation (Appendix 1).

These recommendations are intended to encourage optimal patient care, but cannot ensure the avoidance of adverse outcomes. As with any practice advisory recommendation, these are subject to revision as knowledge of specific complications advances (Table 1).

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Appendix 1

This classification system (Appendix 1) is significantly modified from the American College of Cardiology/American Heart Association construct for classifying strength of evidence.[88]