Effects of Epinephrine in Local Anesthetics on the Central and Peripheral Nervous Systems: Neurotoxicity and Neural Blood Flow

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Epinephrine has been combined with neuraxial and peripheral local anesthetics since Heinrich Braun first experimented with its use as a "chemical tourniquet" in the early 1900s.[1] A century of use attests to the general safety of adjuvant epinephrine, yet we have only modest understanding of its intended effects, which include prolonging block duration, reducing plasma concentration of local anesthetics, reducing surgical bleeding, and intensifying anesthesia and analgesia.[2-5] The long-held belief that epinephrine exerts most of these effects, including any associated complications, by causing vasoconstriction is doubtlessly too simplistic and has been recently challenged. The few controlled studies that focus on adverse side effects of adjuvant epinephrine are often difficult to interpret and compare because of interspecies differences in neural blood flow,[6,7] the technical challenges of measuring epinephrine's evanescent physiologic effects, and the confounding hemodynamic influences of local anesthetics. After briefly considering the pharmacology of epinephrine, this review examines evidence for its untoward effects when applied to the neuraxial or peripheral nervous systems as part of a regional anesthetic technique. Information is organized by how neurotoxicity is manifested—histopathologic and behavioral effects, physiologic effects, and undesirable clinical consequences.[8]

Pharmacology of Epinephrine

Epinephrine's pharmacologic profile is dose-related and linked to its affinity for adrenergic receptors. Low-dose epinephrine stimulation of β_2-adrenergic receptors (1 to 2 μg/min) results in arterial vasodilation, while moderate doses (2 to 10 μg/min) stimulate both β_2 receptors and β_1 receptors (increased chronotropy and inotropy). High-dose epinephrine (>10 μg/min) causes arterial vasoconstriction via stimulation of α_1 receptors and venous α_2 receptors. In addition, presynaptic α_{2A} subtype agonists, such as epinephrine and clonidine, enhance spinal analgesia. Epinephrine is metabolized in the circulation, central nervous system (CNS), liver, and kidneys by monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT). Once exposed to these enzymes, epinephrine's half-life is extremely short. Clinically, effects from an intravenous epinephrine bolus would be expected to last <3 minutes, while those following discontinuation of a nonintravascular infusion will dissipate within <40 to 120 minutes, depending on how termination of the effect is measured.[2,3,9-12]

Neuraxial Effects

Histopathologic and Behavioral Effects

Single intrathecal injection of plain epinephrine (up to 0.5 mg) is not associated with histologic injury in rabbits[13,14] or rats.[15,16] Similarly benign results are reported after repeated[16] or continuous injection, except at exceedingly high (10 times normal) doses in monkeys.[17] Conversely, epinephrine worsens histologic spinal cord injury when added to 5% lidocaine in rats[15] or 1% to 2% tetracaine in rabbits.[14] Such injury is likely secondary to reduced clearance of and prolonged exposure to local anesthetics, rather than epinephrine-induced ischemia.[15] Whether these findings apply to clinical situations is unclear, but they suggest that adjunctive epinephrine potentially lowers the maximum safe intrathecal dose of local anesthetics. This may be particularly relevant if high concentrations of subarachnoid local anesthetics are present, as may occur with sacral pooling or reinjection.

Rabbits receiving subarachnoid epinephrine (0.3 to 0.75 mg) developed behavioral effects, such as

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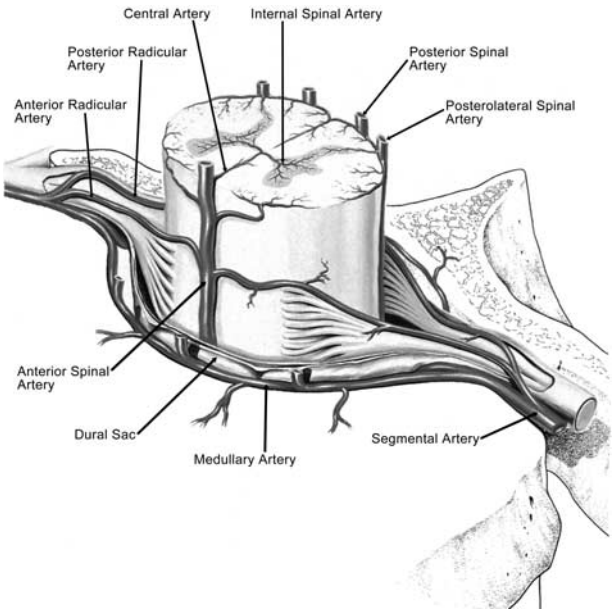

Fig 1. Vascular anatomy of the spinal cord. Note that the radicular arteries traverse the epidural space before giving rise to the single anterior spinal artery and the paired posterior spinal arteries. (Reprinted with permission.[87])

tonic convulsions and anesthesia, but fully recovered.[13] Rats exposed to high concentrations of intrathecal lidocaine and epinephrine demonstrated persistent sensory impairment that was worse than observed with lidocaine alone.[15] In humans, 50 μg epinephrine added to intrathecal 10 mg lidocaine plus 10 μg sufentanil did not grossly affect spinothalamic, dorsal column, or motor function.[18]

Physiologic Effects of Epinephrine

The prolongation and enhancement of neuraxial local anesthetic block has been partially ascribed to the vasoconstrictive properties of epinephrine.[2,3,12] These purported effects have led to concerns over epinephrine causing or enhancing spinal cord ischemic injury. To understand epinephrine's potential impact on spinal cord blood flow (SCBF), the anatomy and regulation of the spinal vasculature is reviewed below.

Anatomy and Regulation of Spinal Vasculature

In general, the spinal cord is richly perfused and has adequate collateral flow, but interruption of blood supply or loss of autoregulation potentially places certain segments of the spinal cord at risk for ischemic injury. Blood supply to the spinal parenchyma arrives via paired posterior spinal arteries (PSA) and a single longitudinal anterior spinal artery (ASA) (Fig 1). Although these longitudinal systems are continuous and connected by circumflex vessels, their diameter varies greatly. The ASA and PSA arise from radicular arteries that branch from segmental arteries, which in turn arise from the intercostal and vertebral systems (Fig 2). Dorsal and ventral branches of the radicular arteries accompany spinal nerve roots (SNR) and together traverse the epidural space, where they can be exposed to drugs deposited there (Fig 1). Only 5 to 8 radicular arteries supply the majority of spinal cord circulation.[19] This arrangement leads to midthoracic segments of the spinal cord being less perfused than the cervical and the lower thoracic and lumbar segments (Fig 2), albeit the middle segment has lower metabolic requirements. Although rare, interruption of blood supply to the spinal cord (as may occur during aortic surgery) can lead to ischemia or infarction, particularly in those areas susceptible to decreased blood flow. Fortunately, collateral flow does exist. Aortic cross-clamping reduces SCBF, but likely does not eliminate it,[20] because the ASA, PSA, and spinal capillaries are capable of bidirectional flow between adjacent radicular artery supply zones (Fig 2).[21] In addition, it has been documented in pig models that noncritical segmental arteries help maintain normal ischemic thresholds in the face of diminished spinal cord perfusion pressure, which provides further evidence for collateral flow.[22] Thus conceptually, the normal human spinal cord is capable of receiving several avenues of blood supply and should not be thought of as an "end organ." The spinal venous system parallels the arterial system, with spinal cord and dural blood draining into the epidural and paravertebral venous plexuses.[19]

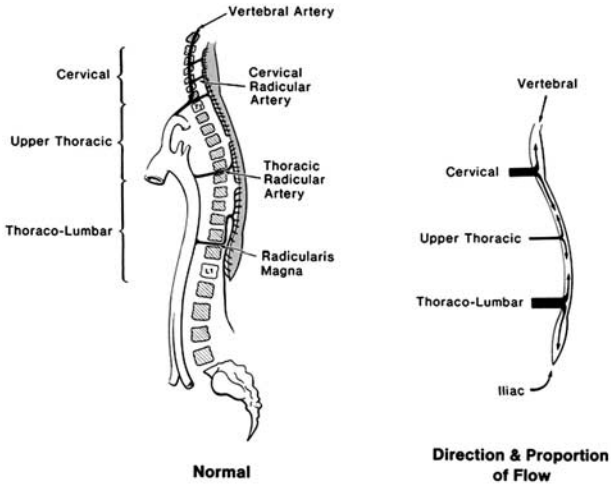

Fig 2. Spinal cord vascular supply. The left diagram depicts normal segmental arterial configuration. The right diagram illustrates bidirectional blood flow and its relative proportion to various spinal segments. (Modified and reprinted with permission.[87])

The SNR have been described as unique regions of the CNS, as their structure, vasculature, and metabolism differ from both the spinal cord and peripheral nerves.[23] Blood supply to the SNR is from the extrinsic radicular arteries that anastomose with an intrinsic parenchymal capillary plexus. The SNR vasa nervorum are dissimilar from those found in peripheral nerves.[23] Lumbar SNR reside outside of the blood-brain barrier[24] and within the dural cuffs, where they receive up to 58% of their nutrients via diffusion from the cerebrospinal fluid (CSF).[25,26] This implies a degree of metabolic independence from radicular blood flow. Furthermore, epidural epinephrine does not affect SCBF in pigs,[27] which indirectly argues against radicular artery blood supply to the SNR being significantly affected by epinephrine. However, no specific data exist regarding the regulation of the SNR blood supply or specific effects of epinephrine. Thus, it is unclear if SNR are more or less prone to ischemia than the spinal cord or peripheral nerves.

Human vertebral arteries contain α_2 and β, but not α_1, adrenergic receptors in the smooth muscle and endothelial layers,[7] which may partially explain the cerebral vasodilator effects of clinically relevant epinephrine concentrations. Similar to the cerebral circulation, SCBF is highly autoregulated at the microvascular level.[28] Autoregulation occurs between mean arterial pressure (MAP) 50 and 135 mm Hg, and is highly dependent on, and varies directly with, p_aCO_2 and hypoxemia. Animal studies suggest a primacy of local autoregulation over other influences from systemic vasoactive compounds or the autonomic nervous system. Spinal cord vessels (like cerebral vessels) are unresponsive to reflex stimuli from carotid baroreceptors or chemoreceptors.[28] Histologic studies confirm the existence of smooth muscle in anterior spinal arteries[29] and radicular veins,[30] suggesting the capacity of these vessels to alter SCBF in response to intrinsic or extrinsic vasoactive drugs; yet despite extensive sympathetic innervation, spinal cord vessels are less reactive to vasoactive agents than are extraneural vessels.[31,32] Indeed, autoregulation is mediated primarily by nonadrenergic endothelial factors in response to metabolic demand.[21]

In summary, the spinal cord vasculature is potentially at risk, but in the absence of anatomic disruption or MAP outside the limits of autoregulation, SCBF is locally controlled in response to its environment. Although the exact mechanisms regulating SCBF are incompletely understood, there is no evidence that endogenous or exogenous vasoactive drugs adversely affect autoregulation. Thus, autonomic innervation and vasoactive drugs contribute minimally to the regulation of SCBF,[21] implying a similarly minimal effect from exogenous epinephrine.

Some methodologies to evaluate SCBF, such as hydrogen clearance, are less accurate than others.[24,33] Laser Doppler flowmetry is considered accurate for quantifying the effects of vasoactive drugs on vascular flow rates. Radioactive microspheres reliably measure blood flow to spinal cord parenchyma. The latter 2 methods are enhanced by concurrent measurement of systemic blood flow, to control for systemic effects of locally deposited drugs. Finally, measurement of vessel diameter is used to ascertain the vasoconstrictive effects of drugs applied directly to dural blood vessels.

Epinephrine may gain access to the spinal cord via 3 pathways—direct intrathecal injection, redistribution via the systemic circulation, or transfer from the epidural space.

Direct Intrathecal Injection

The vasoactive consequences of intrathecal epinephrine are evaluated by measuring its effect on SCBF or dural blood flow (DBF). Plain intrathecal epinephrine (up to 0.5 mg) does not significantly alter SCBF in dogs or cats, whether measured by hydrogen clearance[34] or microspheres.[35,36] Its effects are more complex when admixed with local anesthetics. For instance, intrathecal lidocaine or tetracaine either increase[9,37] or have no effect on SCBF.[36,38] When epinephrine is added to these local anesthetics, SCBF normalizes[9,37] or remains unaltered.[36,38] Conversely, intrathecal plain bupivacaine or ropivacaine caused a transient, dose-dependent reduction in SCBF. Adjuvant epinephrine 0.2 mg caused no further reduction of SCBF in dogs given bupivacaine,[39] while in rats epinephrine 5 μg/mL reduced SCBF beyond that seen with bupivacaine alone. For comparison, the maximum decrease in SCBF was 40% $\pm$ 6% for bupivacaine with epinephrine, 37% $\pm$ 6% for plain ropivacaine, and 27% $\pm$ 7% for plain bupivacaine.[40]

DBF is significantly less robust than spinal cord or spinal nerve root flow,[24] even though the dura itself is remarkably vascular (Fig 3).[41] DBF is evaluated by directly measuring flow or by observing pial vessel diameter changes in response to topically applied drugs. Epinephrine alone[35] or in combination with bupivacaine[39] decreased DBF, but normalized the dural hyperemia seen after intrathecal lidocaine or tetracaine.[9,37] When directly applied to pia mater arterioles, norepinephrine[42] and epinephrine[43] consistently caused a small decrease in vessel diameter. For example, epinephrine in concentrations up to 50 μg/mL reduced pial arteriole diameter by 10.6% $\pm$ 8% and venule diameter

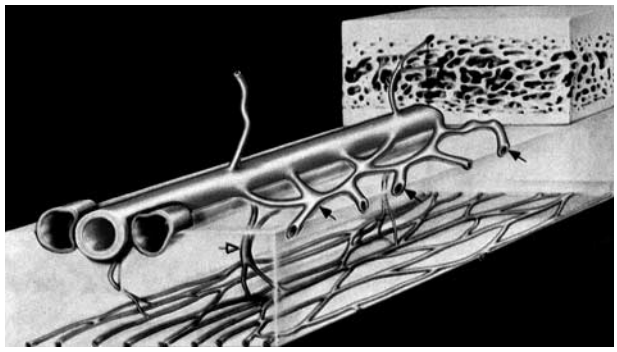

Fig 3. Illustration of the extensive dura mater microvasculature. The primary anastomotic artery and veins are seen on the outer periosteal layer. Secondary anastomotic arteries (solid arrows) and penetrating arterioles (open arrows) feed a rich capillary network. (Modified and reprinted with permission.[41])

by <5%.[43] Importantly, because the dura is an "end organ" that receives its blood supply from terminal dural branches of the segmental arteries,[24] alteration of DBF has no direct impact on SCBF.

Another consideration with intrathecal epinephrine is the effect of the low pH of epinephrine-containing solutions deposited into the CSF. Theoretically, and especially in light of the poor buffering capacity of CSF, increasing CSF acidity should stimulate increased SCBF. However, several concentrations of epinephrine ranging in pH from 2.60 to 3.29 failed to alter SCBF in dogs.[34]

Analysis of these studies suggests the following conclusions regarding the effects of directly administered intrathecal epinephrine on SCBF. First, plain intrathecal epinephrine does not decrease SCBF nor does its systemic uptake alter hemodynamics in a manner that significantly impacts spinal vasculature autoregulation.[36] Second, epinephrine's vasoconstrictive effect on DBF does not impact SCBF.[43] Third, when combined with local anesthetics other than bupivacaine, epinephrine does not reduce SCBF below baseline. Whether further reduction of SCBF when epinephrine is added to intrathecal bupivacaine is of clinical relevance is unclear, because the minimum ischemic threshold for SCBF has not been defined. Clinical experience suggests that a bupivacaine/epinephrine combination is not harmful, yet this combination's potential to cause a 40% reduction in SCBF approaches the 50% reduction of cerebral blood flow (CBF) where electroencephalographic changes are observed.[40] Because local anesthetics also reduce the metabolic requirements of spinal tissues, SCBF reduction may simply be a normal response to lower metabolic demand,[44] and therefore local anesthetics may actually offer some degree of spinal cord protection in the event of altered SCBF.[21]

In summary, there are no data implicating intrathecal epinephrine in the development of spinal cord ischemia in intact animals. Whether SCBF could be adversely affected during compromised autoregulation, as from severe hypotension or spinal cord injury, has not been studied.

Systemic Redistribution of Epinephrine

Another pathway leading to the spinal cord is the systemic vascular redistribution of epinephrine absorbed or transferred from the highly vascular epidural space.[45,46] Because direct intrathecal injection of 500 μg epinephrine causes no injury in animals, it is difficult to imagine that 100 μg epinephrine injected as part of a typical epidural dosing regimen would significantly affect SCBF, even if totally injected via accidental dural puncture. The more probable intravenous bolus injection of a 15-μg epinephrine test dose is unlikely to have more than a 3-minute effect on systemic hemodynamics.[11] Normal systemic absorption of epidural epinephrine affects systemic hemodynamics, primarily causing reduced MAP and increased cardiac output. These alterations are the consequence of β-adrenergic effects on peripheral capacitance vessels with a resulting decrease in peripheral vascular resistance.[4,11,46-48] As long as MAP does not decrease below 50 mm Hg, SCBF autoregulation is preserved. Because the hemodynamic effects of absorbed epidural epinephrine appear to be primarily β-adrenergic, there is no reason to expect α_1-adrenergic receptor-induced spinal vascular vasoconstriction would occur, especially in humans in whom CNS arterial α_1 receptors do not exist in the vertebral, and possibly other, arteries.[7] Furthermore, although α-adrenergic receptors exist within the walls of spinal vasculature in cats and dogs, intra-arterial norepinephrine does not affect SCBF as long as the spinal cord/blood barrier remains intact.[42,49]

Animal data suggest that normal MAP may be more important for maintaining SCBF in infants than in adults. Infants generally have lower local anesthetic plasma concentrations during epidural anesthesia than adults, implying a differential response to local anesthetics and/or epinephrine. In adult rabbits, epidural 2% lidocaine with or without epinephrine 1:200,000 did not alter SCBF. In young rabbits, however, SCBF was decreased in tandem with decreased MAP after 2% lidocaine, but the addition of epinephrine caused no further reduction. Plain epinephrine did not reduce SCBF in adult or young rabbits.[50]

In summary, there is no animal evidence that systemic redistribution of epidural epinephrine adversely affects the spinal vasculature. Assuming normal autoregulation, hemodynamic alterations consequent to the uptake of epidural epinephrine also have no effect on SCBF and indeed are more likely to increase SCBF as a consequence of increased cardiac output.[47]

Transfer of Epidural Epinephrine to the Spinal Cord

The final pathway by which epinephrine may reach the subarachnoid space is via transfer from the epidural space. Classically, 3 potential routes have been described for this transfer—by way of the spinal nerve root cuff, by uptake into the radicular artery, or by diffusion across the meninges. A rare mechanism for possible entry of epinephrine into the spinal cord is from an endoneural injection tracking along a peripheral nerve centrally to the spinal cord.[51] Bernards and Hill[52] have analyzed the role of these various routes in a series of animal studies regarding the transfer of epidural opioids to the spinal cord. Opioids were chosen because of their general absence of confounding systemic hemodynamic effects as compared with local anesthetics, although caution is warranted in extrapolating opioid data to other drugs. These investigators found that the spinal nerve root cuff is not the preferred route of redistribution of drugs from the epidural space to the spinal cord.[52] Likewise, diffusion into the radicular artery is not a means by which drugs are transferred to the spinal cord, either directly or via systemic uptake and redistribution.[20] The remaining route of diffusion is across the meninges, where the arachnoid is the major diffusion limiting barrier.[53] Spinal meninges contain enzymes capable of metabolizing neurotransmitters, including COMT, the primary metabolizing enzyme for epinephrine. Most epinephrine is therefore metabolized by meningeal and epidural space COMT either before it reaches the subarachnoid space or is subsequently cleared from the CSF by meningeal enzymes, thus leaving only small amounts to enhance anesthesia via spinal cord α_2-adrenergic stimulation.[54]

The mechanisms by which neuraxial epinephrine could contribute to spinal cord ischemia are therefore limited and likely inconsequential. The highest concentrations of epinephrine used in clinical practice are achieved when it is injected directly into the subarachnoid space, where admixing with CSF rapidly dilutes it and meningeal enzymes metabolize it. Animal studies of intrathecally administered epinephrine fail to demonstrate reduced SCBF. Similarly, epinephrine redistributed from the epidural space to the systemic circulation has no adverse effect on SCBF. In fact, circulating epinephrine levels following nonintravascular injection are less than those typically seen with exercise or stress.[55] Finally, epidural epinephrine can only be transferred to the spinal cord via diffusion across the meninges and does so in amounts far less than normally injected during routine spinal anesthesia. Thus, there is no evidence that epinephrine adversely affects SCBF or contributes to spinal cord injury. Indeed, recent studies place into question whether epinephrine exerts vasoconstrictive effects on the epidural vasculature at all.

Epinephrine Effects in the Epidural Space

The mechanism(s) for drug clearance from the epidural space is controversial. An earlier mechanism theorized that vascular absorption of epidural drugs (such as local anesthetics) occurred mostly in the epidural capillaries and that the rate-limiting step was blood flow rather than capillary wall permeability.[45] Under this theory, epinephrine intensified anesthetic block by causing vasoconstriction of the epidural venous plexus, thereby reducing blood flow and uptake, and exposing nerves to higher local anesthetic concentrations.[2] In a recent experiment utilizing pigs (where the spinal vasculature resembles humans), Bernards et al[27] demonstrated that epidural epinephrine had no effect on SCBF, implying that epinephrine had no vasoconstrictive effects on epidural vasculature. In this experiment, the addition of epinephrine resulted in higher epidural space, but lower epidural vein, opioid concentrations. Decreased epidural vein drug concentrations places in doubt that any drug diffuses into the epidural veins. Vasoconstriction in the spinal cord cannot explain these decreased venous concentrations because SCBF did not change, thus eliminating the possibility of radicular artery or venous plexus constriction. The explanation for increased epidural space opioid concentration is likely that epinephrine reduced its clearance from nonneural structures, such as epidural fat and areolar tissues, and/or from the dura. Indeed, clearance of epidural drugs is most likely mediated primarily by reduced blood flow in the highly vascular dura mater (Fig 3), especially for those drugs that are more flow dependent for clearance (e.g., hydrophilic drugs, such as lidocaine, but not hydrophobic drugs, such as bupivacaine). This mechanism is consistent with the observation of Kozody et al[35] that epinephrine reduces DBF. Thus, epinephrine-induced prolonged exposure to local anesthetic contributes to increased anesthetic duration and

intensity as previously theorized, but not as a consequence of epidural venous plexus vasoconstriction.[27] Another nonvasoconstriction dependent theory may explain the observation that local anesthetic peak plasma concentrations are lower when epinephrine is added to epidural drug mixtures. Epinephrine causes increased cardiac output (promoting hepatic uptake and renal excretion) and increased volume of distribution (a consequence of increased capacitance), either of which could account for reduced plasma concentrations.[56] This mechanism does not appear to apply to the clearance of epidural opioids.[27] Enhanced anesthetic block intensity is then partially explained by an analgesic effect via epinephrine-induced α_2-adrenergic stimulation at the spinal cord from small amounts of diffused epinephrine.[5,57-60] Indeed, epidural epinephrine results in segmental hypoanalgesia even when infused without accompanying local anesthetic.[61] In summary, there are scientific reasons to question the degree and significance of vasoconstriction of epidural vascular structures—an observation that further negates any contribution of epidural epinephrine to spinal cord ischemia.

Human Studies of Epinephrine

Despite most animal data exonerating epinephrine as a cause of spinal cord injury, some investigators have questioned its continued use in lidocaine spinal anesthesia[62] because of animal studies demonstrating the potential of epinephrine to worsen *local anesthetic-induced* spinal cord injury,[14,15] and isolated case reports of neural injury in presumably normal patients who received standard doses of subarachnoid lidocaine with epinephrine.[63] However, large human surveys fail to identify adjuvant epinephrine as a clear risk factor for significant neuraxial injury. Dripps and Vandam[64] reported minor neurologic sequelae in 17 of 10,098 patients undergoing spinal anesthesia, and only 5 of those 17 received epinephrine. In their subsequent study of patients with pre-existing neurologic disease who suffered sequelae after spinal anesthesia, only 3 of the 12 received epinephrine.[65] Moore and Bridenbaugh[66] reported no permanent neurologic injury in a retrospective review of 11,574 spinal anesthetics, 59% of which contained epinephrine. Horlocker et al[67] found no link between epinephrine and neurologic injury in 2 retrospective studies, one of spinal and epidural anesthesia, and the other of continuous spinal anesthesia. In the former study of 4,767 procedures, none of the 6 patients with neurologic injury received epinephrine.[67] Four of 603 patients undergoing continuous spinal anesthesia experienced persistent paresthesia or cauda equina syndrome, but none of them received epinephrine.[68] Furthermore, adjunctive epinephrine did not increase the incidence of transient neurologic symptoms (TNS) in a clinical study[69] or in an epidemiological survey of 1,863 patients.[70] Other large surveys of neuraxial complications do not specifically report whether epinephrine was used.[71-74] Given that exact numerators and denominators are inherently absent in both large population studies and isolated case reports, it nevertheless appears that injury following neuraxial anesthesia is extremely rare, and most of the reported cases have actually occurred in the absence of epinephrine.

Over a century of experience, which includes millions of patients with compromised vascular systems, strongly supports the assertion that additive epinephrine is safe in routine spinal and epidural anesthesia. What remains uncertain is whether or not epinephrine ever increases the risk of spinal cord ischemia in patients with compromised spinal circulation, as may occur with diabetes or arteriosclerosis. If there is a warning from animal studies, it is that epinephrine may potentiate local anesthetic-induced injury. While there is no clinical data upon which to base any recommendation, it seems prudent to avoid epinephrine in those situations known to increase the risk of local anesthetic neurotoxicity, such as supernormal doses, subarachnoid reinjection, or sacral pooling of local anesthetics. Of note, beneficial anesthetic and analgesic effects of epidural epinephrine are possible using very low concentrations (1:300,000 to 1:500,000 dilutions).[3,4] If one wishes to completely avoid intrathecal epinephrine during spinal anesthesia, 10 to 20 μg fentanyl offers the advantage of similar increase in anesthetic intensity and duration while avoiding any epinephrine-induced prolonged time to micturition.[75]

Peripheral Nerve Effects

In contrast to its feared but probably inconsequential effects on SCBF, epinephrine does cause significant reduction in peripheral nerve blood flow (PNBF). The clinical significance of this is negligible in most patients. Importantly, anatomic differences between peripheral nerve blood supply, and that of the spinal cord or SNR, precludes generalization of experimental findings from one system to the other.

Physiologic Effects of Peripheral Epinephrine

Peripheral nerves have a dual blood supply (Fig 4). The extrinsic system consists of non-nutritive vessels that are responsive to adrenergic stimuli. Extrinsic arteries, which are present in the

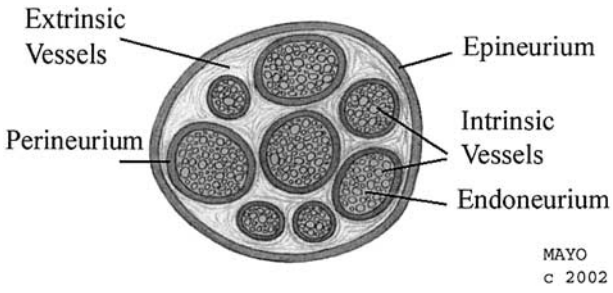

Fig 4. Peripheral nerve vascular supply. Note the dual extrinsic (under adrenergic control) and intrinsic blood supply. Extrinsic vessels are located within the epineurium and perineurium; intrinsic vessels are located within the endoneurium. (Reprinted with permission of Mayo Foundation.)

epineurium and perineurium, anastomose with the intrinsic vessels of the endoneurium. The intrinsic system provides nutrition to the peripheral nerve and is not under adrenergic control.[76] Because peripheral nerves are susceptible to adrenergic influences, drugs with α_1-adrenergic agonist properties can reduce PNBF. In rats, lidocaine 2% reduced blood flow to 81% of control, while plain epinephrine 5 μg/mL reduced it to 55%. Their combination further reduced PNBF to 20% of normal (Fig 5).[76] Other investigators, considering simultaneous changes in systemic blood flow, failed to demonstrate significant decreases in rat sciatic PNBF following plain lidocaine $\leq$2% or epinephrine 10 μg/mL; but also noted a small and significant decrease when both agents were combined.[77] Alteration of PNBF is local anesthetic specific and dose-dependent. In a rat sciatic nerve model, increasing doses of lidocaine resulted in progressive diminution of PNBF, while increasing doses of bupivacaine actually improved flow. Low-dose plain epinephrine

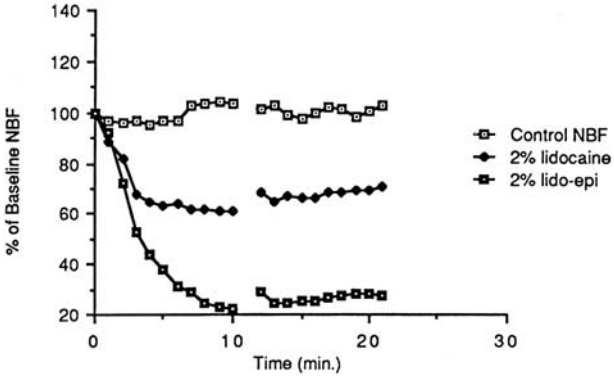

Fig 5. Effects of 2% lidocaine, with and without 5 μg/mL epinephrine, on rat neural blood flow (NBF). Saline washout occurred at 10 minutes. (Reprinted with permission.[76])

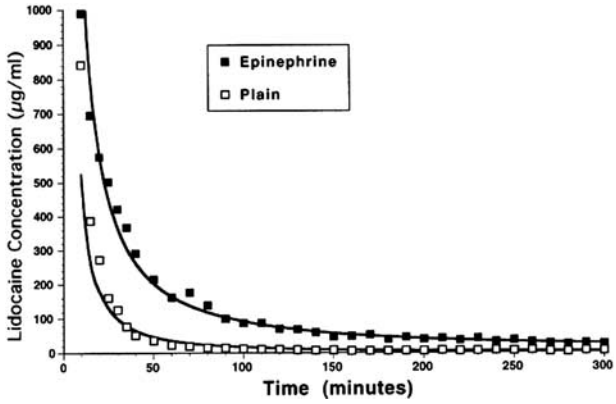

Fig 6. Perineural lidocaine concentrations over time in volunteers undergoing peripheral nerve block. The higher lidocaine concentrations in the epinephrine group are indicative of reduced peripheral clearance secondary to regional vasoconstriction. (Reprinted with permission.[80])

(2.5 μg/mL; 1:400,000) transiently increased PNBF (presumably by β-adrenergic effects) before returning to baseline. However, in one study, higher epinephrine concentrations (5 or 10 μg/mL) resulted in persistent 20% and 35% reduction of PNBF, respectively,[78] whereas 10 μg/mL caused no change in another.[77] In general, epinephrine is more likely to reduce PNBF when combined with a local anesthetic, just as it appears to potentiate local anesthetic-induced toxicity in animal models.

Evidence for peripheral epinephrine causing vasoconstriction, thereby limiting local anesthetic clearance is incompletely understood.[77,79-81] Vasoconstriction and reduced clearance are inferred from lower plasma concentrations of local anesthetics measured after admixture with epinephrine. Using a microdialysis technique in volunteers, Bernards and Kopacz[80] demonstrated that this effect is mirrored at a peripheral nerve injection site, thus indicating reduced perineural drug clearance consequent to vasoconstriction-induced decrease in regional blood flow (Fig 6). Conversely, Palmer et al[77] failed to demonstrate blood flow reduction to rat perineural *muscle tissue* as a consequence of injected lidocaine 1% with epinephrine 10 μg/mL, leading them to suggest that factors other than perineural vasoconstriction may also contribute to block prolongation. Their findings are consistent with the effects of local anesthetics on PNBF being opposite of those on *muscle arterioles,* where low concentration lidocaine causes vasoconstriction and higher concentrations cause vasodilation.[82] A pharmacodynamic effect of epinephrine is not likely to explain the potentiation of peripheral neural blockade. Bernards and Kopacz[80] were unable to

demonstrate a pharmacodynamic (α_2-adrenergic agonist) effect of epinephrine on human peripheral nerve, while an effect, if any, on rat sciatic nerve only occurred during the first 10 minutes of blockade.[81]

Clinical Studies of Peripheral Epinephrine

Despite clear evidence for decreasing PNBF, the relationship of epinephrine to nerve injury following peripheral nerve block is unclear. The etiology of transient or permanent nerve injury is multifactorial and must include consideration of surgical trauma, positioning injury, or direct local anesthetic or adjuvant neurotoxicity. Specific injury data for peripheral nerve blocks containing epinephrine are sparse, but general experience and closed claims analysis suggest injury following peripheral nerve block is quite low, even if increasing as a percentage of claims filed.[83] Even though 2% lidocaine with epinephrine reduces PNBF to 20% of baseline in rats,[76] this is presumably well tolerated in most patients, as some clinicians use this combination of drugs routinely. Indeed, this reduction in PNBF is comparable with that typically induced by the application of pneumatic tourniquets.[78] However, on a theoretical basis, patients with compromised vascular integrity due to diabetes, chemotherapy, or arteriosclerosis may not tolerate severely reduced PNBF. For instance, diabetic rats are more susceptible to injury from high concentrations of lidocaine (without epinephrine) than are healthy control animals.[84] Injured peripheral nerves may be less tolerant of epinephrine. For example, topical application of bupivacaine and epinephrine to intact rabbit nerve caused no damage, but the addition of epinephrine worsened injury after an intraneural injection or destruction of the nerve/blood barrier.[85] In a single clinical study, all patients with nerve injury following axillary block had received epinephrine.[86]

In summary, the potential of epinephrine to cause or potentiate nerve injury following peripheral block is exceedingly low in normal patients, in whom lower than normal PNBF is apparently well tolerated. Yet animal studies warn that this may not be the case when circulation is compromised or the structural integrity of the nerve is altered. Because there is a ceiling effect for prolonging block duration and also for side effects, such as tachycardia,[48] it appears reasonable to use lower doses of adjuvant epinephrine in peripheral nerve blocks. For instance, at 1:400,000 concentration (2.5 μg/mL), epinephrine prolonged block slightly less than a 1:200,000 concentration[48] and actually caused a transient increase in PNBF, suggesting that α_1-adrenergic effects on PNBF are absent at this low dose.[78]

Conclusions

Neuraxial application of adjunctive epinephrine appears safe based on animal studies and large human experience, with the caveat that it can potentiate local anesthetic-induced neuraxial injury in animal models. Epinephrine's vasoconstrictive effects on spinal vasculature are minimal and therefore should not be implicated as a cause of spinal cord ischemia. The peripheral application of epinephrine enjoys an excellent safety profile based on extensive human experience, but worsens animal nerve injury in the setting of physical nerve damage or local anesthetic neurotoxicity. The clinical relevance of this observation is unknown, but suggests that reduction of peripheral epinephrine dose or avoidance in select patients may be prudent.

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