Complications of peripheral nerve blocks

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Key points
- Serious complications of peripheral nerve blocks include nerve injury, catheter infection, bleeding, andLAST.
- Intraneural injection occurs frequently with nerve stimulator or ultrasound-guided techniques. It is rarely associated with nerve injury.
- Lipid emulsion therapy is effective in treating severe LAST.

Summary Complications of peripheral nerve blocks are fortunately rare, but can be devastating for both the patient and the anaesthesiologist. This review will concentrate on current knowledge about peripheral nerve injury secondary to nerve blocks, complications from continuous peripheral nerve catheter techniques, and local anaesthetic systemic toxicity.

Keywords: complications; nerve, damage (postoperative), local anaesthesia; regional anaesthesia

Peripheral nerve injury

Peripheral nerve injury is an infrequent complication of regional anaesthesia. Because neurological injuries after peripheral nerve blocks are so rare, it is extremely difficult to obtain reliable and consistent data about their incidence. Retrospective studies estimate an incidence of 0.5–1.0%, but one prospective study suggests an incidence of 10–15%.1 Incidence clearly depends on the definition of nerve injury. For major complications resulting in permanent nerve damage, a 1.5/10 000 incidence has been reported.2 Fortunately, most injuries are transient and often subclinical, or present as mild mononeuropathies. The incidence of transient neurological deficits is higher, and the incidence of transient paraesthesia might be as high as 8–10% in the immediate days following the block.3 6 Whereas intraneural injections were once considered forerunners of neural injury and practitioners were careful to avoid them, they occurred despite the use of nerve stimulation (NS) or ultrasound (US) guidance. Through the use of US guidance, we have learned that intraneural injections do not necessarily result in permanent injury.5 It is also now possible to visualize and differentiate between perineural (outside the nerve), intraneural (below the epineurium), and intrafascicular (within the perineurium) injections, and possibly determine their association with postoperative neurological complications.

The progression from anatomic and paraesthesia techniques to NS and then to US guidance has greatly improved the success, onset, and quality of peripheral nerve blocks.5 Owing to the very low incidence of major complications and the heterogeneity of studies performed, it is difficult to conclude that US guidance improves the safety of peripheral nerve blocks. It most likely does improve safety,5 but large trials would be required to demonstrate this. US guidance offers the ability to visualize what has previously been performed blindly. Practitioners are able to appreciate the nerves and their adjacent structures, and determine the location of the needle tip and observe the spread of local anaesthetic. Even with these advances, it is interesting that the incidence of neurological injury related to peripheral nerve blocks has not decreased. In a study of 1010 consecutive US-guided peripheral nerve blocks, including single-shot and continuous interscalene, supraclavicular, infraclavicular, femoral, and sciatic nerve blocks, the rate of postoperative neurological complications was similar to the low rates previously reported with traditional techniques, possibly reflecting the fact that most post-block neurological complications are the result of non-block related causes.6 In a more recent study of more than 7000 peripheral nerve and plexus blocks performed with US (13%), NS (30%), US with NS (50%), and other (7%) techniques, 30 patients (0.5%) were referred for neurological assessment. Of these 30 patients, only three met criteria for nerve injury related to peripheral nerve block (0.04% incidence). Although this does not demonstrate that US improves the safety of blocks, it confirms that post-peripheral nerve block neurological deficits are indeed rare, and reminds us that neurological follow-up until resolution or stabilization of the condition is mandatory.

Anatomic considerations

Why can we puncture nerves with impunity? In order to understand neural injury, we need to examine nerve anatomy (Fig. 1). Individual nerve fibres which are enveloped by the endoneurium are organized within the fascicles surrounded by the perineurium. These fascicles are embedded within stromal tissue and surrounded by the epineurium. The nerves in the axilla have little or no surrounding fascia and there is a large amount of stroma around the fascicles. A blunt needle piercing these nerves may be less likely to puncture a fascicle. As the nerves are not constrained by a
fascia, they are freer to swell. Studies have shown that from proximal to distal, there is an increase in the number of fascicles and a decrease in their diameter. For example, in the proximal regions of the brachial plexus, that is, interscalene and suprascapular, the nerves are more solid and oligofascicular, whereas more distally, the fascicles are more widely dispersed, polyfascicular, and there is more stromal tissue. Also, the perineurium is unlikely to be penetrated by a short, blunt-bevel needle because of its tough, resistant nature. Therefore, this may explain why simple penetration of the epineurium does not always lead to neural damage, and intraneural injections of local anaesthetic do not necessarily yield postoperative neural injury.

Peripheral nerves have a dual blood supply: intrinsic exchange vessels in the endoneurium and an extrinsic plexus of vessels in the epineurial space that crosses the perineurium to anastomose with the intrinsic circulation. Ischaemia has been identified as one of the causes of peripheral nerve injury. Topical application of local anaesthetic to the rat sciatic nerve demonstrated acute reductions in peripheral nerve blood flow but no significant histological changes. Direct neurotoxicity of local anaesthetics is related to exposure to excessive concentrations or doses. Although all local anaesthetic agents have some neurotoxic potential, it is likely that ropivacaine is less toxic than other agents such as lidocaine. However, it is known that ropivacaine, whether injected intraneurally, extraneurally, or intrafascicularly, is associated with histological damage, including axonal destruction and Wallerian degeneration in rodent sciatic nerves. Despite this, Iohom and colleagues found that intraneural injection of clinically relevant concentrations of ropivacaine had no deleterious effect on sciatic nerve motor function in rat models.

Chan and colleagues inserted blunt-tipped insulated 22 G needles directly into 28 pig axillary brachial plexus nerves, elicited electrical stimulation, and visualized nerve expansion by US in 24 cases when injecting 5 ml of dye-stained dextrose. Upon histological examination of the nerves, the dye had penetrated the epineurium in all cases of US-visualized nerve expansion, and there was no evidence of fascicular dysplasia. They concluded that motor response above 0.5 mA might not exclude intraneural needle placement, and that US might be helpful in detecting intraneural injection of as little as 1 ml of injectate. Lupu and colleagues confirmed these results in a porcine model, demonstrating that US visualization of nerve expansion during intraneural injection of clinically relevant volumes of local anaesthetic (up to 20 ml) results in histological (inflammatory) changes but not functional nerve injury.

Animal studies suggest that it is intrafascicular injection in combination with high injection pressures that result in neural injury and neurological deficit, while injection within the epineurium results in low pressures and preservation of normal neurological function. Altermatt and colleagues determined that US images compatible with nerve swelling during injection were consistent with histological evidence of true intraneural injections. They also found that the intensity of stimulating current required to elicit motor responses did not correlate with intraneural needle placement. Intraneural injections were associated with low injection pressures when there was no evidence of fascicular injury. In a study of canine sciatic nerves, needles were placed epineurally or intraneurally under direct vision and 4 ml of lidocaine was injected. All perineural injections resulted in pressures of <5 psi. Eight of the 20 intraneural injections resulted in high pressures of 20–38 psi at the beginning of injection, and 12 of the intraneural injections resulted in pressures of <12 psi. Neurological function returned to baseline within 3 h after perineural injections and within 24 h after intraneural injections in the 12 cases with initial injection pressures of <12 psi. Neurological deficits persisted for 7 days after all eight of the cases of high-pressure intraneural injections. One week after injection, histological examination of these affected nerves revealed axonal degeneration and cellular infiltration (inflammatory changes). High injection pressures during intraneural injection might indicate intrafascicular injections and predict development of neural injury.

**Needle choices**

Needle choice might also play a role in peripheral nerve injury when intraneural injections are involved. Selander and colleagues compared two different injection needles, one with a 14° long-bevel and the other with a 45° short-bevel, for intraneural injections in rabbit sciatic nerves by tracing Evans Blue-albumin dye with fluorescence microscopy. They noticed that the nerve fascicles easily slid or rolled away from the needle tip, especially when using the short-bevelled needle. More injuries occurred with the long-bevelled needle which impaled the nerves. The frequency of fascicular injury did not change with orientation of the bevel. However, the degree of fascicular injury varied with orientation of the long-bevelled needle, with greater fascicular injury produced when the needle was oriented transversely to the nerve fibres. These results were confirmed by Macias and colleagues in a study performed in rats comparing 14° long-bevel and 45° short-bevel needles, with the greatest injury produced by the 14° long-bevel needles. Bigeleisen performed US-guided...
intraneural injections during axillary brachial plexus block with long-bevel 22 G needles in 20 patients. This resulted in lasting nerve injuries in four patients, of which three had resolution of injury within 3 months and the fourth within 12 months. Although there is considerable evidence concerning the dangers of long-bevel needles, a study by Rice and McMahon in rat sciatic nerves suggests that should a nerve fascicle be impaled during nerve block, lesions induced by short-bevelled needles (27° compared with 12°) are more severe, more frequent, and take longer to repair. Maruyama produced injury to rabbit sciatic nerves with each of four types of 21 G needles—bevelled (Quincke type), short-tapered needle (Whitacre type), long-tapered needle (Sprotte type), and long-tapered double needle (inner pencil-point fine needle with outer truncate conical needle). Each histological specimen was stained and the numbers of damaged axons were counted. All needle types caused interruption of the myelin sheaths. Both long-tapered needles produced significantly fewer transected axons than the bevelled needles.

Pre-existing pathology

Although the exact mechanism is unclear, patients with underlying nerve pathology are more susceptible to peripheral nerve complications, including prolonged duration of block and increased neurotoxicity to local anaesthetic agents. Many post-procedure neural injuries occur within nerves with pre-existing pathology. This may be related to the increased sensitivity of already damaged nerves, such as in patients with diabetic neuropathy or those having been exposed to neurotoxic chemotherapy or to the disruption of neural blood supply. It is unknown whether the use of epinephrine as an adjuvant in peripheral nerve blocks predisposes these at-risk patients to further nerve injury, that is, a ‘double-crush’.

Unavoidability of intraneural injections

NS cannot prevent injection into a motor fascicle, and paraesthesias do not prevent injection into a sensory fascicle. In a study of 22 interscalene brachial plexus nerve blocks performed with insulated needles and NS, motor response was obtained at 0.5 mA, and the peripheral nerve stimulator (PNS) was turned off. The needle was advanced and paraesthesia was elicited in 21 patients. The PNS was then turned on again and motor response with <0.5 mA were elicited in only 13 patients. It can be deducted that motor responses can be achieved at a small distance from a nerve whereas paraesthesia requires more intimate contact, or motor fibres are located in a more superficial position and are encountered first. Perlas and colleagues visualized a 22 G block needle in 102 patients for axillary block. With needle to nerve contact, the patients were asked to describe any feeling of paraesthesia and the PNS was turned on to maximum current of 2.0 mA. There were 39 (38.2%) true positive and 63 false negative paraesthesias; and there were 76 true positive (74.5%) and 26 false negative motor responses at <0.5 mA. This study demonstrated that NS and paraesthesia techniques have low sensitivity for localizing nerves—38.2% for paraesthesias and 74.5% for motor response to PNS. More recently, a stimulation current of 0.2 mA or less was found to be reliable for detection of intraneural placement of the needle, and currents of 0.2–0.5 could not rule out intraneural position.

It might be unnecessary to avoid intraneural injections, and in fact could be preferable to inject below the epineurium. Robards and colleagues studied 24 patients having popliteal sciatic nerve blocks, with a technique that involved either NS with a ‘twitch’ achieved between 0.2 and 0.5 mA or intraneural needle placement visualized by US. In 20 of the patients, the needle was seen below the epineurium before motor response was elicited by NS, whereas in the remaining four patients, the needle was seen intraneurally without response to NS even at 1.5 mA. All patients in the study had intraneural injections with low pressures of <20 psi resulting in adequate surgical anaesthesia and no postoperative neurological complications. Therefore, the absence of motor response to NS does not preclude intraneural needle position and seeking NS confirmation of a needle that is seen to be intraneural by US could lead to unnecessary attempts at localization. Figure 2 shows the appearance of a subepineurial injection in the sciatic nerve in the popliteal fossa.

Bigeleisen performed US-guided axillary nerve blocks in 26 patients undergoing base of the thumb surgery using a 22 G short-bevelled needle and injection of each of the four nerves (radial, median, ulnar, and musculocutaneous) with 2–3 ml of local anaesthetic. Complete surgical anaesthesia was achieved in 100% of patients. In 72 of the 104 injections, nerve swelling was observed and considered evidence of an intraneural injection, with the remaining injections immediately outside the epineurium. Sensory and motor testing before nerve block and at 6 months post-injection were unchanged. Bigeleisen developed the theory that intraneural injections with blunt needles do not result in neurological damage because the fascicles in the axillary nerves are separated by large amounts of stromal tissue thereby preventing the needles from penetrating the perineurium. This was also described in a case report of an inadvertent intraneural injection of the musculocutaneous nerve during axillary block that was detected only after review of the images; the patient remained neurologically intact. Blanch and colleagues examined 42 patients undergoing hallux valgus repair under NS-guided popliteal sciatic nerve block. When motor response was elicited at <0.5 mA, 40 ml of local anaesthetic was injected under US visualization. Nerve diameters were recorded before and after injection, and the presence of nerve swelling and local anaesthetic diffusion were noted. In 66% of these patients, there was intraneural injection, and nerve swelling was present in 88%. However, none of the patients developed post-procedure neurological complications.

Similarly, femoral nerve impalement and intraneural injection with 35 ml of local anaesthetic was recognized on
A retrospective review of recorded US images in a patient with intact quadriceps muscle function 24 h after operation and sensory block resolving the following day. The authors hypothesized that with nerve impalement, barriers to local anaesthetic diffusion were disrupted and resulted in increased susceptibility to conduction blockade. Because the femoral nerve increases in diameter in the inguinal region, the nerve fibres are dispersed within the nerve. This polyfascicular architecture might decrease the amount of pressure within the nerve during intraneural injection and therefore, no significant nerve damage results.

Although the use of US guidance has not been shown to decrease the rate of neural complications secondary to peripheral nerve blocks, it has markedly increased our understanding of the anatomical findings that allow nerve blocks to be performed successfully with few complications.

**Peripheral nerve catheters**

Both anaesthetists and surgeons recognize the benefits of peripheral nerve catheters (PNCs). The continuous infusion of local anaesthetic near a peripheral nerve or plexus produces fewer systemic side-effects than i.v. opioids, increases postoperative patient satisfaction, and can allow for faster functional recovery of the operated limb. Recently, intra-articular and subacromial pain pump catheters have been associated with glenohumeral joint chondrolysis, giving PNCs an even more important role for pain management after orthopaedic surgery. Despite the benefits and widespread use of continuous PNCs, few studies exist regarding the prevention of complications during PNC placement, management, and removal.

**Placement**

Ideally, PNCs are placed on the first attempt, without patient discomfort and provide surgical anaesthesia, postoperative analgesia, or both. In clinical practice, however, the nerve can be hard to locate, the catheter difficult to thread, or the local anaesthetic might not achieve optimal spread. Practitioners also experience inadvertent vascular puncture, haematoma formation, or both. Both NS and US-guided techniques offer high success rates for PNC catheter placement. Gasparini and colleagues reported a 96% success rate using a nerve stimulator for both upper and lower extremity PNCs in 433 patients. Eighty-seven per cent of their catheters were placed on the first attempt, 10% placed on the second, and 3% placed with greater than two attempts. The success rate of first attempts improved as their study progressed, highlighting the importance of operator skill in limiting the number of needle punctures.

Even with a high success of nerve localization (98.6%), difficulty threading the catheter can occur (9.5%). Insertion site plays a role, with popliteal and femoral catheters easier to thread than interscalene catheters. When catheter insertion is difficult, a bolus of normal saline 20 ml can be injected through the needle to successfully ease catheter insertion. Saline use, however, can decrease the ability to elicit a subsequent motor response if a nerve stimulator technique or stimulating catheter is used. Dextrose solutions might better preserve neurostimulation. A recent study comparing no injection vs a 10 ml dextrose injection through a Tuohy needle did not support the concept of ‘opening the space’ around the femoral nerve to facilitate catheter threading.

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**Fig. 2** The US image on the left is the pre-injection sciatic nerve in the popliteal fossa. The image on the right shows subepineural distension secondary to injection of local anaesthetic.
Block failure

Occasionally, there are instances when the catheter is passed easily but the nerve block fails to provide adequate anaesthesia or analgesia. Whether or not this is a technique-related complication of catheters or failure of adequate supplementation with oral or i.v. analgesics remains controversial. Some practitioners inject an adequate amount of local anaesthetic for surgical anaesthesia through the block needle and then thread the catheter and achieve a successful rate of intraoperative (primary) and postoperative (secondary) analgesia. Others insert the catheter and then inject local anaesthetic through it. A 0.75% primary block failure rate was reported for 400 popliteal catheters placed with the nerve stimulator technique, a non-stimulating catheter, and injection of local anaesthetic after catheter threading. Secondary failure rate of PNCs ranges from 10% to 40%. The introduction of stimulating catheters has been reported to hasten block onset time and possibly decrease secondary failure rate. An observational study found the ability to elicit a motor response with the stimulating catheter correlated with successful postoperative analgesia in 124 of 130 cases for a secondary failure rate of 5%. Subsequent radiography confirmed correct catheter position for these cases. In contrast, a recent randomized, controlled, double-blind study found equally high success rates of secondary analgesia and no difference between stimulating catheters and blind advancement of femoral nerve catheters placed for total knee arthroplasty.

Recent small studies comparing US with NS techniques with and without stimulating catheters suggest that US-guided PNCs are placed faster, with less patient discomfort and with lower failure rates than those placed with NS. Another study demonstrated improved primary success and reduced secondary catheter failure of continuous infraclavicular blocks placed under US guidance with NS assistance when compared with non-stimulating and stimulating catheters without US.

Inadvertent catheter removal

Inadvertent catheter removal complicated 1% of cases where a popliteal catheter was primarily secured by tunnelling under the skin. Accidentally, premature catheter removal occurred in 1.4% of femoral catheters secured with adhesive strips or transparent dressings alone. Suturing catheters has also been shown to decrease premature catheter removal. 2-Octyl cyanoacrylate (Dermabond) Topical Skin Adhesive has been used safely to secure catheters as it binds to the epidermis and sloughs off naturally with the skin over the course of 5–10 days. However, catheter removal can be difficult and can cause minor abrasions when removal is required shortly after securing the catheter. With so many advancements for securing PNCs, catheter site is becoming less of a risk factor for inadvertent or premature removal because superficially placed catheters in highly mobile areas are being secured more effectively. Fredrickson and colleagues reported a 1% incidence of accidental removal for 300 ambulatory interscalene catheters secured with 1 ml skin sealant and an epidural catheter locking device. This is similar to the above reported rates for other catheter sites.

Adverse events associated with tunnelling and suturing can occur. Compere and colleagues and Despond and Kohut both reported cases where the catheter was cut during suture removal. Rose and McLarney reported inadvertently cutting an indwelling catheter while moving the tunnelling needle through the skin. Surgical exploration was unsuccessful in retrieving the catheter. Similar to a retained fragment of an epidural catheter, it has been suggested not to retrieve a fractured PNC unless the fragment is in an area at high risk for infection or is causing neurological symptoms. The authors also suggest avoiding magnetic resonance imaging to visualize the catheter fragment due to a theoretical concern of heat injury and catheter migration, especially with metallic catheters.

Catheter kinking, knotting, and looping

Fortunately, catheter knotting and looping is rare. It has been suggested that superficial catheters be advanced 3 cm past the needle tip and deeper catheters (such as femoral or sciatic) advanced 5–10 cm beyond the needle to avoid catheter kinking, knotting, and looping. Fluoroscopy-guided retrieval of knotted catheters might be necessary when patient repositioning and catheter tension or traction is unsuccessful.

In an interesting case report, a stimulating interscalene catheter (Stimucath, Teleflex, Le Faget, France) was entrapped without kinking, knotting, or looping. The catheter had been inserted 2 cm beyond the needle tip and functioned well for 48 h. Attempted removal on the third postoperative day was difficult and repeated traction on the catheter merely stretched the distal portion. Because the patient experienced neurological symptoms, the catheter was removed surgically. Other catheters can be stretched to more that 300% of their original length without breaking.

Infectious complications of PNCs

Localized inflammation is infrequent (0–13.7%), and local infection (0–3.2%), abscess formation (0–0.9%), and sepsis occur even more rarely. Bacterial rates of colonization of PNCs, on the other hand, are high and range from 7.5% to 57% depending on the location of the catheter and the number of colonies used to determine colonization. Femoral and axillary catheters have the highest rates of colonization, whereas the rates for popliteal catheters are low. It is speculated that the higher density of sebaceous glands (which have been shown to decrease the efficacy of skin disinfectants) in the groin and axilla make colonization more likely. The skin flora are usually the source of colonizing bacteria; the most common organism is Staphylococcus epidermidis. Despite aseptic techniques, contamination of
catheters can occur at the time of removal, which might artificially inflate the rate of reported colonization.

Several factors in addition to catheter site affect the incidence of PNC infection. Intensive care unit admission, trauma, immune compromise including diabetes mellitus, nerve catheter indwelling >48 h, male sex, and the absence of antibiotics independently increase risk of infection. Pre-existing surgical site infection has not been shown to increase risk.

Infection rates can be kept low with adherence to aseptic technique, including the use of chlorhexidine which is considered to be the best skin disinfectant currently available. The use of sterile gowns is unnecessary since studies with PNCs catheters have shown similar rates of bacterial colonization with and without their use. Studies support tunnelling as a method to prevent infection, but this, and also the use of bacterial filters, remain minor factors. One study suggests that the Tuohy needle increases the incidence of catheter colonization when compared with short-bevel needles. The authors suggest that the higher degree of trauma induced by the Tuohy needle could explain this finding.

The optimal dressing to prevent catheter-related infections is unknown. Transparent dressings are used to reduce the number of dressing changes while appropriately monitoring the site for signs of inflammation. Early, reproducible number of dressing changes while appropriately monitoring infection as previous studies using continuous infusions. The authors report similar rates of local inflammation and infection when compared with dry gauze covered by a transparent dressing.

In order to prevent infection, many studies support the administration of at least one, and likely more than one, dose of antibiotics when placing PNCs. Optimum duration of antibiotic therapy is unknown, but Morin and colleagues found that postoperative administration of antibiotics for at least 24 h significantly reduced the risk of catheter colonization. Bergman and colleagues reported a case of superficial axillary infection in a non-surgical patient who received a PNC catheter to treat reflex sympathetic dystrophy and who did not receive antibiotics. The use of antibiotic therapy for PNCs in non-surgical patients requires further investigation. Repeated manual dosing or refilling of catheter pumps might increase the infection rate. Wiegel and colleagues used intermittent boluses (without a pump) and reported similar rates of local inflammation and infection as previous studies using continuous infusions. Strict aseptic technique should always be used when handling local anaesthetics and catheters.

Accidental vascular puncture and haematoma formation
Vascular puncture during PNC placement is not uncommon. Wiegel and colleagues reported a vascular puncture incidence of 5.7% and 6.6% for femoral and sciatic catheters, respectively. Reports of vascular puncture and intravascular catheter migration exist for other PNC locations as well. Recent studies suggest that US might decrease the risk of inadvertent vascular puncture. Significant bleeding and serious complications due to vascular puncture occur rarely. In a study of 405 patients receiving axillary PNCs, only one developed a haematoma, and that patient was receiving heparin. Similarly, a case of retroperitoneal haematoma and pressure-induced quadriceps weakness occurred after femoral nerve catheter placement in a patient who had not disclosed aspirin therapy. In a case of the right external jugular vein puncture during interscalene catheter placement, the catheter was dislodged on postoperative day 2 and a small neck haematoma was noted. The catheter was replaced near the haematoma and removed 3 days later. On postoperative day 8, the patient returned to her surgeon and was ultimately diagnosed with Staphylococcus aureus sepsis originating from her neck. Haematoma formation near the site of catheter entry was suspected of providing a nidus for bacterial seeding. The authors suggest that it is ill advised to maintain a PNC when a haematoma has formed near the site of catheter entry.

PNCs and anticoagulation
The American Society of Regional Anesthesia’s Third Consensus Conference on Regional Anesthesia and Anticoagulation recommends that patients undergoing deep plexus or peripheral nerve block be treated with the same guidelines as those pertaining to neuraxial techniques. No randomized controlled trials specifically address PNCs and anticoagulation; however, case reports of bleeding complications related to both deep and superficial PNCs have appeared. An extensive retroperitoneal haematoma occurred after continuous lumbar plexus block, and significant ecchymoses developed which interfered with physical therapy and delayed hospital discharge in three patients after removal of femoral and sciatic catheters. All of these patients were being treated with enoxaparin after operation, and the authors suggest that PNC removal did not coincide with the peak enoxaparin effect.

PNCs remain an important technique in the modern practice of anaesthesiology and can be performed for a wide variety of clinical scenarios with relatively few complications.

Local anaesthetic systemic toxicity and its treatment
Local anaesthetic systemic toxicity (LAST) ranges from mild systemic symptoms (auditory changes, circumoral numbness, metallic taste, and agitation), to central nervous system (CNS) findings (seizure, coma, respiratory arrest) and cardiovascular events (hypertension, hypotension, tachycardia, bradycardia, ventricular arrhythmias, cardiac arrest). In the past, treatment was supportive—application of supplemental oxygen, pharmacological treatment of seizure activity, and management of cardiovascular effects. However, LAST continues to be a major source of morbidity and mortality in the practice of regional anaesthesia.
History

Fewer than 15 yr have elapsed since Weinberg described his observation that pre-local anaesthetic administration or post-arrest treatment with lipid emulsion infusion shifts the dose–response to bupivacaine-induced asystole in rats. This early study consisted of two protocols. In the first, anaesthetized rats were pretreated with saline or various concentrations of lipid emulsion ranging from 10% to 30% then subjected to 0.75% bupivacaine boluses i.v. The lethal dose of bupivacaine was significantly higher with lipid emulsion pretreatment. In the second protocol, animals were anaesthetized and administered various doses of i.v. bupivacaine. Resuscitation consisted of discontinuation of the general anaesthetic, chest compressions, and either a saline or lipid bolus. The LD₅₀ for bupivacaine was 12.5 mg kg⁻¹ in rats treated with saline and 18.5 mg kg⁻¹ when resuscitated with lipid emulsion.⁶⁸

In similar experiments conducted with a larger animal model, hounds were anesthetized and administered 10 mg kg⁻¹ i.v. bupivacaine. All animals experienced a cardiac arrest and after 10 min of cardiac massage, were randomized to receive either a 4 ml kg⁻¹ bolus of 20% lipid emulsion or saline followed by an infusion at 0.5 ml kg⁻¹ min⁻¹ for 10 min. Survival for lipid emulsion-treated dogs was 100%, but was 0% for saline-treated control dogs.⁶⁹

Lipid infusions in humans

The first use of lipid emulsion infusion to treat LAST in humans was reported in 2006.⁷⁰ A 58-yr-old 86-kg male with a history of myocardial infarction and coronary artery bypass surgery with persistent angina was undergoing arthroscopic repair of a rotator cuff tear using an interscalene block. A nerve stimulator technique was performed and after biceps stimulation was elicited at 0.34 mA, 0.5% bupivacaine 20 ml and 1.5% mepivacaine 20 ml were injected in 5 ml aliquots, with aspiration between. Thirty seconds after the completion of the injection, the patient experienced a tonic-clonic seizure that was treated with propofol 50 mg, and supplemental oxygen was provided with a self-inflating resuscitation bag. Ninety seconds after resolution, the seizures recurred and the ECG revealed ventricular arrhythmias which rapidly deteriorated to cardiac arrest. The patient’s trachea was intubated and was followed by cardio-pulmonary resuscitation (CPR), including chest compressions, cardioversion, and epinephrine. Only after infusion of 100 ml of 20% lipid emulsion did the patient recover a perfusing cardiac rhythm, and he had no neurological sequelae.⁷⁰ Later that year, reports of lipid infusion reversing LAST from ropivacaine and levobupivacaine were published.⁷¹ ⁷²

To date, there have been more than 10 case reports describing the successful treatment of LAST with lipid infusions, and also multiple reports in humans and animal models of using lipid infusions to treat toxicity from other lipophilic agents, including verapamil, clomipramine, propranolol, lamotrigine, amfebutamone, and haloperidol.⁷³ ⁷⁷

Mechanism of lipid rescue

The exact mechanism of lipid rescue has yet to be elucidated. The theory of the infusion acting as a ‘lipid sink’, drawing the local anaesthetic into the lipid layer, is attractive as the bupivacaine lipid:aqueous partition coefficient is 11.9.⁵⁸ There might also be metabolic advantages to using lipid. The availability of free fatty acid could help reverse the ischaemia-induced switch from lipid to glucose metabolism that occurs in the stunned myocardium.⁷⁸ Bupivacaine is known to inhibit mitochondrial oxidative phosphorylation. During episodes of cardiac toxicity, fatty acids are unable to enter cardiac mitochondria where they would provide myocardial energy needs. Lipid infusions, providing high plasma triglyceride concentrations, might serve as alternative substrates overwhelming this inhibition.⁷⁹

Lipid infusions are emulsions in water of soybean oil (predominantly neutral triglycerides) made isotonic with glycerin. Egg yolk phospholipid 1% is the emulsifying agent and creates particles 0.5 μm in diameter. When used for parenteral nutrition, reactions to soybean oil, pyrogenic reactions, and problems with contamination can occur. Patients with normal lung function or pulmonary compromise without acute respiratory distress syndrome (ARDS) do not demonstrate decreases in oxygenation or pulmonary vascular changes, but those with ARDS do have pulmonary changes secondary to enhanced inflammation with excessive rates of administration, albeit transient.⁸⁰ Reports of pancreatitis secondary to lipid infusion are sporadic and seem only to occur in patients with underlying debilitating conditions.⁸¹ ⁸³

The safety of large-dose lipid emulsion therapy has yet to be established. Hiller and colleagues⁸⁴ looked at the LD₅₀ of lipid infusions in rats. Twenty per cent lipid (20, 40, 60, or 80 ml kg⁻¹) or saline (60 or 80 ml kg⁻¹) was administered over 30 min, after which the animals were observed for 48 h and then euthanized. Three animals were given lipid emulsion at 60 ml kg⁻¹ and euthanized at 1, 4, and 24 h after infusion. None of the animals had neurological findings (seizures, motor abnormalities), although animals in the 80 ml kg⁻¹ group were lethargic for several hours after the infusion, and none had haemodynamic changes. Although all had elevated triglyceride levels immediately after the infusion, they all returned to baseline by 48 h. Elevated phosphorus amylase, AST, and serum urea nitrogen were seen in many of the rats at 48 h. Histological analysis of their organs revealed microvesicular steatosis in 70–80% of hepatocytes at 1 h post-infusion, but in only 10% of cells at 24 h. All doses of lipid administered in this study were in excess of those used for lipid rescue in humans.

Resuscitation with lipid infusions

Along with attempting to confirm the safety of lipid for treatment of LAST, research is focusing on the optimal combination of agents to use in resuscitation. A study in rats given bupivacaine 20 mg kg⁻¹ to produce asystole suggested that doses of epinephrine >10 μg kg⁻¹ administered with lipid, while being associated with a rapid return of...
The onset of cardiac arrest. Vasopressors to achieve coronary perfusion sufficient to cardial compressions in the pig and vasopressin might be secondary to less efficient the lipid group did. This positive outcome with epinephrine All pigs in the vasopressin group survived, whereas none in normal shocks were administered if ventricular fibrillation occurred. CPR was initiated and animals were given either vasopressin with epinephrine or 20% lipid emulsion, and up to three monophasic counter-shocks were administered if ventricular fibrillation occurred. All pigs in the vasopressin group survived, whereas none in the lipid group did. This positive outcome with epinephrine and vasopressin might be secondary to less efficient cardiac compressions in the pig vs the rat model, requiring vasoconstrictors to achieve coronary perfusion sufficient to support return of spontaneous circulation. It is also possible that in this model, hypoxia is allowed to occur before initiation of CPR, whereas in the rat models, CPR began with the onset of cardiac arrest.

The American Society of Regional Anesthesia recently published an advisory on LAST that reviews the history, prevention, diagnosis, and treatment of this condition. It stresses (i) preparedness by having 20% lipid available when administering local anaesthetics, (ii) risk reduction, by limiting doses of local anaesthetics to the minimal amount required for the desired outcome and considering use of pharmacological markers like epinephrine in test doses and aspiration before injection, and (iii) vigilance, by monitoring patients for signs and symptoms for longer (>10 min) after injection. These recommendations for treatment of LAST appear in Table 1.

Conflict of interest
None declared.

References
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Table 1 Recommendations for treatment of LAST

<table>
<thead>
<tr>
<th>Airway management</th>
<th>Seizure suppression</th>
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<td>BCLS/ACLS</td>
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<tr>
<td>Use small initial doses of epinephrine (10–100 μg boluses)</td>
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<td>Vasopressin is not recommended</td>
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<tr>
<td>Avoid calcium channel blockers, beta-adrenergic blockers, and local anaesthetics (lidocaine, procaine)</td>
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Consider lipid emulsion therapy at first signs of LAST

1.5 ml kg⁻¹ bolus of 20% lipid emulsion
Infusion at 0.25 ml kg⁻¹ per min for at least 10 min after return of circulatory stability
Consider giving a second bolus and increasing infusion to 0.50 ml kg⁻¹ if circulatory stability not attained
Upper limit of lipid emulsion recommended is 10 ml kg⁻¹ over the first 30 min
Consider cardiopulmonary bypass if lipid emulsion treatment fails

spontaneous circulation, are not associated with sustained recovery. This could be because epinephrine is arrhythmogenic, increases myocardial oxygen demand, reduces subendocardial perfusion, and causes pulmonary oedema. Vasopressin, too, when used for resuscitation from LAST in rat models has been shown to produce poorer outcomes than lipid and to be associated with a high-incidence pulmonary haemorrhage. Conversely, Mayer performed a study comparing the combination of epinephrine and vasopressin with lipid emulsion in resuscitating pigs which suffered asphyxial cardiac arrest after i.v. injections of bupivacaine. Animals were given 5 mg kg⁻¹ of 0.5% bupivacaine and ventilation was stopped for 2 min until asystole occurred. CPR was initiated and animals were given either vasopressin with epinephrine or 20% lipid emulsion, and up to three monophasic counter-shocks were administered if ventricular fibrillation occurred. All pigs in the vasopressin group survived, whereas none in the lipid group did. This positive outcome with epinephrine and vasopressin might be secondary to less efficient cardiac compressions in the pig vs the rat model, requiring vasoconstrictors to achieve coronary perfusion sufficient to support return of spontaneous circulation. It is also possible that in this model, hypoxia is allowed to occur before initiation of CPR, whereas in the rat models, CPR began with the onset of cardiac arrest.

The widespread use of single-shot and continuous regional anaesthetic techniques is associated with few complications, but neurological deficits, PNC-related issues, and LAST still occur. Understanding the aetiologies of these complications and implementing methods to minimize their occurrence will promote the safe practice of regional anaesthesia.


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