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Perioperative nerve injury and regional anaesthesia

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Peripheral nerve anatomy

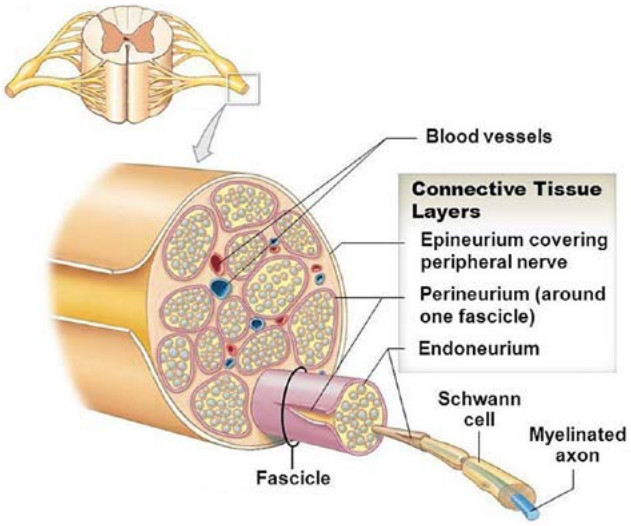

Figure 1: Schematic representation of a peripheral spinal nerve (cross-sectional view) showing its layers and components[1]

Peripheral nerves consist of axons and dendrites which make up the parenchyma, as well as stroma consisting of connective tissue.[1] The parenchyma is thus the conducting and neurologically functional element.[2] Each axon is covered by an endoneurium. Axons are grouped together into fascicles which are surrounded by a perineurium. The perineurium forms a physical and chemical barrier and protects the peripheral nerve fascicles.[2] Between the fascicles is stromal or connective tissue and blood vessels. The fascicles, connective tissue and blood vessels are held together into a unit by the epineurium.

Peripheral nerves have varying proportions of fascicles can comprise between 20% and 70% of the cross-sectional area of a peripheral nerve.[2] For example the connective tissue within the sciatic nerve can comprise 72–75% of the cross-sectional area of the sciatic nerve. As a consequence of the high ratio of connective tissue versus nerve tissue, the risk of fascicular injury after nerve puncture is low as the needle is more likely to separate than pierce a fascicle.[3] Conversely, 80% of the ulna nerve is comprised of nerve tissue. Therefore, an intraneural injection of the ulna nerve carries a high risk of nerve injury.[2]

The anatomy closely associated with nerve tissue may be complex. Some peripheral nerves, such as the sciatic nerve, have two extraneural connective tissue sheaths which surround the sciatic nerve from the subgluteal area to the popliteal fossa. Karmakar[4] has described an outer epimysium, the innermost epineurium and the paraneural sheath in between. In other words, subparaneural is deemed extraneural and sub-epineural is intraneural. The two different extraneural layers are often only visualised with high-resolution ultrasound machines. The clinical significance of the paraneurium is that a subparaneural, as opposed to a subepimysial injection, is associated with faster block onset, higher block success rate and prolonged block duration.[4] With this complex anatomy in mind, when performing ultrasound-guided regional anaesthesia, the question is where optimal needle placement should be to achieve a successful block yet prevent nerve injury. In other words: "how close is close enough?"[5]

Peripheral nerves have two independent but interconnected blood supplies. The extrinsic blood supply consists of vessels within the epineurium. The intrinsic supply runs within the endoneurium and fascicles. Within the fascicles, the capillaries are nonfenestrated and contribute to the barrier effect. As these capillaries reach the perineurium, the capillaries become fenestrated. There are also vessels that traverse the perineurium that form anastomosis between the two vascular systems.[6]

Incidence

Perioperative nerve injury is complex as there are anatomical, anaesthetic, patient and surgical factors interacting to make the diagnosis and cause thereof challenging. The incidence of severe long-term (6–12 months) peripheral nerve block-(PNB)-related nerve injury is estimated to be 2–4 per 10 000 peripheral nerve blocks.[6,7] The term *peripheral nerve injury (PNI)* has now been replaced by *postoperative neurologic symptoms (PONS)*.[8] This change in terminology is a more appropriate reflection of the relatively common and transient neurological symptoms that present during the short-term postoperative period as opposed to the rare long-term or permanent nerve injury. In light of this expanded terminology, Lam et al.[9] found the incidence of neurological symptoms lasting less than ten days was 14.4% of patients who had received a PNB. They reported an

Table I: The classification of nerve injury by Seddon and Sunderland[11,12]

Seddon	Sunderland	Nerve injury
Neuropraxia	First degree	Segmental demyelination
Axonotmesis	Second degree	Axon severed but endoneurium intact
	Third degree	Axonal and endoneurial discontinuity, perineurium and fascicular arrangement preserved
	Fourth degree	Axonal, endoneurial, perineurial and fascicular discontinuity. Epineurium intact
Neurontmesis	Fifth degree	Loss of continuity of entire nerve trunk

incidence of 1:1 000 of new prolonged (more than ten days) of PONS following surgery and regional anaesthesia. However, only 0.2:1 000 of these cases appeared to be PNB related.

Ultrasound and regional anaesthesia

Currently, ultrasound imaging is considered mainstream practice for regional anaesthesia.[10] Ultrasound-guided regional anaesthesia (UGRA) allows for direct visualisation of the target nerve, surrounding tissue and injectate spread. These advantages are not available with anatomical landmark, paraesthesia, transarterial or nerves stimulator methods of localisation. It may seem that a consequence of utilising ultrasound for PNBs, would be decreased nerve injury.[8] However, current literature has shown that ultrasound has no significant effect on the incidence of PONS. However, because serious long-term PONS is so infrequent, proving a statistically significant reduction of long-term nerve injury with the utilisation of ultrasound is unlikely to occur because it would require an inordinately large number of subjects.

There is however, class 1 evidence that ultrasound can detect intraneural injection, but images of needle-nerve interface are not consistently obtained by all operators in all patients.[6] In addition, current ultrasound technology does not have adequate resolution to discriminate between interfascicular and intrafascicular injection.[6]

UGRA has facilitated more accurate deposition of local anaesthetic and given practitioners the confidence to use lower volumes.[8] Studies have shown that volumes of 5–10 ml reduced the incidence and intensity of hemidiaphragmatic paresis associated with interscalene blocks. Unfortunately this reduction occurs in an unpredictable manner.[7,8]

A pragmatic view on the impact of ultrasound on the safety of PNB is that it does not rely on one single technology. On the other end of the ultrasound machine, has to be a well-trained practitioner who pays attention to indication, block and patient selection, anatomy, pharmacology, equipment and techniques; in addition to demonstrating nontechnical skills such as communication and situational awareness.[10] Ultrasound does provide us with a monitor to reduce block-related mechanical nerve injury and enable appropriate local anaesthetic spread outside of the epineurium. In addition, ultrasound allows for a reduction in local anaesthetic dosage and volume, and it has stimulated the emergence of new blocks with perhaps a safer profile.

Pathophysiology of nerve injury

PONS may be related to anaesthetic or surgical technique, patient positioning or anatomical variation, tourniquet-related injury, exacerbation of a pre-existing injury or multifactorial. Mechanisms of regional anaesthesia-related injury include traumatic (mechanical) injury, ischaemic (vascular injury or prolonged pressure), neurotoxic (chemical) injury and inflammatory. Non-anaesthetic factors include patient factors such as pre-existing neurological conditions and anatomical variations. Surgical factors include compression, stretching and ischaemic injuries.

Nerve injury has been classified by Seddon[11] and Sunderland[12] based on the degree of damage to the nerve axon and surrounding structures. (Table I).

Both the Seddon and Sunderland classifications are pathological classifications based on histological findings. Practically, nerve biopsy is rarely indicated in PONS and therefore it is usually clinically unknown as to which category of nerve injury a patient falls into.

Mechanical and injection injury

Direct needle trauma may result in a mechanical compression injury from forceful needle-nerve contact or intraneural injection. Nerve compression can cause a conduction block and if prolonged, a focal demyelination.[6] Intraneural injection may lead to increased intraneural pressure, which, if it exceeds capillary occlusion pressure, will cause ischaemia.[6] The main cause of block-related nerve injury is intrafascicular injection causing rupture of the perineurium and loss of the protective environment within the fascicle. This results in myelin and axonal degeneration.[6] Even intrafascicular injection of saline can cause axonal degeneration. Therefore, although neurotoxicity is an important factor, the location of the needle tip during injection of local anaesthetic is crucial.[6]

Vascular injury

Damage to the nerve vasculature during PNBs may result in local or diffuse ischaemia related to direct injury, acute occlusion of the arteries supplying the vasa vasorum or from haemorrhage within the nerve sheath. The extrinsic or epineurial circulation accounts for 50% of the nerve's blood supply.[6] Nerves with a higher proportion of connective tissue may be less susceptible to compression as external forces are not transmitted directly to the epineurial vessels.

Chemical injury

Chemical injury results from injection of solutions which cause tissue toxicity. These solutions may include local anaesthetics, alcohol, phenol or additives. Injection into or adjacent to the nerve may cause an inflammatory reaction or chronic fibrosis involving the nerve.[6] There is evidence that nearly all local anaesthetics can have myotoxic, neurotoxic and cytotoxic effects with a direct correlation between concentration of local anaesthetic and duration of exposure.[6]

Local anaesthetics can also directly constrict vasculature causing ischaemic injury. The site of local anaesthetic injection may be the most important factor in determining whether neurotoxicity will occur, with intrafascicular injection being the worst.

Inflammatory injury[6]

Nonspecific inflammatory responses involving peripheral nerves can occur distant from or near the site of surgery and may also be delayed. Surgery and tissue trauma may set up a response resulting in adhesions, fascial thickening, vascular changes and scar tissue. Of note, animal data suggest that ultrasound gel can lead to inflammation around peripheral nerves. It may be difficult to distinguish inflammatory injury from other causes of PNI.

Surgical factors[6]

Patient positioning for surgical requirements can cause PONS as patients are placed in positions they would not tolerate awake and not for an extended period. Surgical mechanisms of injury include traction, transection, compression, contusion, ischaemia and stretch. Nerve roots are especially susceptible to traction and compression because roots lack epineurial and perineurial tissue. The superior trunk of the brachial plexus is especially vulnerable as it is attached medially to the transverse process and laterally by the entry of these nerves into the muscle. Loss of muscle tone during general anaesthesia results in traction to the neural elements.

The use of tourniquets can result in mechanical and/or ischaemic injury. Tourniquet neuropathy usually results in motor fallout and decreased touch, vibration and proprioception, whilst the senses of heat, cold and pain are maintained. To mitigate tourniquet neuropathy, the following measures can be used: using wider tourniquets, lower cuff pressures and limiting the duration of inflation

Patient factors[6]

Patients may have preoperative neurological compromise which may be overt or unmasked post-surgery. This compromise may result from entrapment, metabolic, ischaemic, toxic, hereditary and demyelination. Entrapment neuropathies can involve the ulnar, median, radial, lateral femoral cutaneous and peroneal nerves. Risk factors for ulnar neuropathy include male sex, extremes of body habitus and prolonged admission. Carpal tunnel syndrome is the most common upper limb neuropathy. Diabetic neuropathies include a broad range of clinical entities and chronic ischaemia may compromise diabetic nerve fibres. Any medical condition which affects the microvasculature of peripheral nerves increases the risk of PNI. These include peripheral vascular disease, vasculitis, cigarette smoking and hypertension. Toxic aetiologies include alcohol and cisplatin chemotherapy. Other patients at risk include those with hereditary neuropathy.

Prevention of nerve injury

We have established that needle trauma is an important aspect of PNI. To minimise this risk, nerves should be handled with care. Forceful needle contact and application of needle pressure displacing a peripheral nerve may cause inflammatory changes. It is accepted that intraneural injection should be avoided. However, unintentional unrecognised intraneural injection may occur more frequently than we like to think.[6] Ultrasonically, a circumneural spread should be aimed for as this corresponds to an adventitial extraneural injection.[13] For popliteal sciatic nerve blocks, positioning the needle in the common nerve sheath between the tibial and peroneal components and aiming for a circumneural spread surrounding both divisions seems to be the safest option producing rapid anaesthesia.[13] For axillary and infraclavicular approaches to the brachial plexus, ultrasound-guided perivascular injection aiming for circumferential spread around the artery appears to be a safe target as opposed to individual targeted nerve injections.[13] For interscalene blocks, an injection into the fascial sheath but far from the plexus are as effective as an injection adjacent to the nerve structures.[13]

The epineurium is usually tougher than the surrounding tissue, so nerves tend to be pushed away from an advancing needle, especially if it is a short-bevelled as opposed to a long-bevelled needle.[9] However, if the nerve is punctured, short-bevelled needles appear to cause more damage.[9] An increased needle diameter also worsens the severity of nerve injury after intraneural injection.

To avoid intraneural injections, it is usually recommended to perform PNBs in awake or lightly sedated adult patients.[9] If the patient complains of pain or paraesthesia, injection should be stopped immediately and the needle withdrawn. However, it must be noted that the absence of paraesthesia does not reliably exclude needle-nerve contact and/or the development of PNI.[6]

In addition, if nerve swelling or fascicular separation is noticed on ultrasound during injection, this is indicative of epineurial intraneural injection and is not recommended.[13] Injection should be stopped immediately and the needle withdrawn.

With respect to peripheral nerve stimulation as a modality to prevent PNI, Coulomb's Law must be kept in mind. According to Coulomb's Law, the minimum stimulating current (MSC), which is the threshold current required to elicit a motor response, exponentially decreases as the needle tip advances towards the nerve. An association between a very low MSC and subsequent

PNI has been described.[14] A MSC of less than 0.2 mA is a specific, but not sensitive, indicator of intraneural needle placement.[6]

Electrical impedance monitoring is featured in newer nerve stimulators and measures the resistance to flow of an alternating current in an electrical circuit. Electrical impedance is very sensitive to changes in tissue composition.[6] Nerves have greater electrical impedance than the surrounding muscle and interstitial fluid because of their low water and high lipid content. Unfortunately, there is substantial variance within the data and an absolute value at which intraneural needle placement occurs has not been determined.[6] Therefore, further research is required regarding the potential clinical applicability of this modality.

An association with intrafascicular injection and high injection pressures has also been described.[15] The intrafascicular space consists of densely packed fascicles and a higher opening pressure is required to inject into this space; as opposed to the interfascicular space which consists of loose connective tissue. It has been suggested that documentation of resistance to injection should standard.[6] However, a syringe-feel technique is subjective and differs according to syringe size. Pressure monitoring devices are available on the market. Injection pressure monitoring is useful for its negative predictive value and it appears to be prudent to avoid injection pressures of more than 15 psi.[6]

With respect to vascular injury, a meta-analysis has shown that UGRA reduces the incidence of vessel puncture.[16] Local anaesthetic and adjuncts reduce neural blood flow in an agent and concentration-dependent manner. Adrenaline can cause vasoconstriction and decreases neural blood flow to a greater degree than local anaesthetics alone. However, its role in nerve ischaemia and injury is controversial.[6] If using a long-acting local anaesthetic to perform a PNB, it would seem that the addition of adrenaline will not offer much benefit and may, indeed, cause harm. Therefore, perhaps the judicious practice to reduce vascular injury would be to omit adrenaline for PNBs; use the least volume and concentration of local anaesthetic to do the job and to utilise ultrasound guidance.

To further minimise the risk of chemical injury, practitioners should be meticulous about not exposing peripheral nerves to alcohol or ultrasound gel.

In summary, PONS has complex and diverse aetiology. Patients' risk for PONS is variable and peripheral nerves are variable in location, structure and susceptibility to injury. The main cause of PNB-mediated PONS is most likely mechanical fascicular injury and/or injection of local anaesthetic into a fascicle causing myelin and axonal degeneration.[6] There is no evidence that ultrasound guidance or any other nerve localisation techniques reduce the incidence of PNI.[6] However, common sense should prevail and perhaps it is wise to retain practices which do not add extra cost nor risk to the patient, but may detect or mitigate intraneural injection and/or subsequent injury.

Investigation of nerve injury

PONS may cause high levels of anxiety for both patient and practitioner. It is reassuring that most deficits are limited in severity and can be expected to resolve fully with time.[17] A practical approach is to stratify firstly the urgency and the scope of diagnostic testing and consultation necessity, initiating appropriate treatment and defining follow-up and symptom management.

It is, of course, important to first recognise perioperative nerve injury. Factors exist which may delay recognition, namely: sedation, postoperative pain or analgesia, the presumption that all symptoms are due to the block, patient perioperative naivety or uncertainty, postoperative activity restrictions and dressings, drains or castings.[17] Late presentations more likely have non-anaesthetic or operative-related causes.[17] Ideally patients should have written information on potential anaesthetic complications and contact information should there be a problem.

In addition, any pre-existing neurological deficits should be recognised and documented. The double crush principle arises from a situation whereby a patient may be more susceptible to clinical deficits from a second injury if they have a pre-existing nerve injury resulting in limited neurological reserve.[17]

In a patient with PNI, the first consideration is whether there is an ongoing process causing neurological impairment. Examples include anticoagulation or bleeding tendencies and ischaemic complications from compression due to dressings or compartment syndrome. If an ongoing insult is present, urgent imaging may be required and the cause would have to be dealt with immediately.

Appropriate work-up requires a detailed history of comorbidities, presurgical injury or deficit, surgical and anaesthetic details and the presenting postoperative symptoms. A specialist neurologist may be enlisted to guide neurophysiological tests and diagnostic imaging. However, given the rarity of these injuries, there is no consensus as to the best timing and approach for investigations. Diagnosing the aetiology of PONS is demanding, complex and labour-intensive.[9] Features of PONS resulting from different aetiologies may overlap. The differential diagnosis must include non-neuropathic causes such as local inflammation and postsurgical changes as well as central nervous system processes (cervical or lumbar spine disease).

If peripheral neuropathy is confirmed by neurophysiological tests, the differentiation between surgical versus block-related causes may be inferred based on the identity of nerves and muscles involved. Neuropathy has been defined as a new onset of sensory or motor deficit consistent with nerve/plexus distribution and one of the following:

1. Electrophysiological evidence of nerve damage
2. New neurological signs
3. New onset of neuropathic pain or paraesthesia in a nerve distribution lasting more than five days[9]

Symptoms suggestive of neuropathy may occur with normal neurophysiological tests. Lam et al.[9] described these cases as *neuropathic symptoms of undetermined aetiology*. They postulated that this may occur when there is mild neuropraxia that is below the diagnostic threshold of neurophysiological testing.

If the neurological deficits persist beyond the duration of the local anaesthetic, are within the distribution of the PNB and the symptoms are purely sensory, observation and reassurance are appropriate because most of these symptoms will resolve over days to weeks.[17] If symptoms persist, neurological consultation is appropriate. If the patient has functionally limiting deficits or difficult-to-localise neurological impairment, neurological consultation is appropriate.[17]

The role of electrodiagnostic studies (nerve conduction studies and electromyography) in the setting of PNI is to confirm the suspected neurogenic process, localise it, exclude mimickers, identify subclinical disease, confirm conduction block or focal slowing for mononeuropathies at common sites of compression and to define the degree of axonal loss (which aids in predicting expected recovery time).[17]

Neuropraxia from compression or transient dysfunction of myelin can be identified with nerve conduction studies acutely which show conduction block or focal slowing. Clinically, patients with predominantly sensory symptoms and/or evidence of neuropraxia have an excellent prognosis with expected complete recovery within three months.[17]

When there is more severe injury, it is important to differentiate between axonotmesis and neurontmesis. Peripheral nerve axons will regenerate if the neural tube is intact (axonotmesis), but not in neurontmesis. Electrodiagnostic studies cannot differentiate between these two scenarios with a single study. With axonotmesis, serial studies performed two to three-monthly will show axonal regeneration and proceeding distally with time. Electrodiagnostic evidence of axonal recovery will precede clinical motor improvement. With neurotmeses, no recovery will be seen on serial studies. These patients should be referred for surgical repair which should occur no later than six to nine months from the time of injury.[17]

The role of electrodiagnostic studies is limited in the acute perioperative period. Neuropraxia can be identified acutely, but axonal damage is only evident when Wallerian degeneration has occurred and there has been muscle denervation. This may take up to three weeks from the time of injury. Therefore, electrodiagnostic studies are more useful 14–21 days after nerve injury to localise the injury and to define its severity and prognosis. It must be remembered that electrodiagnostic tests localise a lesion but do not elucidate the cause.[17]

There is a growing recognition of inflammatory causes of postsurgical neuropathies that are unrelated to anaesthetic or surgical techniques. Typical features include severe pain hours to up to 30 days after a stressor (such as surgery) that is out of keeping with the expected. As the pain improves spontaneously, weakness becomes apparent. Usually, the weakness is multifocal or diffuse but focal postoperative neuropathies have been reported as well.[17] If an inflammatory neuropathy is suspected, biopsy of the nerve will demonstrate a lymphocyte-mediated inflammation and possibly microvasculitis.[6] Corticosteroid therapy in these cases is unproven but seems rational based on the microvasculitic pathology and is commonly practiced.[17]

Management of nerve injury

Unfortunately, once an active process has been excluded (vascular, compressive, inflammatory), there is nothing that can be done to significantly improve the neurological outcome for a postsurgical nerve injury. What can be addressed is patient education, expectations and pain. If appropriate, functional assistance can be supported by physio- and occupational therapy.

Referral to a chronic pain specialist may be appropriate if pain is present and one of the following:[17]

- Severe
- Functionally limiting
- Progressive
- Multifocal or difficult to localise
- Unexplained neurological impairment outside the block region or region of common compression
- Associated with allodynia, oedema, hyperhidrosis, uninvolved extremity
- Increasing or problematic opioid escalations

Conclusion

The literature does not provide us with overwhelming evidence for practices to mitigate PONS. However, common sense tells us as clinicians to be mindful of the indications, type of PNB and patient selection. Prior to PNB, the patient should be screened for risk factors, any pre-existing neurological deficits documented, and comprehensive informed consent should be obtained. Ultrasound should be utilised if it is available and if a motor nerve is to be blocked, peripheral nerve stimulator should be used if available. If pressure monitors are available, they should be employed; otherwise, the person injecting local anaesthetic should be aware of the pressure required. The minimum concentration and volume of local anaesthetic should be used and if a peripheral nerve is to be targeted, adrenaline should be avoided. Needling technique should be to avoid intraneural injection and to keep a respectful distance from neural tissue. PNBs should be performed in awake patients if possible. Physicians should pay meticulous attention to avoid contamination of needles with alcohol or ultrasound gel. All patients who have had PNBs should be followed up postoperatively and be given contact details should there be a problem. Fortunately, neurological injury after regional anaesthesia is rare. Most PONS consist of mild symptoms which

can be adequately managed with patient reassurance, education and scheduled follow-up to assure symptom resolution.

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