Neural blockade in the evaluation and management of chronic pain: An overview

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Local anesthetic and neurolytic nerve blocks have been used for over a century in the evaluation and management of chronic pain, despite the dearth of evidence supporting their application. This article provides a general overview of the physiology and pharmacology of nerve blocks and suggests how they may affect pathophysiological mechanisms of chronic pain. Following a discussion of the rationale, clinical application and potential complications of nerve blocks, existing evidence of efficacy is reviewed. Further research evaluating mechanisms and efficacy of nerve blocks is vital to define their role in chronic pain management.

Key Words: Autonomic nerve block; Controlled clinical trials; Local anesthetic; Neoplasm; Nerve block; Pain pathophysiology; Pain therapy; Spinal cord; Treatment outcome

The neurophysiological effects and technical aspects of local anesthetic nerve blocks are well understood and have been described extensively (1). Neural blockade is a safe and highly effective technique, and is an important modality in the management of acute postoperative pain (2). However, due to the complex nature of chronic pain and the obstacles to rigorous testing of the efficacy of nerve blocks in this setting, evidence supporting neural blockade in chronic
pain is limited. Nevertheless, percutaneous injections that block nerve conduction are commonly applied by anesthesiologists, neurosurgeons, physiatrists and dentists in the evaluation and management of chronic pain (3). This article provides a basic review of the physiology, pharmacology and fundamental clinical aspects of neural blockade for chronic pain and is intended as an introduction for readers not familiar with these techniques.

HISTORICAL PERSPECTIVE

Following the discovery of cocaine and description of its local anesthetic effects, Koller (4) reported the clinical use of cocaine as a topical anesthetic for ocular surgery in 1884. In 1899, Bier (5) described surgical anesthesia with the spinal injection of cocaine. In 1907, Schlösser (6) reported the percutaneous injection of 80% alcohol into sensory nerves to treat chronic pain in patients with trigeminal neuralgia. The introduction of these clinical techniques, together with the advent of safer local anesthetics such as procaine in 1905 and tetracaine in 1932, stimulated enthusiasm and the clinical development of neural blockade techniques, leading to more widespread use in pain management (7). However, in 1954, Vandam and Eckenhoff (8) proposed a shift in emphasis from analgesic nerve blocks to a more integrated approach aimed at understanding the fundamental nature of pain. This led to the establishment of multidisciplinary pain clinics in the 1960s (9) and a more critical outlook on the role of nerve blocks in pain management, as discussed by Bonica (10) at the first international symposium on pain in 1973. Although neural blockade continues to be used for chronic pain, evidence of efficacy is lacking, and further research is necessary to clarify its proper role in the clinic (11-13).

PHYSIOLOGY AND PHARMACOLOGY OF NEURAL BLOCKADE

Neurophysiology of pain transmission

Painful stimuli are transmitted from the periphery to the spinal cord via specialized, sensory nociceptive neurons. The cell bodies of these afferent neurons reside in the segmental dorsal root ganglia and their axons project peripherally to skin, muscle, bone and viscera, and centrally to the spinal cord dorsal horn (Figure 1). Peripheral nerve endings are structurally and functionally diverse such that they respond to thermal, mechanical or chemical noxious stimuli (14). According to the Erlanger/Gasser (15) classification, which characterizes peripheral nerve fibres according to their state of myelination, diameter and conduction velocity, nociceptive information is normally transmitted by A-delta and C fibres. Myelinated axons are surrounded by Schwann cells that are wrapped many times around the axon and provide electrical insulation. The continuity of the myelin sheath is interrupted at the nodes of Ranvier, spaced at interval lengths, where the axonal membrane is in direct contact with extracellular fluid. A-delta fibres are myelinated, small diameter (1 to 5 µm), medium velocity (12 to 30 m/s) neurons, and C fibres are unmyelinated, very small (less than 1 µm), slow velocity (0.5 to 2 m/s) neurons. Postganglionic, efferent sympathetic fibres that mediate vasoconstriction course within somatic and visceral nerves and may also play a role in certain chronic pain conditions. Adapted with permission from reference 60
blocking nerve impulse conduction
tional changes that normally mediate cell depolarization, thus 
channel. Binding to the sodium channel inhibits the conforma-
tional changes that normally mediate cell depolarization, thus blocking nerve impulse conduction.

spread of the current from node to node in a process called saltatory conduction.

Pharmacological mechanisms of local anesthetics
Through scores of sophisticated electrophysiological studies, the mechanism of action of local anesthetics was determined to be via the blockade of voltage-gated sodium ion channels in the axonal membrane (19). Clinically used local anesthetics are compounds classified as tertiary amine bases. These weak bases consist of a tertiary amine group that is linked to an aromatic group by an ester linkage (the ester local anesthetic molecule, bupivicaine, in equilibrium between its protonated charged form and basic uncharged form). The uncharged form of the local anesthetic (LA) gains easy access to the lipid bilayer and binds to the membrane side of the sodium channel. The charged form (LA+) accesses the cytoplasm from where it binds to another site on the inner aspect of the sodium channel. Binding to the sodium channel inhibits the conformational changes that normally mediate cell depolarization, thus blocking nerve impulse conduction.

neurally mediated cell depolarization and thus blocks nerve impulse conduction (19).

It has long been clinically observed that local anesthetics exert a differential block on various peripheral nerve functions. For example, the onset of an anesthetic injection generally produces a temporal progression of blockade, ie, loss of sympathetic function (eg, vasodilation) followed by loss of pin-prick sensation, light touch and temperature, and finally loss of motor function (20). This pattern of action has distinct advantages such as during epidural anesthesia for labour and delivery, where the use of bupivicaine results in effective sensory block while preserving motor function. The neurophysiological explanation for the differential block was initially thought to be related to differences in fibre thickness; however, discrepancies between laboratory and clinical studies leave this question unresolved (21).

**HOW DO NERVE BLOCKS AFFECT CHRONIC PAIN?**

Underlying processes leading to chronic pain are often unclear. In many situations, pain may be associated with long-standing changes in sensory processing by the peripheral and central nervous systems as well as psychological factors that further complicate evaluation and management. However, recently identified pathophysiological processes, particularly those following nerve injury, may be affected by neural blockade (Table 1).

**Central sensitization**

Evidence from experimental and clinical studies suggests that nociceptive transmission causes sensitization of spinal neurons, resulting in an exaggerated response to, and a decreased threshold for, subsequent noxious stimulation, and that these changes play a role in chronic pain syndromes (22). Pre-emptive analgesia, the concept that suppressing nociceptive transmission can prevent or diminish these changes, has

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Functional consequence</th>
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<tbody>
<tr>
<td>Neurora formation and/or proliferation of sodium channels at nerve injury site</td>
<td>Spontaneous shooting pains, paresthesias (increased nociceptor activity may lead to central sensitization)</td>
</tr>
<tr>
<td>Ectopic firing of nociceptors at level of dorsal root ganglion following nerve injury</td>
<td>Spontaneous shooting pains, paresthesias (increased nociceptor activity may lead to central sensitization)</td>
</tr>
<tr>
<td>Sprouting of central A-beta terminals toward dorsal horn superficial laminae following nerve injury</td>
<td>Pain evoked by light touch (allodynia)</td>
</tr>
<tr>
<td>Sympathetic fibre sprouting and increased expression of alpha-adrenergic receptors</td>
<td>Spontaneous pain, sympathetically maintained pain</td>
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**TABLE 1**

Chronic pain mechanisms potentially affected by neural blockade

Pain Res Manage Vol 5 No 1 Spring 2000
These changes may lead to perpetuation of pain by efferent expression of alpha-adrenoreceptors on injured axons (27). The nerve block. However, nerve injury may also result in ec- and prevent spinal sensitization, at least for the duration of infection proximal to the site of these changes may block the pain result in excessive and inappropriate firing of nociceptive neu-rons to cause spontaneous pain and lead to spinal sensitization (25). Neuromas are small tufts of regenerating nerve fibres that are observed to grow at the site of a nerve injury and accompany an excessive proliferation of sodium channels along the axon (26). Interrupting nerve transmission proximal to the site of these changes may block the pain and prevent spinal sensitization, at least for the duration of the nerve block. However, nerve injury may also result in ectopic firing in the cell body at the level of the dorsal root ganglion (26), in which case it would be necessary to block conduction even more proximally, for example, with a spinal or epidural block. Other pathophysiological mechanisms following nerve injury include the sprouting of sympathetic nerve fibres around nociceptor cell bodies and the new expression of alpha-adrenoreceptors on injured axons (27). These changes may lead to perpetuation of pain by efferent sympathetic activity, referred to as sympathetically maintained pain, which can be affected by blocking the conduction of sympathetic nerve fibres.

received much attention in the setting of postoperative pain (23) but also may be relevant to the concept of interrupting neural activity and perpetuating chronic pain (24). Certain changes observed following nerve injury may result in excessive and inappropriate firing of nociceptive neurons to cause spontaneous pain and lead to spinal sensitization (25). Neuromas are small tufts of regenerating nerve fibres that are observed to grow at the site of a nerve injury and accompany an excessive proliferation of sodium channels along the axon (26). Interrupting nerve transmission proximal to the site of these changes may block the pain and prevent spinal sensitization, at least for the duration of the nerve block. However, nerve injury may also result in ectopic firing in the cell body at the level of the dorsal root ganglion (26), in which case it would be necessary to block conduction even more proximally, for example, with a spinal or epidural block. Other pathophysiological mechanisms following nerve injury include the sprouting of sympathetic nerve fibres around nociceptor cell bodies and the new expression of alpha-adrenoreceptors on injured axons (27). These changes may lead to perpetuation of pain by efferent sympathetic activity, referred to as sympathetically maintained pain, which can be affected by blocking the conduction of sympathetic nerve fibres.

TABLE 2
Anatomical classification of nerve blocks in chronic pain

<table>
<thead>
<tr>
<th>Type of nerve block</th>
<th>Site of injection</th>
<th>Procedure (illustrative examples)</th>
<th>Common indication</th>
</tr>
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<tbody>
<tr>
<td>Local infiltration</td>
<td>Intramuscular</td>
<td>Trigger point injection</td>
<td>Myofascial pain syndrome</td>
</tr>
<tr>
<td>Somatic nerve*</td>
<td>Peripheral nerve</td>
<td>Ilioinguinal nerve block</td>
<td>Genitofemoral neuralgia</td>
</tr>
<tr>
<td>Somatic plexus*</td>
<td>Brachial plexus</td>
<td>Brachial plexus block</td>
<td>Upper extremity cancer pain</td>
</tr>
<tr>
<td>Visceral plexus*</td>
<td>Celiac plexus</td>
<td>Celiac plexus block</td>
<td>Pancreatic cancer pain</td>
</tr>
<tr>
<td>Sympathetic ganglion</td>
<td>Cervical sympathetic chain</td>
<td>Stellate block†</td>
<td>Complex regional pain syndrome</td>
</tr>
<tr>
<td></td>
<td>Lumbar sympathetic chain</td>
<td>Lumbar sympathetic block</td>
<td>Complex regional pain syndrome</td>
</tr>
<tr>
<td>Epidural*</td>
<td>Epidural space</td>
<td>Lumbar epidural injection</td>
<td>Chronic low back pain</td>
</tr>
<tr>
<td>Spinal*</td>
<td>Intrathecal (cerebrospinal fluid)</td>
<td>Spinal injection</td>
<td>Chronic neck pain</td>
</tr>
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*Also involves an element of sympathetic blockade; †See Figure 3

CLINICAL RATIONALE FOR NEURAL BLOCKADE

For descriptive purposes, nerve blocks can be classified according to the anatomical site of injection as local infiltrations, blocks of somatic nerve, somatic plexus, visceral plexus, sympathetic ganglion, and epidural or spinal (intrathecal) injections (28-37) (Table 2). Percutaneous needle access allows the delivery of local anesthetic or neurolytic agent solutions onto neural structures. Because sympathetic nerve fibres course within somatic and visceral nerves, somatic, visceral plexus, epidural and spinal blocks all produce an element of sympathetic blockade. Selective sympathetic blockade can be applied with injections along the cervical or lumbar sympathetic chains, or more peripherally with intra-venous injections of adrenergic antagonists such as guanethidine or bretylium using a tourniquet technique (38,39). Technical approaches to neural blockade also are used to deliver other drugs, as in the case of epidural steroid and spinal opioid injections (40-42). Reviewing the clinical rationale for nerve blocks is facilitated by classification according to intended clinical goals, ie, diagnostic, prognostic and therapeutic (43).

Anesthetic injections may be useful in localizing a particular source of pain. For example, immediate and complete relief of back pain following local anesthetic injection into a facet joint implicates that structure as the source of pain. Similarly, nerve blocks may help differentiate between somatic and visceral pain. For example, the lack of effect of somatic intercostal nerve blocks in a patient with chest pain points to a visceral rather than a somatic cause. Despite these apparently decisive examples, several limitations to the diagnostic utility of nerve blocks include the likelihood of a variable and unpredictable placebo response, communication problems, inappropriate measurement of pain intensity and relief, possibility of a ‘false positive’ result due to systemic effects of local anesthetics, and variability in the quality of the anesthetic block due to anatomical and/or technical issues (12). Evidence that casts doubt upon the utility of diagnostic nerve blocks includes the following points: (a) from Newcastle, Australia, and another from Baltimore, United States in the form of controlled clinical trials – both showing poor specificity of diagnostic nerve blocks in low back pain and sciatica (44,45).

For the patient and the clinician, diagnostic nerve blocks simulate the effects likely to follow a corresponding neurodestructive procedure and confirm the expected analgesic benefit. For example, a positive response to temporary paravertebral spinal nerve block may support the decision to perform a neurosurgical posterior rhizotomy (46). However, given the diagnostic limitations listed above and the potentially irreversible effects and complications of a neurodestructive procedure, extreme caution must be used when interpreting such responses.

Therapeutic nerve blocks with local anesthetics likely have a limited role in chronic pain management. Despite the brief duration (in the range of hours) of local anesthetic blocks, analgesic effects have often been observed to outlast the conduction block, sometimes by days or weeks (11). Rea-
**Figure 3** Stellate ganglion block. A thorough understanding of relevant anatomy is essential to performing nerve block injections such as blockade of the cervical sympathetic chain illustrated here. a Artery; m Muscle; v Jugular vein. Adapted with permission from reference 49.

**GENERAL PRINCIPLES OF NERVE BLOCK PROCEDURES**

Bonica and Butler (43) have outlined several principles of application for clinicians who perform nerve blocks to promote appropriate use and to optimize results in pain management. These principles include knowledge of pain syndromes and their applicable diagnostic measures, advantages, disadvantages and complications associated with indicated treatments; thorough evaluation of the patient’s history, physical examination and relevant laboratory studies, even when referred by respected colleagues; maintenance of technical skills and thorough knowledge of the anatomical basis of the procedure, local anesthetic pharmacology and the necessary approaches for immediate treatment of possible complications (eg, resuscitation); thorough explanation to the patient of the procedure, and its purpose (ie, diagnostic versus therapeutic) and expected results; and careful evaluation and documentation of the patient’s response to the procedure.

Nerve blocks should be performed in a monitored setting with readily available equipment for cardiopulmonary resuscitation. As well, practitioners should have a thorough knowledge of local anesthetic pharmacology and maximal safe doses for each drug. The common technique of percutaneous needle injection involves a sterile approach by cleaning the skin surrounding the injection site with an antiseptic solution and draping the area to provide a wide sterile environment. The skin and subcutaneous tissue superficial to the injection site should be anesthetized by local infiltration with dilute local anesthetic through a thin (25 to 30 gauge) needle. The patient should be warned before each step of the procedure, eg, before needle insertion, to minimize unexpected distress. The neural structure to be blocked may be localized by eliciting paresthesias with the needle, by using a nerve stimulator to elicit a motor response, or for deeper structures such as the celiac plexus, with the aid of radiographic equipment (40). As an illustrative example, Figure 3 describes the anatomical aspects of performing a nerve block of the cervical sympathetic chain, referred to as a stellate ganglion block (49).

**ADVERSE EFFECTS AND COMPLICATIONS**

Serious complications of local anesthetic nerve blocks, though rare, have been reported (40) (Table 3). The potential for such complications underscores the necessity to perform these procedures in a monitored environment with well trained personnel to respond appropriately. Also, these risks further emphasize the importance of carefully evaluating the risk-benefit profile of nerve blocks in each individual.

**TABLE 3**

<table>
<thead>
<tr>
<th>Cause</th>
<th>Complication</th>
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<tr>
<td>Needle contact with nerve</td>
<td>Nerve dysfunction, neuralgia</td>
</tr>
<tr>
<td>Unintentional intravascular</td>
<td>Systemic toxicity (confusion, seizures, may lead to cardiac arrest)</td>
</tr>
<tr>
<td>injection or excessive dose</td>
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<tr>
<td>of local anesthetic</td>
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<tr>
<td>Hypersensitivity or allergy to</td>
<td>Hypersensitivity or anaphylactic reaction</td>
</tr>
<tr>
<td>local anesthetic</td>
<td></td>
</tr>
<tr>
<td>Unintentional lung puncture</td>
<td>Pneumothorax</td>
</tr>
<tr>
<td>Leak of cerebrospinal fluid</td>
<td>Postdural puncture headache</td>
</tr>
<tr>
<td>through dural puncture</td>
<td></td>
</tr>
<tr>
<td>Very high or total spinal</td>
<td>Hypotension, respiratory arrest</td>
</tr>
<tr>
<td>anesthetic</td>
<td></td>
</tr>
<tr>
<td>Epidural abscess or hematoma</td>
<td>Spinal cord injury (may lead to paraplegia)</td>
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**PERMANENT BLOCKADE WITH NEUROYLYTIC AGENTS**

In select circumstances where diagnostic temporary blockade has proven helpful, neurolytic agents may be applied to impair or permanently destroy a nerve. Clinical agents used for neurolytic blockade include alcohols such as ethanol and phenol. Other neurodestructive procedures include radiofrequency thermocoagulation, cryoneurolysis and ionizing radiation (50,51).

Topical administration of alcohols such as 100% ethanol results in the extraction of cholesterol, phospholipids and cerebrosides from the nerve causing the coagulation of lipoproteins and mucoproteins (52), leading to a destructive process called Wallerian degeneration (53). This process
involves axonal breakdown and hydrolysis by lysosomal enzymes, coupled with a proliferation of surrounding Schwann cells and a corresponding interruption in peripheral nerve conduction. Axonal regeneration begins days to weeks after the initial insult and functional recovery depends on the degree of damage to the endoneurium.

Potentially devastating, although infrequent, complications of neurolytic injections include unwanted sympathetic, sensory or motor block due to extravasation or malplacement of the solution onto other nerves and anesthesia dolorosa, the development of intractable pain in the anesthetic area (50). Furthermore, neurolytic blockade is not permanent, and pain may return within weeks to months after the procedure. For these reasons, treatment with neurolytic blocks are generally restricted to patients with malignant pain and limited life expectancy, following a clear demonstration of benefit with a diagnostic block (54). One of the most common and useful applications of neurolytic blockade is the celiac plexus block. This procedure is used to treat visceral pain related to cancer of the pancreas (32).

EVIDENCE FOR EFFICACY OF TEMPORARY OR PERMANENT NERVE BLOCKS

Levels of evidence for health interventions include meta-analyses or systematic reviews of randomized, controlled trials (RCTs), one or more individual RCTs, case-control or cohort studies, and expert opinion based on case series, individual cases or experimental evidence (55). Neurolytic celiac plexus block (NCPB) for upper abdominal cancer pain is the neural blockade procedure, perhaps, for which the strongest evidence exists. In 1995, Eisenberg and colleagues (56) published a meta-analysis of 59 reports of NCPB. Twenty-four of these reports included the experience of at least two patients; two were prospective RCTs, one was a prospective, uncontrolled study and 21 were retrospective studies. Based on this analysis, the authors concluded that NCPB imparts long lasting benefit in 70% to 90% of patients with upper abdominal cancer and is associated with common, mild and transient adverse effects such as local pain and diarrhea. Weaker evidence supporting neurolytic lumbar sympathetic block for patients with rest pain and skin ulceration, because of peripheral vascular disease, comes in the form of a case series of 386 patients. Among these patients, relief was demonstrated completely in 49%, partially in 31% and ineffectively in 20% (57). The application of lumbar sympathetic or stellate ganglion temporary blocks in the treatment of complex regional pain syndrome appears to provide satisfactory analgesia of prolonged duration in 46% of patients, based on a review of seven studies (58) of over 500 patients altogether. However, these studies (58) used differing methods, techniques and criteria. Finally, a review of several case series and retrospective reports on the use of sympathetic nerve blocks for herpes zoster infection suggested a beneficial effect during the acute phase but was inconclusive regarding prevention of postherpetic neuralgia (47).

Methodological challenges to evaluating the efficacy of neural blockade for chronic pain syndromes include the identification of an appropriate placebo control intervention (24) and of ethical considerations for randomly assigning chronic pain patients to such a procedure. The research in this field continues and the evidence supporting efficacy of nerve blocks is currently under review by the Cochrane Pain, Palliative Care and Supportive Care Group (59).

CONCLUSIONS

Procedures that block nerve conduction have been used for over a century and are relatively safe when performed by technically experienced clinicians who are knowledgeable in the diagnosis and management of chronic pain syndromes. Well designed, carefully controlled clinical trials are necessary in order to evaluate rigorously the safety and efficacy of neural blockade for specific painful conditions.

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