



Grahame C. Sydney. *Cross*, 1976. Tempera on gesso on board 624 × 675 mm. Auckland Art Gallery Toi o Tamaki, purchased 1980.

For cancer-related pain that remains uncontrolled despite oral or transdermal options, the use of nerve blocks, spinal administration of anesthetics, and surgical interventions may be beneficial.

Interventional Treatment of Cancer Pain: The Fourth Step in the World Health Organization Analgesic Ladder?

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Background: For most patients with cancer pain, the World Health Organization's three-step analgesic ladder provides adequate management with oral or transdermal options. However, some cancer patients are not well palliated with these approaches.

Methods: The author reviews interventional options that include nerve blocks, spinal administration of local anesthetics, opioids, alpha-2 agonists, spinal cord stimulation, and surgical interventions.

Results: Numerous interventional options are readily accessible and most can be performed on an outpatient basis. They can be used as sole agents for the control of cancer pain or as useful adjuncts to supplement analgesia provided by opioids, thus decreasing opioid dose requirements and side effects.

Conclusions: Cancer-related pain can be controlled with several interventions when oral or transdermal opioids are inadequate. A risk:benefit ratio should be considered before implementing invasive analgesic methods.

Introduction

In 1986, the World Health Organization established a three-step ladder as a guideline for the treatment of cancer pain (Fig 1A).¹ This ladder has been shown to

provide adequate analgesia to 90% of cancer patients² and to more than 75% of terminally ill cancer patients.³ The ladder is an effective guide to assist physicians with selecting medications and with determining the need to move to the next level of intensity when previous options have failed. However, some problems have been identified with use of the ladder. Among those are the treatment of bone pain, where some believe that the second step is useless and progress should rapidly be made to the third step, as patient condition dictates. Perhaps the most important deficiency in the ladder is that it does not address those patients who have failed oral or transdermal options.

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Failure can include the inability to achieve adequate pain relief or the development of undesirable/intolerable side effects, such as sedation, nausea/vomiting, constipation, and confusion. In this light, serious consideration should be given to the addition of a fourth step to the ladder (Fig 1B). This fourth step is "interventional" and includes the use of nerve blocks, spinal (epidural and subarachnoid) administration of local anesthetics, opioids, alpha-2 agonists, spinal cord stimulation, and surgical interventions, as dictated by patient condition.

Pain Diagnosis

The incidence and severity of pain vary depending on the type of malignancy. For example, due to poor compliance of bone, bony pain occurs early and is intense. Other types of cancers have different incidences of pain as a major problem (Table 1).

Pain can originate from a variety of sources. It may be related to the tumor or therapy, or it may have no relation to the underlying oncologic process. Pain associated with tumors can occur secondary to nerve plexus invasion/compression (eg, superior sulcus syndrome) or intestinal obstruction. Therapeutic causes of

Table 1. — Cancer Type and Its Association With Pain

Type of Cancer	Patients With Pain (%)
Bone	85
Oral Cavity	80
Genitourinary (men/women)	75/78
Breast	52
Lung	45
Gastrointestinal	40
Lymphoma	20
Leukemia	5

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pain may include peripheral neuropathies secondary to chemotherapy (eg, vinca alkaloids) or pain syndromes secondary to operations (eg, postmastectomy pain syndrome or postthoracotomy pain syndrome). Pain may develop from other causes, such as a herniated intervertebral disc or progression of underlying osteoarthritic states. When developing a pain workup, any pain in a patient with a history of cancer should be considered a recurrence until proven otherwise after exhaustive diagnostic testing (eg, carcinoembryonic antigen, computed tomography, magnetic resonance imaging).

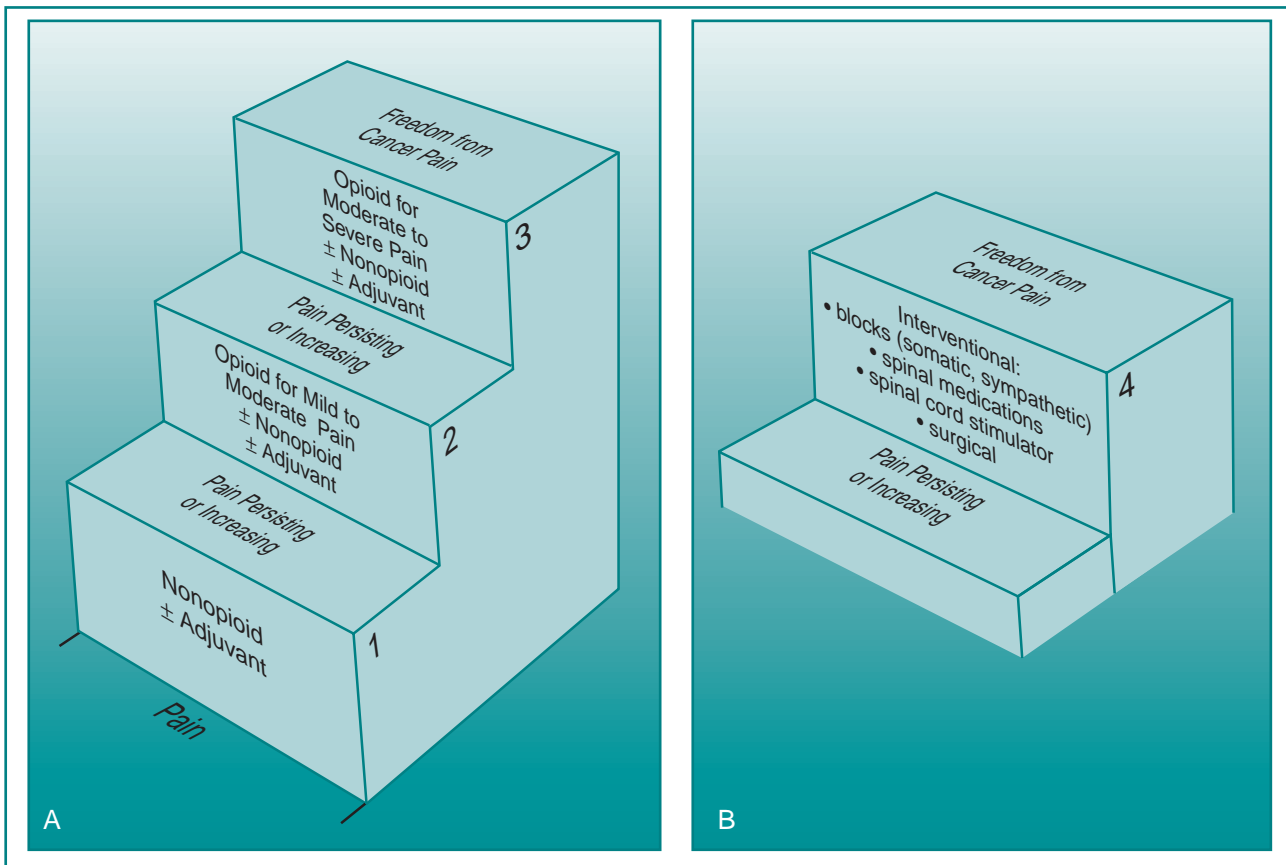


Fig 1A-B. — A. The 3-step analgesic ladder developed by the World Health Organization. Reproduced by permission of WHO. *Cancer Pain Relief*. Geneva: WHO; 1986. B. The proposed 4th step.

Table 2. — Options for Neuropathic Pain Treatment

Neuroactive oral medication
Tricyclic antidepressants (amitriptyline, nortriptyline)
Anticonvulsants (gabapentin, DPH, carbamazepine)
Oral local anesthetics (mexilitine)
Nerve blockade
Somatic or sympathetic (local anesthetics, chemical or surgical neurolysis)
Spinal cord stimulation
Alpha-2 adrenergic agonists
Subarachnoid/epidural (guanabenz, clonidine, dexmedetomidine)

The characteristics of cancer-related pain need to be identified as they can guide the selection of the most appropriate and effective therapy. Pain may be visceral, somatic, or neuropathic. Visceral pain is commonly described as a diffuse or pressure-type sensation, which is poorly localized. Somatic pain has a squeezing sharp pain nature that the patient can locate exactly. Both of these types of pain respond well to exogenous and endogenous opioids, which should be the first line of therapy. Neuropathic pain may present as a burning, tingling sensation with a lancinating component. This is the most difficult type of pain to treat, and medical therapy often fails to provide adequate relief. This is probably the primary indication for adding a fourth step to the analgesic ladder. Neuropathic pain may respond to several interventions (Table 2).

Sympathetic Blockade

The sympathetic chain exists along the vertebral column, amenable for intervention at appropriate levels for respective pain complaints (Fig 2). The sympathetic chain carries much nociceptive information, so blockade of sympathetic ganglia may improve visceral pain as well as sympathetically mediated pain. This may be considered an attractive and simple option for the diagnosis of pain and possible long-term pain relief. The cervicothoracic ganglion (fusion of the inferior cervical and superior thoracic ganglia, commonly named stellate gan-

glion) can be blocked easily by the injection of local anesthetics at the neck at the level of C6 and is useful for treating ipsilateral facial pain, postmastectomy pain syndrome, and superior sulcus syndrome, among others. Abdominal pain may be controlled by blockade of the celiac plexus, which is responsible for nociceptive information from the entire abdominal contents (with the exception of the descending colon and pelvic structures). Celiac plexus blockade has been used most commonly for the control of pain associated with pancreatic cancer but is also useful for pain originating from all upper abdominal structures. While it has been used with some success for nonmalignant pain,⁴ its most beneficial and frequent use has been in the treatment of intra-abdominal cancer pain. It is a relatively simple and safe technique with CT guidance for neurolysis and has been accessed by the anterior (utilizing CT or ultrasound, Fig 3A)⁵ or posterior approach (retrocrural or, more correctly, splanchnic nerve block, Fig 3B) or the transaortic approach. The results are amplified elsewhere in this issue.^(pp 142-148)

The lumbar sympathetic ganglion receives nociceptive information from the lower extremities and the ipsilateral pelvis. Blockade may be performed by a single injection at L2, site of the most active sympathetic ganglion. Perhaps the most significant recent develop-

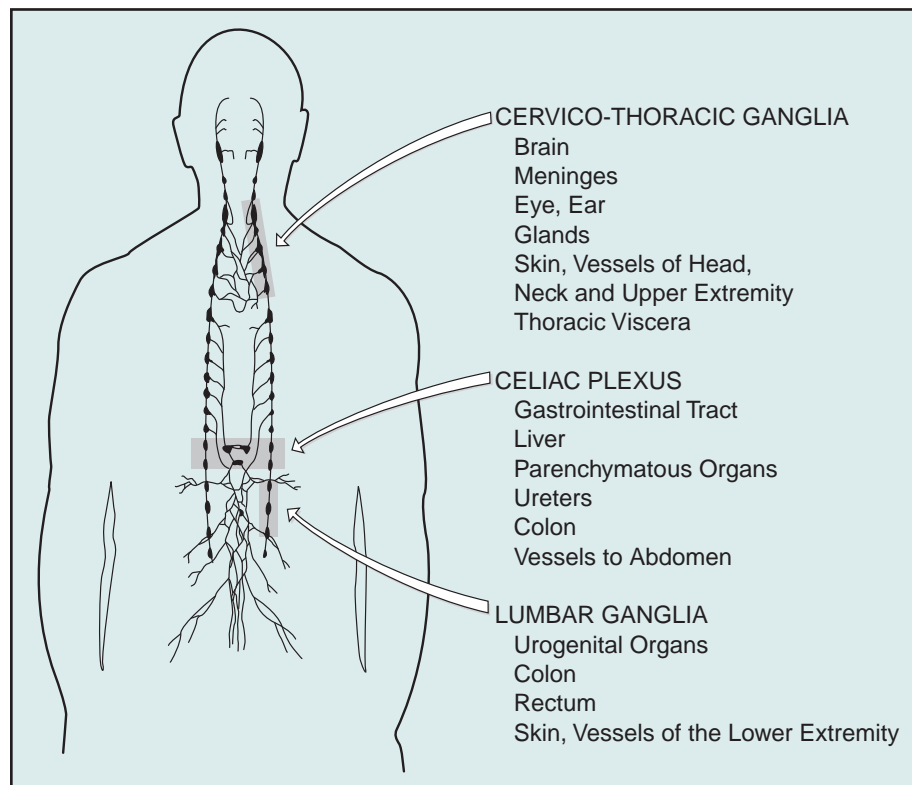


Fig 2. — Anatomy of the sympathetic chain. From Breivik H, Cousins MJ, Lofstrom JB. Sympathetic neural blockade of upper and lower extremity. In: Cousins MJ, Bridenbaugh PO, eds. *Neural Blockade in Clinical Anesthesia and Management of Pain*. 3rd ed. Philadelphia, Pa: Lippincott-Raven Publishers; 1998:413. Reprinted with permission.

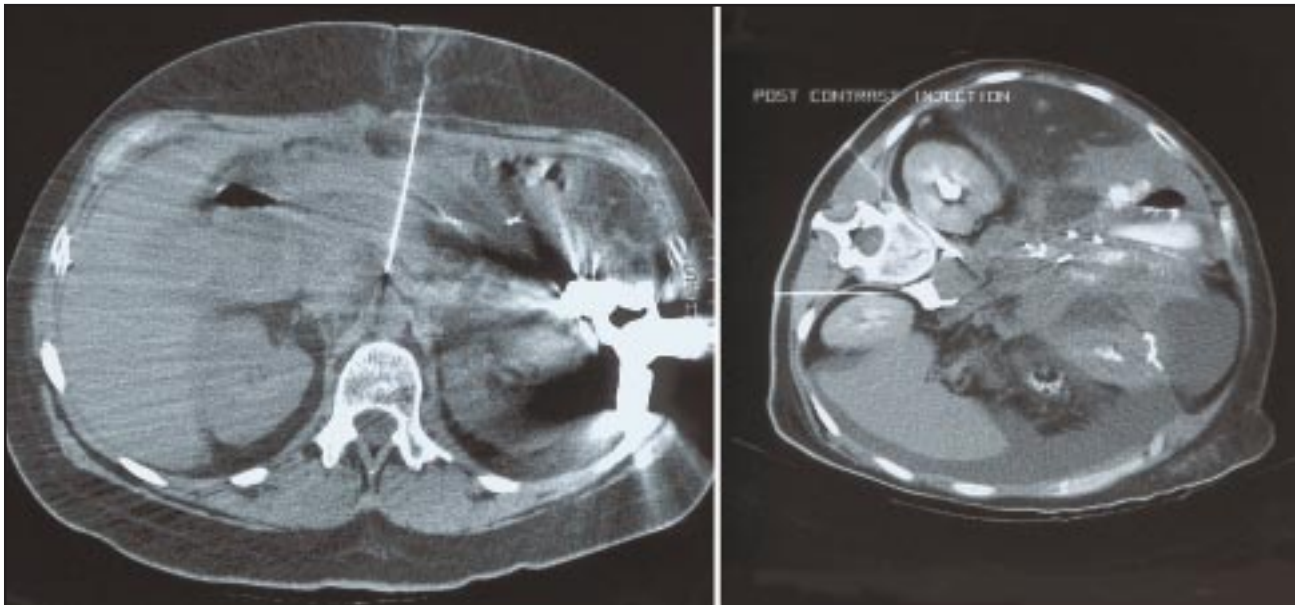


Fig 3. — CT-directed celiac plexus block using anterior approach (left image) and posterior approach (right image).

ment in the treatment of pelvic pain is the description of the superior hypogastric ganglion block by Plancarte in 1990.⁶ The superior hypogastric sympathetic ganglion transmits nociceptive information from the entire pelvis with the exception of the distal third of the Fallopian tube and ovaries. It is useful for pain of sympathetic origin from cervical cancer or for any type of pelvic pain except ovarian pain. The surgical equivalent of this block is the presacral neurectomy commonly performed by gynecologic oncologists during large pelvic resections. The inferior hypogastric ganglion is distributed over a large area of the lower pelvis and is not amenable for blockade. Walther's ganglion, the only unpaired sympathetic ganglion in the body, is located at the level of the sacrococcygeal junction. Neurolytic block has been used with some success in controlling perineal pain.

Spinal Analgesia

The knowledge that the dorsal horn of the spinal cord was richly endowed with opioid mu-receptors led Wang and colleagues⁷ in 1979 to deposit morphine in the subarachnoid space in order to control pain in cancer patients. Since then, the spinal route for opioid administration has been used to achieve effective reversible spinal analgesia with increasing popularity. The number of agents that have been deposited in the spinal canal has increased and now includes opioids, local anesthetics, spasmolytics, and alpha-2 agonists (Table 3). This trend of identifying new agents for spinal dosing is certain to continue. Evidence regarding the safety and efficacy for each drug needs to be clearly identified prior to considering spinal adminis-

tration. For the purposes of this discussion, the term "spinal" will refer to both subarachnoid and epidural routes of administration, although there are distinct differences between the two.

Medications delivered to the subarachnoid and epidural spaces behave differently. Since the subarachnoid route provides direct communication with the spinal cord, the dose of opioids required with this subarachnoid route is one tenth the dose required for epidural dosing. This dosage difference, however, does not apply to local anesthetics. Local anesthetics depend on concentration and volume for their efficacy in both areas, but the volume required to spread through sever-

Table 3. — Spinal (Subarachnoid and/or Epidural) Medications

Visceral and Somatic Pain	
Opioids:	morphine hydromorphone fentanyl sufentanil
Local anesthetics:	lidocaine bupivacaine tetracaine
Neuropathic Pain	
Local anesthetics:	lidocaine bupivacaine tetracaine
Alpha-2 agonists	clonidine dexmedetomidine*
Antispasmodics	baclofen
* Currently under study.	

al dermatomes is larger with the epidural route. With epidural dosing, direct contact with the respective dermatome is needed, while an interruption of conduction affects the dermatomes below the level of subarachnoid infusion. For example, an epidural infusion of 0.1% bupivacaine would be infused at 4 to 6 mL per hour to affect 2 to 4 dermatomes. The same area could be covered with a higher concentration of local anesthetic using a smaller volume (eg, 0.8 mL per day of 0.75% bupivacaine).

The adrenergic alpha-2 agonists comprise another class of medication that may reduce neuropathic pain when administered via the spinal canal. While originally used for blood pressure control, agents such as clonidine directly act on alpha-2 receptors, which serves to inhibit pain transmission along adrenergic pathways at the spinal cord. At least one study⁸ has demonstrated no action on visceral or somatic pain but documented efficacy treating neuropathic pain by decreasing opioid requirements and/or improving pain relief in terminal cancer patients. Side effects such as sedation and orthostatic hypotension are generally mild and short lived.

To provide chronic treatment, tunneled subcutaneous catheters are commonly connected to pumps with reservoirs. The pumps may be gas-driven or mechanically driven to access the subarachnoid space. Gas-driven pumps (eg, Arrow M-3000, Walpole, Mass) apply continuous pressure to a drug reservoir contained within a bellows system that offers a continuous flow without the option for boluses. An ingenious feature of this pump is that if a bolus is needed, a special noncoring needle with a shaft aperture may be introduced through the refill reservoir, allowing a direct bolus to be given into the catheter. This feature eliminates the need for a side port, which decreases the pump size and omits the requirement to search for a side port. The pump has a reservoir of approximately 30 mL and needs to be refilled monthly on an outpatient basis. The mechanical pump (SynchroMed, Medtronic Inc, Minneapolis, Minn) uses pacemaker technology to generate programmability. It is attractive in that it offers continuous or complex programming. For example, if a patient complains of pain at 2:00 AM that interferes with sleep, a bolus dose may be programmed to be received at midnight in order to control pain and thus improve nighttime sleep. The pump can be modified with a computer wand through the skin to reduce the risk of contamination. The pump has a reservoir of 18 mL, and the refill time varies according to the rate of infusion (eg, at a rate of 0.25 mL per day, the pump would need to be refilled every 2 months). Because of the small volume of its reservoir and the large volume required for epidural infusion, the pump is not appropriate for epidural administration.

While the use of externalized continuous subarachnoid catheters is an uncommon approach in the United States, it is popular in Europe for controlling pain of moderate to long duration (ie, weeks to months). More commonly, however, the epidural space is accessed to the exterior, especially when the duration of required analgesia is 4 months or less. These catheters may be threaded directly to the exterior (DuPen catheter, Bard Access Systems, Salt Lake City, Utah) or connected to a subcutaneous portal (Port-a-Cath, Pharmacia Deltec, St. Paul, Minn). While epidural dosing may be done intermittently, a more common approach is connecting the catheter to an external pump that may or may not be controlled by the patient and may provide the option of a patient-controlled bolus. Medications or doses can be easily changed. Varieties of different battery-operated ambulatory pumps are available that are carried in "fanny packs." The greater risk of infection in an externalized system needs to be considered when selecting one technique vs another.⁹

The decision to implant an analgesic delivery system is also affected by cost. Patients with a long life expectancy in need of spinal analgesia have traditionally been regarded as good candidates for totally implanted systems. However, discussion has focused on when the cutoff time occurs. In a nonrandomized, unblinded study, Bedder et al¹⁰ found that after 3 months, savings accrue when patients are managed with a totally implanted system compared with an externalized epidural catheter system. Others¹¹ have found that the "crossover" point of costs between a tunnelled epidural catheter and implanted subarachnoid pump and catheter occurs at 6 to 7 months. At our center, the cutoff time used is 4 to 6 months since predictions are estimates and the occasional cost savings of an implanted pump may justify the increase in time (vs 3 months).

Spinal Cord Stimulation

The use of electricity in pain control dates back to the pre-Christian era, when electric eels and torpedo fish were applied to painful areas. Benjamin Franklin also experimented with electricity as an analgesic tool. In the late 1960s, Shealy and associates¹² used dorsal cord stimulation, but the technique fell into disrepute, probably due to poor equipment (battery failure and lead fracture) and improper patient selection. The mechanism of analgesia produced by spinal cord stimulation (SCS) is still unclear. Some hypotheses involve antidromic activation of A-beta afferents ("gate control" theory), activation of central inhibitory mechanisms, increase in substance-P release, and actual block of transmission of electrochemical information anywhere

in the dorsal spinothalamic tract. Regardless of the mechanism of action, it is clear that its efficacy is limited to neuropathic pain of a variety of origins (eg, failed back surgery syndrome, arachnoiditis, reflex sympathetic dystrophy, deafferentation pain). Due to the effect of SCS on sympathetic fibers, actual improvement in flow has been documented in peripheral vascular disease, and the technique is used extensively in Europe for intractable angina.

The attractiveness of SCS lies in the potential to provide analgesia to severe neuropathic states without the need for medication. Patients control the stimulation (on/off and intensity) with a small battery-operated control. SCS has a low incidence of infection since it is not accessed except for a battery change, which may be needed every 2 to 4 years, depending on the level and frequency of stimulation.

The use of electrostimulation in patients with cancer pain is limited, but neuropathic states are amenable to therapy, and a reduction of supplemental opioids is commonly seen depending on the amount of neuropathic contribution to overall pain. Postthoracotomy pain, postherpetic neuralgia, and radicular lower extremity pain after radical pelvic tumor resection are possible candidates for SCS therapy. At our institute, SCS has been used in a patient after pelvic exenteration with severe, intractable pain due to radiation necrosis. A 40% to 60% reduction in pain was achieved, allowing a decrease in opioid consumption and an improvement in quality of life for longer than 3 years.

Neurolysis

Injections of neurolytic agents to destroy nerves and interrupt pain pathways have been used for many years.¹³⁻¹⁶ The results of such injections are essentially the same as nerve sectioning, although the effect is usually seen for only 3 to 6 months. The use of neurolysis has decreased significantly in recent years due to advances in spinal analgesia and increased life expectancies in patients with cancer. However, neurolysis is still an attractive option for pain control in many cancer patients. Neurolysis is indicated in patients with severe, intractable pain in whom less aggressive maneuvers are ineffective or intolerable because of either poor physical condition or the development of side effects. Another consideration is that the painful area has responded to diagnostic blockade with a local anesthetic. An example in which a trial injection is useful is in areas where pain is limited to a very circumscribed section, such as rib invasion/metastases treated with intercostal neurolysis. In this case, the procedure is a relatively minor

one and the benefit obtained may be significant. The duration and quality of life are significant considerations since the goal of neurolysis (analgesia) may produce undesirable side effects, including sphincter weakness and limb paralysis. In most but not all cases, these are unacceptable complications. Neurolysis rarely is permanent, and pain returns either from a regrowth of neural structures or by progression of the underlying disease beyond the treated area.

Neurolysis may be chemical, thermic, or surgical. Today, chemical neurolysis today is generally limited to alcohol or phenol.

Alcohol is popular due to its ready access using concentrations of 50% to 100%. Due to its greater incidence of dysesthesia, it may be more appropriate in blocking sympathetic nerve fibers or when life expectancy is short. The incidence of painful dysesthesias increases significantly when alcohol injections are done with myelinated nerve fibers; therefore, that practice should be avoided. Alcohol is a painful injection that spreads readily due to its low viscosity. One scenario where alcohol is commonly used and has a very favorable risk:benefit ratio is in celiac plexus neurolysis for pancreatic and upper abdominal neoplasms. The risk of paralysis is exceedingly rare (and is reversible, when using 50% alcohol). The response rates of 65% to 85%¹⁷ makes this a valuable adjunct in the management of selected patients with abdominal pain.

Phenol is commonly used in concentrations of 7% to 12%. It has a reversible local anesthetic effect at concentrations under 7%, which renders it essentially useless for long-term analgesia at those lower concentrations. It has a greater affinity for vascular tissue than does alcohol, making it a less attractive choice with major vessels in the immediate area and large amounts of neurolytic agents are being injected (eg, celiac plexus blockade). Compared with alcohol, phenol is much less painful on injection. A hospital pharmacist generally prepares it, as it is not available as a ready-to-use pharmaceutical preparation. It is highly soluble in glycerin and is commonly mixed in a glycerin preparation. The advantage of mixing with glycerin is that it diffuses slowly and infiltrates less, giving a more concentrated area of coverage and thus decreasing spread to unintended areas. Phenol has been prepared in sterile water, normal saline, diatrizoate meglumine (Renografin), and metrizamide to guide its spread fluoroscopically during injection. All aqueous phenol solutions appear to be far more potent than those prepared in glycerin. Since phenol is hyperbaric, it will settle if injected into a liquid medium such as the cerebrospinal fluid-containing subarachnoid space. Positioning is critical in this regard. The patient needs to

be placed face up, affected side down at a 45° angle so that the neurolytic medication settles near the posterior sensory rootlets. Since alcohol is hypobaric with respect to cerebrospinal fluid, the patient is placed in the opposite position (ie, face down, affected side up at a 45° angle).

The use of neurolytic agents for peripheral nerve neurolysis has great potential for benefit. In the case of rib metastases, it is a simple procedure to inject 2 mL of 7% to 10% phenol at three to four levels to control pain. Similarly, in pelvic/perineal recurrences, injection of sacral nerves is a relatively simple procedure that can be used for perineal pain after abdominal perineal resection (S4-S5) or pain emanating from rectal cancer (S4).

Thermal Neurolysis

Cryoanalgesia using the Joule-Thompson effect of expansion of compressed gases produces temperatures lower than -75° C. It is safe, with no capacity to produce painful postprocedural dysesthesias due to preservation of the neurolemma, which provides scaffolding for regenerating nerves. However, it must be in direct contact with the nerve to be frozen as the ice ball that forms needs to encompass the entire nerve. Another drawback with this technique is that its benefit is commonly short lived.

Radiofrequency lesioning has achieved popularity by producing a very exact and circumscribed heat nerve lesion percutaneously. It has been used in lesions of the facet joints, lumbar sympathetics, and peripheral nerves. While heat was thought to be the primary method of nerve lesioning with radiofrequency, some have postulated that the electromagnetic field that is produced may be the determining factor in production of the lesion. The importance of the electromagnetic field is emphasized by the fact that pulsed radiofrequency fields (allowing for revascularization and temperature equilibration) that produce no conventional RF lesion with no potential for neuritis or damage to surrounding structures are being evaluated.

Surgical Analgesic Techniques

Despite use of all the aforementioned techniques for interventional pain management, pain may persist. Some patients may be candidates for neurosurgical analgesic techniques. The most important factor is proper patient selection. In older, more debilitated patients, chemical neurolysis or a pump with spinal catheter insertion may be more appropriate. The pain must be refractory to other more commonly used pain

relief methods. Neuroablative surgical analgesic procedures are often accompanied with significant morbidity (eg, paralysis, paresthesias, urinary dysfunction, sleep apnea) and mortality. Percutaneous chordotomy is associated with a lower incidence of the same complications, especially when the anterior low-cervical approach is used as opposed to the more traditional lateral high-cervical approach.¹⁸ Chordotomy is appropriate for unilateral pain below C5 of the lateral chest/abdomen, lumbosacral plexus, pelvis, or lower extremities. Rhizotomies for unilateral and bilateral pain distal to the intervertebral foramina or commissurotomies for bilateral pain have also been used. Pain of cervical, facial, or brachial origin may respond to stereotactic neuroablative procedures such as cingulotomy, medullary tractotomy, and lesioning of various thalamic targets. These techniques are used less frequently due to other improvements in analgesic therapy. Also, despite the relatively high risk and interventional nature, pain returns in 40% of patients within 1 year.¹⁹ However, certain situations merit some limited surgical considerations, such as the use of percutaneous vertebroplasty with injection of methylmethacrylate to stabilize vertebra weakened by metastatic disease.

Conclusions

Cancer pain is amenable to various types of analgesic interventions. While oral or transdermal opioids play the dominant role in controlling pain in cancer patients, other options are available. While increasing opioid doses may provide analgesia in most patients, higher doses of opioids are often accompanied with undesirable side effects. The search for effective analgesia should include consideration of interventional techniques. Numerous interventional options are readily accessible and most can be performed on an outpatient basis. They can be used as sole agents for the control of cancer pain or as useful adjuncts to supplement analgesia provided by opioids while decreasing opioid dose requirements and side effects.

A risk:benefit ratio should be considered prior to implementing invasive analgesic methods. Further research is needed to more accurately identify the situations where interventional pain therapy is justified.

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