Review Article

The Role of Interventional Therapies in Cancer Pain Management

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Abstract

Cancer pain is complex and multifactorial. Most cancer pain can be effectively controlled using analgesics in accordance to the WHO analgesic ladder. However, in a small but significant percentage of cancer patients, systemic analgesics fail to provide adequate control of cancer pain. These cancer patients can also suffer from intolerable adverse effects of drug therapy or intractable cancer pain in advance disease. Though the prognosis of these cancer patients is often very limited, the pain relief, reduced medical costs and improvement in function and quality of life from a wide variety of available interventional procedures is extremely invaluable. These interventions can be used as sole agents or as useful adjuncts to supplement analgesics. This review will discuss interventional procedures such as epidural and intrathecal drug infusions, intrathecal neurolysis, sympathetic nervous system blockade, nerve blocks, vertebroplasty and the more invasive neurosurgical procedures. Intrathecal medications including opioids, local anaesthetics, clonidine, and ziconotide will also be discussed.

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Introduction

Pain is one of the most common symptoms experienced by cancer patients around the world at some point during the course of their illness.[1] Prevalence can range from 40%[2] to as high as 90% with advanced disease.[3] Most of these patients suffer from pain at multiple areas.[4] Pain can be due to cancer at the primary site, from areas of metastases, its treatment, or to another condition.[5]

The greatest fear among these cancer patients and their families is unrelieved pain. When inadequately controlled, the impact of pain can be profound. The aim is to enhance the quality of life and not hasten or delay death. The relief of distressing symptoms may well have a positive impact on the course of the illness.

Cancer patients can present with different types of pain, ranging from somatic to visceral to neuropathic. The pain can be well managed in 80% to 90% of cancer patients with the use of conventional analgesics and adjuvants according to the principles of the World Health Organization (WHO) analgesic ladder for cancer pain relief (Fig. 1).[6-8] Other non-pharmacological treatments for cancer pain will include TENS (transcutaneous electrical nerve stimulation), physiotherapy, acupuncture and psychological techniques such as cognitive behavioural therapy and relaxation therapy.[9]

The remaining 10% to 20% of cancer patients with unrelieved cancer pain may benefit from some form of interventional strategies for pain management.[10,11] This can be considered as Step 4 of the analgesic ladder (Fig. 1).[12,13] It is now recognised that individual cancer patient's responses to different opioids vary greatly and it is important to identify the drug that yield the most favourable balance between analgesia and side effects.[5] The WHO analgesic ladder focuses on the presence or absence of pain relief, and does not take into account the intolerable side effects of opioids. Patients with well-controlled pain and intolerable side effects may likewise benefit from an early interventional pain technique. Interventional strategies may range from simple nerve blocks to more invasive techniques such as regional or neurolytic blocks, or even neurosurgical procedures. The choice to perform an interventional procedure is, therefore, an individualised decision as the risks and benefits may differ for each patient.

Patient Assessment and Selection

Effective interventional management of cancer pain depends greatly on proper patient assessment and selection. A survey among oncologists found that 76% felt that poor assessment of pain was the major barrier to good pain management.[10] The physician should perform a comprehensive assessment by obtaining the current medical

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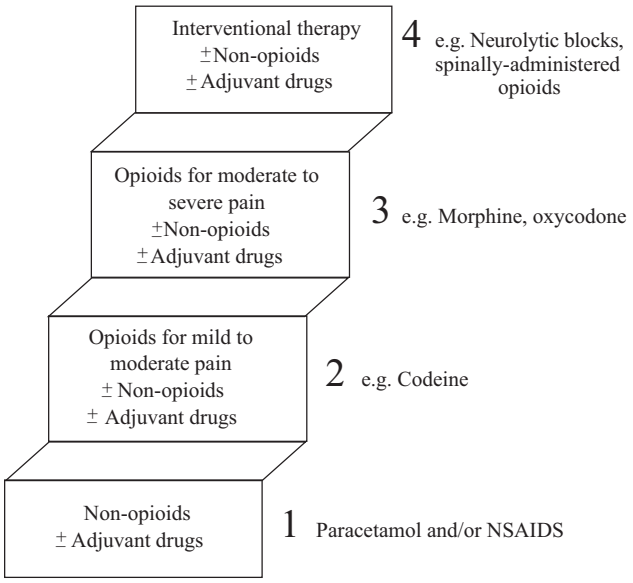

Fig. 1. Adapted from the World Health Organisation's Analgesic Ladder.

history and previous pain management history. Special attention should focus on details that characterise the pain, such as temporal features (onset, pattern and course), location (primary sites and patterns of radiation), severity (usually measured with a Categorical Rating Scale, e.g. mild, moderate, or severe; or a 0-10 Numeric Rating Scale), nature (somatic, visceral or neuropathic) and factors that exacerbate or relieve the pain. These information, when combined with findings from physical examination and review of laboratory and imaging studies, will enable the physician to define a pain syndrome and to plan for appropriate interventions based on the pain pathophysiology.[5,14]

Our understanding of the mechanism of pain has improved considerably over the past few years. The pain pathways are linked directly to and modified by both the midbrain and cortical pathways (anxiety, fear, anger, depression, sleeplessness).[9] Therefore it is essential to assess the emotional, social and psychological status of the cancer patient prior to the intervention as they may directly or indirectly affect the outcome.[15]

The expectations of the patient must be ascertained. In a qualitative study by Jacqueline et al[16] on what patients with cancer wanted to know about pain, some of the common themes identified included understanding cancer pain, describing pain, knowing what to expect, options for pain control and coping with cancer pain. Hence, it is important for the pain physician to determine whether the patient's expectations and what the procedure can achieve are congruent through a well-communicated consultation. If a patient insists on unrealistic treatment end-points, the physician should clarify and attempt to understand the patient's expectations prior to an interventional procedure.

Choice of Technique

The life expectancy of the cancer patient is an important consideration for selection of an appropriate interventional technique. Some techniques may provide analgesia for several days to a few weeks. Others, such as neurolytic blocks, may provide analgesia for a few months while some, like the implantable drug delivery devices, may provide good pain relief for several years. Implantable devices are therefore more appropriate in patients with a life expectancy of at least 1 to 2 years.

The benefits together with the immediate and long-term risks of any planned procedure must be thoroughly explained to the patient. The procedure most likely to be effective should be selected. If there is more than one choice, select the one with the fewest and least serious adverse effects but, at the same time, bears an acceptable probability of achieving the desired pain control.[17]

Regional analgesic techniques, such as neuraxial opioid and local anaesthetic administration, are usually considered first because they do not compromise neurological integrity. Ablative or neurodestructive procedures, which have a narrow risk-benefit ratio, should be deferred as long as pain relief can be achieved with non-ablative modalities. However, some procedures, such as celiac plexus blockade in pancreatic cancer patients, may have a favourable risk-benefit ratio that warrant early treatment with neurolysis.[18] A diagnostic block using a local anaesthetic agent should be used to assess the efficacy of the intended neurolytic procedure prior to the actual procedure. This block is also useful to evaluate the impact of the possible neurological deficits that can result from the ablation. The advantages of neurolytic techniques include fewer follow-ups compared to regional analgesic techniques using continuous neuraxial drug delivery and greater cost-effectiveness for patients with short life expectancy. On the other hand, neurolysis may result in complications such as permanent motor loss, paraesthesia, and dysaesthesia.[14]

Other factors that can influence the choice of technique are patient's expectation and availability of local expertise and trained staff. An appropriately chosen procedure can reduce the requirement for systemic opioid and improve the quality of life.

Central Neuraxial Block

With the identification of opioid receptors in the spinal cord in 1973,[19] delivery of drugs by the epidural[20] or intrathecal[21] route for analgesia have been used. Intrathecal opioids exert their analgesic effect by reducing the release of neurotransmitter presynaptically and inhibit pain transmission by hyperpolarising the membranes of postsynaptic neurons in the dorsal horn.

Continuous neuraxial drug delivery can be achieved using

a percutaneous epidural or intrathecal catheter. The drug can be delivered using an external syringe pump or a totally implanted intrathecal drug delivery (ITDD) system. The European Association of Palliative Care recommends the principal indication for ITDD in cancer patients is the failure of conventional analgesics to achieve satisfactory analgesia despite escalating doses of strong opioids, and/or patients experiencing severe dose limiting side effects.[22] A Cochrane systematic review supports the use of intrathecal opioid therapy for pain that has not been adequately controlled by systemic treatment.[23] Drugs are infused in minute and precise amounts intrathecally and therefore avoid systemic toxicity and side effects.

In a randomised controlled trial, ITDD was associated with improved quality of life, reduced pain scores and increased survival at 6 months (53% of patients in the ITDD arm were still alive compared to 32% of patients in the conventional medical management arm).[24] However, the increased patient survival is not a primary study end point and further work has to be done to confirm or refute this hypothesis.[24]

Although there are no rules to dictate when to choose an epidural over the intrathecal route or vice-versa, it is important to be aware of the advantages and disadvantages of each before making a decision.[25] Important factors such as life expectancy and caregiver support need to be considered. It is also vital to educate family members involved in the care of patients receiving continuous neuraxial drug infusions.[26]

Epidural Infusion Analgesia

Historically, continuous neuraxial drug delivery in patients with cancer pain via the epidural route was very common. The use of epidural analgesia in this group of patients is different from that in the acute pain setting such as postoperative pain or labour pain. Cancer patients often have abnormal coagulation profile and a degree of compromised immune function, putting them at risk of haematoma and infection and hence a near absolute contraindication to epidural catheter placement normally. However, after careful consideration, weighing of risks and discussion with the patient and family, the potential benefits such as reduced pain, decreased opioid requirements with reduced side effects, leading to improvement in quality of life during the limited life expectancy is invaluable.

The principal drug used is an opioid but combining it with a local anaesthetic agent will improve efficacy.[27] Other adjuvants such as clonidine can be added to further improved the efficacy.[28] The normal starting dose of an opioid for epidural infusion can be estimated by calculating the total (oral or parenteral) opioid dose taken by the patient. This has to include the doses for breakthrough pain. It is then converted to the equivalent epidural dose of morphine. Most practitioners use a 10:1 parenteral-to-epidural morphine dose conversion.[29] During the titration of the epidural opioid dose, small doses of a short-acting opioid can be given for breakthrough pain. Using this method, the side effects seen with high doses of oral or parenteral opioids can be avoided while achieving significantly better analgesia. As the volume of infusion and drug doses given epidurally are much more than the intrathecal route, an external syringe pump has to be used because the reservoir capacity of an implanted pump is limited. Pump refilling may increase the risk of infection and it is therefore important to monitor for signs of infection frequently.

In a patient with refractory cancer pain who has a life expectancy of more than 3 to 6 months, epidural analgesia can be use as a trial to assess the effectiveness of pain relief before placement of a permanent implantable ITDD system. Epidural analgesia can be used for considerable periods of time (up to many months with silastic catheters). With good community support and caregiver education, patients with epidural catheters are well enough to go home with the infusion. Accidental removal or dislodgement of the catheter is not an emergency. The pain can be treated with opioids via the conventional route while arranging for the catheter to be reinserted at a convenient time.

Intrathecal Analgesia with ITDD System

There are studies demonstrating improved pain control and fewer complications with the use of intrathecal route for delivery of drugs.[30,31] Intrathecal medications can be administered via an implanted catheter from a drug pump that can either be external or internal (implanted). Intrathecal infusion uses a lower dose and volume compared to an epidural infusion. Most physicians use a 10:1 epidural-to-intrathecal morphine dose conversion. Therefore there is a longer interval between pump refills when using a fully internalised pump system.

Introducing foreign material into the body implies a risk of infection, especially with the external pump system, as there is a connection between the skin and the central nervous system. An entirely implanted ITDD system, therefore, may offer the advantage of a lower infection risk. However, similar infection rates have been reported with intrathecal or epidural administration with antibiotic prophylaxis[32] but there is evidence that intrathecal catheters are safer when they need to be in use for more than 3 weeks.[33,34] If the life expectancy is short (i.e. several days to weeks), the use of external pumps and epidural catheters may be more appropriate. After the placement of the implanted ITDD pump, there must be adequate arrangement for continuing care (pump program changes and refill sessions). The refill interval is also affected by the stability of the selected drug admixtures.[35]

The complications of intrathecal therapy can be broadly classified into catheter-related, pump-related, drug-related and those related to the procedure of catheter insertion itself. Catheter-related complications include wound infection, meningitis, micro-fracture/breakage, malposition, migration, hygroma, blockage from fibrosis and intrathecal catheter tip granulomas causing neurological deficits.[36] Pump-related problems resulting in failure include unexpected battery depletion, motor or component failure and program error. There is a risk of postdural puncture headache[37] due to cerebrospinal fluid leak during catheter placement, haematoma formation and injuries to surrounding structures. Local anaesthetic infusion can cause neurotoxicity and permanent neurological damage.[38]

Intrathecal catheter tip granuloma formation is a serious complication that has the potential risk of causing spinal cord compression and paralysis distal to the mass. Over 100 cases have been reported since the first case in 1991.[39] The incidence seems to be related to the morphine concentration (>25 mg/mL), daily dose (>10 mg/day) and the duration of therapy. However, a review by Yaksh et al[40] noted that 39% of the cases have occurred with morphine concentration less than 25 mg/mL and 30% received daily morphine doses of less than 10 mg/day. Some cases were noted within one month of therapy. Symptoms include low back pain, motor or sensory deficits in the lower extremities and loss of bladder and bowel function. Magnetic resonance imaging (MRI) remains the diagnostic method of choice for most patients but routine imaging to identify cases is not warranted given the low incidence.[41]

The analgesic failure rates can be high in cancer patients. Those who report failure or poor outcome with the central neuraxial drug delivery usually have epidural metastases or spinal stenosis.[42]

There have been a variety of economic studies on intrathecal pumps ranging from cost modelling[43] to cost utility analyses.[44] Intrathecal infusion analgesia is found to be more cost-effective than systemic medication beyond 3 to 6 months for cancer pain and beyond 11 to 22 months for non-cancer pain. Cost analysis by Bedder et al[45] suggests that an external pump system should be used if patient's survival is expected to be less than 3 months, and an intrathecal catheter with an internalised pump should be used for patients with longer life expectancy.

Drugs Administered Intrathecally

(i) Opioids

Morphine remains the current gold standard for intrathecal administration and it is the only opioid approved by the US FDA for intrathecal delivery to treat chronic pain.

A multicentre, prospective, open-label clinical study involving 199 cancer pain patients who had either refractory cancer pain or uncontrollable side effects from opioid therapy was conducted to evaluate an implanted patient-activated intrathecal morphine delivery device.[46] It showed that the pain score decreased from a mean of 6.1 to 4.2 at 1 month (31% decrease) and remained decreased through 13 months (P <0.05). There was also a statistically significant reduction in drug toxicity and oral opioid requirements.

Numerous adverse effects of intrathecal morphine have been reported with fatigue, lethargy and sweating being most common and persistent.[47] Others include pruritus, nausea, vomiting, urinary retention, constipation, oedema, weight gain, loss of appetite, dry mouth, myoclonic jerks/spasms, headaches, sleep disturbances (e.g. insomnia) and sexual disturbances (e.g. loss of libido).[47] Patients receiving intrathecal morphine are mostly opioid-tolerant and therefore early development of respiratory depression is not common.[48] The long-term drug-related side effects reported were respiratory depression, oedema, hyperalgesia and catheter tip inflammatory mass formation.[49]

Hydromorphone, a semisynthetic hydrogenated ketone of morphine, is about 5 times more potent than morphine. It acts faster than morphine due to its greater lipid solubility. It may be used when there is intolerance to intrathecal morphine. The side effect profile of hydromorphone is equivalent to or better than that of morphine.[50] High-dose intrathecal hydromorphone may also lead to granuloma formation.[51] The Polyanalgesic Consensus Conference 2007 on the management of pain by intrathecal (intraspinal) drug delivery recommends the use of morphine as first line for intrathecal analgesia and hydromorphone as an alternative first-line opioid to morphine.[52] (Table 1)

(ii) Local anaesthetics

Intrathecal local anaesthetics exert their effect by blocking sodium channels and inhibiting the action potential in neural tissue in the dorsal horn, hence producing a reversible analgesic effect. They also have an action on the intrathecal part of the nerve root.

Intrathecal bupivacaine is usually used in combination with morphine to provide better pain control for patients suffering from neuropathic pain. There is evidence that bupivacaine acts synergistically with morphine, reducing the need for increases in intrathecal morphine dose.[53,54] However, a multicenter, double-blind randomised study found that the addition of bupivacaine (up to 8 mg/day) did not provide better pain relief than opioids alone.[55]

Intrathecal local anaesthetics can cause sensory deficits, motor impairment, autonomic dysfunction and neurotoxicity. This is less of a problem if continuous infusions rather than boluses are used. Clinically relevant side effects are usually not seen at bupivaciane doses of less than 15 mg per day. However, at higher doses, urinary retention, weakness,

fatigue, somnolence and paraesthesia have been observed.

(iii) Alpha-2 adrenoceptor agonist

Clonidine is an alpha-2 adrenoceptor agonist that has long been in use for spinal administration in Europe but has only acquired the US FDA approval in 1996 for intrathecal use. Intrathecal clonidine is known to have centrally mediated non-opiate anti-nociceptive properties. It binds to alpha-2 receptors on the presynaptic membrane of small primary afferent neurons in the spinal cord, resulting in hyperpolarisation and diminished release of neurotransmitters involved in relaying pain signals. They also activate spinal cholinergic neurons, which may potentiate their analgesic effects.

Clonidine has been shown to be effective in the treatment of cancer pain. It is used in combination with morphine and/or bupivacaine. It acts synergistically with opioids and has been shown to be effective in patients with cancer pain.[28,56,57]

The adverse effects which may be associated with clonidine include nausea, dizziness, confusion, sedation (likely via alpha-2-adrenergic actions in the locus coeruleus), orthostatic hypotension, bradycardia and dry mouth. Depression, insomnia and night terrors have been reported to develop in association with intraspinal clonidine.[58] Rebound hypertension has been observed after abrupt discontinuation of intraspinal clonidine.[59]

(iv) Ziconotide

Ziconotide (formerly SNX-111) is the synthetic equivalent of ω-conopeptide present in the venom of *Conus magus*, a marine snail.[60] Ziconotide is a highly selective reversible blocker of N-type voltage-sensitive calcium channels and produces potent anti-nociceptive effects by blocking neurotransmission from primary nociceptive afferents.[61] It does not affect the peripheral calcium channels of the neuromuscular junction. It is approved by the US FDA for long-term intrathecal use.

Staats et al[61] performed a double-blind, placebo-controlled, randomised trial at 32 study centres in the United States, Australia and the Netherlands to assess the safety and efficacy of intrathecal ziconotide in patients with cancer or AIDS who have refractory pain. Intrathecal ziconotide can be initiated at 2.4 mcg/day and titrated according to analgesic response and adverse effects. Increments should be ≤2.4 mcg/day up to a maximum dose of 21.6 mcg/day. The minimal interval between dose increases is 24 hours. For safety reasons, the recommended interval is 48 hours or more.[62] The expert panel at the Polyanalgesic Consensus Conference 2007 has also added ziconotide as a first-line agent in the algorithm for nociceptive, mixed and neuropathic pain and recommends a lower dosage at 0.5 mcg/day with 0.5 mcg increments every week for titration[52] (Table 1).

Side effects with ziconotide use include dizziness, nausea, nystagmus, gait imbalance, confusion and urine retention. Serious but rare side effects are psychosis, suicide and rhabdomyolysis. Mixture of ziconotide with other intrathecal medications like morphine, hydromorphone, clonidine and bupivacaine can also result in the reduction in ziconotide concentration within a few weeks.[63,64]

Intrathecal Neurolysis

Intrathecal neurolysis plays an important role in the management of cancer pain. It involves the administration of neurolytic agents into the subarachnoid space. The goal is to achieve segmental block that is purely sensory, without causing any motor weakness in the patient. Commonly used chemical agents for neurolysis include alcohol of concentrations of 50% to 100% and phenol 7% to 12%. Alcohol is hypobaric and therefore, the patient needs to be placed in a semi-prone position (face down and affected side up at 45 degrees angle). This will allow alcohol to

Table 1. 2007 Polyanalgesic Algorithm for Intrathecal Therapies

Line 1	morphine	↔	hydromorphone	↔	ziconotide
Line 2	fentanyl	↔	morphine/hydromorphone + ziconotide	↔	morphine/hydromorphone + bupivacaine/clonidine
Line 3	clonidine	↔	morphine/hydromorphone/fentanyl + bupivacaine + clonidine + ziconotide		
Line 4	sufentanil	↔	sufentanil + bupivacaine + clonidine + ziconotide		
Line 5	ropivacaine, buprenorphine, midazolam, meperidine, ketorolac				
Line 6	gabapentin, octreotide, conopeptide, neostigmine, adenosine, experimental drugs (XEN2174, AM336, XEN, ZGX160)				

Adapted from Deer et al[52]

settle near the dorsal root ganglia and produce a sensory blockade when it is injected into the intrathecal space. Since phenol is hyperbaric, the patient needs to be placed in the opposite position (i.e., face up with the affected side down at 45 degrees angle).

Potential problems related to intrathecal neurolysis include inadequate pain control with the progression of tumour size, short duration of effect, weakness of lower limb muscles, and rectal or bladder sphincter dysfunction.[65] It is also important for the patient and family to understand that this procedure is meant to decrease the pain and reduce the need for analgesics and may not completely eliminate the pain.

Candidates for intrathecal neurolysis should include those who have short life expectancy (less than 1 year) with intractable, well-localised cancer pain. The best results are obtained when intrathecal neurolysis is used for somatic pain. A landmark paper by Gerbershagen[66] which reviewed 1908 cancer patients who had undergone intrathecal neurolysis showed that 78% to 84% of patients with somatic pain had favourable response to the treatment. In contrast, good pain control was seen only in 19% to 24% of patients with visceral pain.

Sympathetic Blocks

There are several sites for sympathetic blockade that can be employed to treat cancer pain arising from the visceral organs. The sympathetic chain at the appropriate level can also be targeted and blocked for specific pain complaints. Neurolysis is performed in almost all of the sympathetic blocks as catheter placement is difficult and can be impractical.

The coeliac plexus can be targeted for pain arising from upper abdominal cancers. The superior hypogastric plexus can be blocked for cancer pain from pelvic organs such as ovaries, bladder and prostate. The ganglion impar block is effective for anal or vaginal cancer pain.

Coeliac Plexus Block

The coeliac plexus is situated retroperitoneally in the upper abdomen. It is at the level of the T12 and L1 vertebral bodies, anterior to the crura of the diaphragm. The coeliac plexus surrounds the abdominal aorta and the coeliac and superior mesenteric arteries. The autonomic nerves supplying the liver, pancreas, gallbladder, stomach, spleen, kidneys, intestines and adrenal glands arise from the coeliac plexus.

The efficacy of coeliac plexus neurolysis in the management of abdominal cancer pain has been evaluated in multiple trials.[67-70] A meta-analysis by Eisenberg et al[71] concluded that coeliac plexus blocks provide long-lasting relief for 70% to 90% of patients with pancreatic and other upper abdominal cancers.

Complications include postural hypotension, diarrhoea, pneumothorax, retroperitoneal haematoma and paraplegia due to an acute ischaemic myelopathy (probable involvement of the artery of Adamkievicz).[72,73] The spreading of neurolytic solution posteriorly can sometimes affect the lower thoracic and lumbar somatic nerves, which can potentially result in a neuropathic pain syndrome.[70]

Superior Hypogastric Plexus Block

The superior hypogastric plexus is a retroperitoneal structure that extends bilaterally from the lower third of the L5 vertebral body to the upper third of S1. The block is effective for pain arising from the distal colon and rectum as well as pain from pelvic structures.[74,75]

Several studies have demonstrated the efficacy of neurolytic blocks of the superior hypogastric plexus for the treatment of cancer-related pelvic pain[76-78] as well as reduced opioid use.[78]

Ganglion Impar Block

The ganglion impar, also known as the ganglion of Walther, is a solitary retroperitoneal structure located at the level of the sacrococcygeal junction with a variable position in precoccygeal space. This unpaired ganglion marks the end of the 2 sympathetic chains.[75] Visceral pain in the perineal area associated with malignancies may be effectively treated with neurolysis of the ganglion impar.

Since the first description of technique in 1990, many other approaches to the ganglion impar have been described in the literature,[79-81] including the use of computed tomographic (CT) guidance[82] and ultrasonography.[83]

Peripheral Nerve Blocks

Peripheral nerve blocks or plexus blocks are useful when cancer pain occurs in the territory of one or more peripheral nerves. The role of peripheral nerve blocks as a sole or main modality for pain relief in cancer patients may be limited, as most of these patients experience pain at multiple sites, especially with advanced disease. However, when employed in combination with other concurrent therapy such as chemotherapy and radiation, it allows the relief of one component of a patient's overall pain state.

Neurolytic agents such as alcohol or phenol are traditionally used for peripheral nerve blocks. Alcohol can produce painful dysaesthesia when injected around myelinated nerves. Phenol is much less painful on injection and is a better option for peripheral nerve neurolysis. Other modes of neurodestruction include radiofrequency ablation and cryoablation.

In recent years, there is more interest in the use of local anaesthetic infusions to block peripheral nerves, aided by advances in infusion pump and catheter technology. The use of nerve stimulation or ultrasonography to aid nerve

identification and catheter placement has made nerve blocks easier to perform while achieving better analgesic outcome.

The pain physician can face many challenges when performing peripheral nerve blocks in cancer patients. The presence of overt tissue oedema in advanced malignancy can make landmarks such as bony prominence and peripheral pulses difficult or impossible to identify. The neuroanatomy can be distorted by tumour invasion or compression and from tissue scarring and contractures due to radiation therapy. These can be overcome by performing the block and catheter placement using real-time visualisation with ultrasound guidance.

The peripheral nerve blocks that have been reported include femoral nerve block,[84] sciatic nerve block,[85] brachial plexus block,[86] suprascapular block,[87] psoas compartment block,[88] distal lumbar plexus block,[89] paravertebral block[90] and interpleural blocks.

Interpleural blockade have been used in management of cancer pain due to metastatic bronchogenic carcinoma involving the pleura and chest wall,[91] chronic pain in patients with terminal pancreatic, renal cell, breast cancers and lymphomas.[92] There are description of multiple techniques which have been reviewed extensively by Dravid and Paul.[93]

Other Procedures for Pain Control

Some patients with intractable cancer pain may require more invasive neurosurgical procedures to interrupt pain pathways. These include cordotomy, mesencephalotomy and cingulotomy.[94]

Cordotomy (cutting the spinothalamic tract either through a laminectomy or percutaneously) had been used for treatment of pain in patients with terminal malignancy. The benefits are immediate and extend to both nociceptive and neuropathic pain components but the effects rarely last more than 2 years.[94] Bilateral cordotomy is required for abdominal, pelvic or bilateral extremity pain and if done above C5 vertebra, it carries a risk of respiratory depression. Other complications include urinary retention, hemiparesis, and unmasking of contralateral pain.[95]

Good results have been reported with using mesencephalotomy for malignant head and neck pain that is too high for cordotomy or intraspinal drug delivery.[94] Cingulotomy can be helpful if the affective component of the cancer pain is high. The ablation can be done with MRI-guided stereotactic placement of radiofrequency probe and confers relief in about 50% of patients. The procedure modulates the emotional impact and not the pain itself.[94,96]

Cancer patients with metastases to vertebral bodies can have compression fractures causing severe back pain. Spine restoration can be done with minimally invasive procedure such as percutaneous vertebroplasty (involves injection of polymethylmethacrylate bone cement into a vertebral body) to manage the pain due to structural instability of the vertebral body. Percutaneous balloon kyphoplasty is a modification of vertebroplasty, which inflates a balloon into the collapsed vertebral body to restore height and reduce kyphotic deformity, before stabilisation with bone cement.[97] Possible complications include infection, paraplegia, and cement embolisation.

Conclusion

Cancer pain is complex and multifactorial. Cancer patients will experience pain at some point during the course of their disease. Relieving pain and improving their quality of life has become a fundamental component of end-of-life care. The improved understanding of cancer pain mechanism and pain pathway enable the physician to make a comprehensive evaluation. While oral opioids and adjuvants remain the mainstay of cancer pain management, intolerable side effects and treatment failure are the main limitations. Improved efficacy of interventional techniques has widened the physician's armamentarium to combat intractable cancer pain. These procedures should be considered during patient assessment, individualised and employed as soon as their necessity becomes clear. Although not without risks, appropriately chosen interventional pain procedures may well have a positive impact on the course of the disease.

REFERENCES

1. World Health Organization. World Cancer Report - International Agency for Research on Cancer. In: Stewart BW, Kleihues P, editors. Geneva, Switzerland: WHO, 2003.
2. Higginson IJ. Innovations in assessment: epidemiology and assessment of pain in advanced cancer. In: Jensen TS, Turner JA, Wiesenfeld-Hallin Z, editors. Proceedings of the 8th World Congress on Pain: Progress in Pain Research and Management. Seattle (WA): IASP Press, 1997.
3. Caraceni A, Portenoy RK. An international survey of cancer pain characteristics and syndromes. Pain 1999;82:263-74.
4. Grond S, Zech D, Diefenbach C, Radbruch L, Lehmann KA. Assessment of cancer pain: a prospective evaluation of 2266 cancer patients referred to a pain service. Pain 1996;64:107-14.
5. Portenoy RK, Lesage P. Management of cancer pain. Lancet 1999;353:1695-700.
6. Grond S, Zech D, Schug SA, Lynch J, Lehmann KA. Validation of World Health Organization guidelines for cancer pain relief during the last days and hours of life. J Pain Symptom Manage 1991;6:411-22.
7. Zech DF, Grond S, Lynch J, Hertel D, Lehmann KA. Validation of World Health Organization Guidelines for cancer pain relief: a 10-year prospective study. Pain 1995;63:65-76.
8. Walker VA, Hoskin PJ, Hanks GW, White ID. Evaluation of WHO analgesic guidelines for cancer pain in a hospital-based palliative care unit. J Pain Symptom Manage 1988;3:145-9.
9. Fallon M, Hanks G, Cherny N. Principles of control of cancer pain. BMJ 2006;332:1022-4.
10. Cleeland CS, Gonin R, Hatfield AK, Edmonson JH, Blum RH, Stewart JA, et al. Pain and its treatment in outpatients with metastatic cancer. N Engl J Med 1994;330:592-6.
11. Enting RH, Oldenmenger WH, van der Rijt CC, Wilms EB,

Elfrink EJ, Elswijk I, et al. A prospective study evaluating the response of patients with unrelieved cancer pain to parenteral opioids. Cancer 2002;94:3049-56.
12. World Health Organization (WHO), WHO expert committee on cancer pain relief and active supportive care. Cancer pain relief and palliative care: Report of a WHO expert committee. 3rd ed. Geneva: WHO, 1996.
13. Miguel R. Interventional treatment of cancer pain: the fourth step in the WHO analgesic ladder? Cancer Control 2000;7:149-56.
14. Erdine S. Interventional treatment of cancer pain. Eur J Cancer Suppl 2005;3:97-106.
15. Manchikanti L, Fellows B, Singh V. Understanding psychological aspects of chronic pain in interventional pain management. Pain Physician 2002;5:57-82.
16. Bender JL, Hohenadel J, Wong J, Katz J, Ferris LE, Shobbrook C, et al. What patients with cancer want to know about pain: A qualitative study. J Pain Symptom Manage 2008;35:177-87.
17. Plancarte R, Alvarez J, Arrieta MC. Interventional treatment of cancer pain. Semin Pain Med 2003;1:34-42
18. Eisenberg E, Carr DB, Chalmers TC. Neurolytic coeliac plexus block for treatment of cancer pain: a meta-analysis. Anesth Analg 1995;80:290-5
19. Pert CB, Synder SH. Opioid receptor: demonstration in nervous tissue. Science 1973;179:1947-9.
20. Behar M, Magora F, Olshwang D, Davidson JT. Epidural morphine in treatment of pain. Lancet 1979;1:527-9.
21. Wang JK, Nauss LA, Thomas JE. Pain relief by intrathecally applied morphine in man. Anesthesiology 1979;50:149-51.
22. Hanks GW, Coon F, Cherny N, Hanna M, Kalso E, McQuay HJ, et al; Expert Working Group of the Research Network of the European Association of Palliative Care. Morphine and alternative opioids in cancer pain: the EAPC recommendations. Br J Cancer 2001;84:587-93.
23. Comparative efficacy of epidural, subarachnoid and intracerebroventricular opioids in patients with pain due to cancer. The Cochrane Database of Systematic Reviews. 2006, Issue 1, art no. CD 005178.
24. Smith TJ, Staats PS, Deer T, Stearns LJ, Rauck RL, Boortz-Marx RL, et al. Implantable drug delivery systems study group. Randomised clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain; impact on pain, drug-related toxicity, and survival. J Clin Oncol 2002;20:4040-9.
25. Chambers WA. Nerve blocks in palliative care. Br J Anaesth 2008; 101:95-100.
26. Staats P. Neuraxial infusion for pain control. Oncology 1999;13:58-62.
27. Krames ES, Lanning RM. Intrathecal infusional analgesia for nonmalignant pain: analgesic efficacy of intrathecal opioid with or without bupivacaine. J Pain Symptom Manage 1993;8:539-48.
28. Eisenach JC, DuPen S, Dubois M, Miguel R, Allin D. Epidural clonidine analgesia for intractable cancer pain. The Epidural Clonidine Study Group. Pain 1995;61:391-9.
29. Kedlaya D, Reynolds L, Waldman S. Epidural and intrathecal analgesia for cancer pain. Best Pract Res Clin Anaesthesiol 2002;16:651-5.
30. Dahm P, Nitescu P, Applegren L, Curelaru I. Efficacy and technical complications of long-term continuous intraspinal infusions of opioid and/or bupivacaine in refractory non malignant pain; a comparison between the epidural and intrathecal approach with externalized or implanted catheters and infusion pumps. Clin J Pain 1998;14:4-16.
31. Baker L, Lee M, Regnard C. Evolving spinal analgesia practice in palliative care. Palliat Med 2004;18:507-15.
32. Gestin Y, Vainio A, Pergurier AM. Long-term intrathecal infusion of morphine in the home care of patients with advanced cancer. Acta Anaesthesiol Scand 1997;41:12-7.
33. Sjoberg M, Karlsson PA, Nordborg C, Wallgren A, Nitescu P, Appelgren L, et al. Neuropathologic findings after long-term intrathecal infusion of morphine and bupivicaine for pain treatment in cancer patients. Anaesthesiology 1992;76:173-86.
34. Penn RD, Paice JA, Gottschalk W, Ivankovic AD. Cancer pain relief using chronic morphine infusion. Early experience with a programmable implanted drug pump. Neurosurgery 1984;61:302-6.
35. Classen AM, Wimbish GH, Kupiec TC. Stability of admixture containing morphine sulfate, bupivacaine hydrochloride, and clonidine hydrochloride in an implantable infusion system. J Pain Symptom Manage 2004;28:603-11.
36. Devulder J, Ghys L, Dhondt W, Roily G. Spinal analgesia in terminal care: risk versus benefit. J Pain Symptom Manage 1994;9:75-81.
37. Mercadante S. Problems of long-term spinal opioid treatment in advanced cancer patients. Pain 1999;79:1-13.
38. Rigler ML, Drasner K, Krejcie TC, Yelich SJ, Scholnick FT, DeFontes J, et al. Cauda equina syndrome after continuous spinal anesthesia. Anesth Analg 1991;72:275-81.
39. North RB, Cutchis PN, Epstein JA, Long DM. Spinal cord compression complicating subarachnoid infusion of morphine: Case report and laboratory experience. Neurosurgery 1991;29:778-84.
40. Yaksh TL, Hassenbusch S, Burchiel K, Hildebrand KR, Page LM, Coffey RJ. Inflammatory masses associated with intrathecal drug infusion: A review of preclinical evidence and human data. Pain Med 2002;3:300-12.
41. Deer TR. A prospective analysis of intrathecal granuloma in chronic pain patients: A review of the literature and report of a surveillance study. Pain Physician 2004;7:225-8.
42. Applegren L, Nordborg C, Sjoberg M, Karlsson PA, Nitescu P, Curelaru I. Spinal epidural metastasis: implications for spinal analgesia to treat 'refractory' cancer pain. J Pain Symptom Manage 1997;13:25-42.
43. Mueller-Schwefe G, Hassenbusch SJ, Reig E. Cost effectiveness of intrathecal therapy for pain. Neuromodulation 1999;2:77-87.
44. Southall JL, Beddall C, Raphael JH. Cost utility analysis of intrathecal pump implant for chronic nonmalignant low back pain. Neuromodulation 2006;9:156-7.
45. Bedder MD, Burchiel K, Larson A. Cost analysis of two implantable narcotic delivery systems. J Pain Symptom Manage 1991;6:368-73.
46. Rauck RL, Cherry D, Boyer MF, Kosek P, Dunn J, Alo K. Long-term intrathecal opioid therapy with a patient-activated, implanted delivery system for the treatment of refractory cancer pain. J Pain 2003;4:441-7.
47. Kumar K, Kelly M, Pirlot T. Continuous intrathecal morphine treatment for chronic pain of nonmalignant etiology: Long-term benefits and efficacy. Surg Neurol 2001;55:79-86.
48. Scherens A, Kagel T, Zenz M, Maier C. Long-term respiratory depression induced by intrathecal morphine treatment for chronic neuropathic pain. Anesthesiology 2006;105:431-3.
49. Ruan X. Drug-related side effects of long-term intrathecal morphine therapy: A focused review. Pain Physician 2007;10:357-366.
50. Anderson VC, Cooke B, Burchiel KJ. Intrathecal hydromorphone for chronic nonmalignant pain: A retrospective study. Pain Med 2001;2:287-97.
51. Coffey RJ, Burchiel K. Inflammatory mass lesions associated with intrathecal drug infusion catheters: Report and observations on 41 patients. Neurosurgery 2002;50:78-86.
52. Deer T, Krames ES, Hassenbusch SJ, Burton A, Caraway D, Dupen S, et al. Polyanalgesic Consensus Conference 2007: Recommendations for the Management of Pain by Intrathecal (Intraspinal) Drug Delivery: Report of an Interdisciplinary Expert Panel. Neuromodulation 2007;10:300-28.
53. Akerman B, Arwestrom E, Post C. Local anaesthetics potentiate spinal morphine antinociception. Anesth Analg 1988;67:943-8.
54. van Dongen RT, Crul BJ, van Egmond J. Intrathecal coadministration of bupivacaine diminishes morphine dose progression during long-term intrathecal infusion in cancer patients. Clin J Pain 1999;15:166-72.
55. Mironer EY, Haasis JC, Chapple I, Brown C, Satterthwaite JR. Efficacy and safety of intrathecal opioid/bupivacaine mixture in chronic nonmalignant pain: A double blind, randomized, crossover, multicenter study by the National Forum of Independent Pain Clinicians (NFIPC). Neuromodulation 2002;5:208-13.
56. Coombs DW, Saunders RL, Lachance D, Savage S, Ragnarsson TS, Jensen LE. Intrathecal morphine tolerance: use of intrathecal clonidine, DADLE, and intraventricular morphine. Anesthesiology 1985;62:358-63.

57. Coombs DW, Saunders RL, Fratkin JD, Jenson LE, Murphy CA. Continuous intrathecal hydromorphone and clonidine for intractable cancer pain. J Neurosurg 1986;64:890-4.
58. Bevacqua BK, Fattouh M, Backonja M. Depression, night terrors, and insomnia associated with long-term intrathecal clonidine therapy. Pain Practice 2007;7:36-8.
59. Fitzgibbon D, Rapp S, Butler S, Terman G, Dolack G, Dupen S, et al. Rebound hypertension and withdrawal associated with discontinuation of an infusion of epidural clonidine. Anesthesiology 1996;84:729-31.
60. Olivera BM, Cruz LJ, de Santos V, LeCheminant GW, Griffin D, Zeikus R, et al. Neuronal calcium channel antagonists. Discrimination between calcium channel subtypes using omega-conotoxin from Conus magus venom. Biochemistry 1987;26:2086-90.
61. Staats PS, Yearwood T, Charapata SG, Presley RW, Wallace MS, Byas-Smith M, et al. Intrathecal ziconotide in the treatment of refractory pain in patients with cancer or AIDS: a randomized controlled trial. JAMA 2004;291:63-70.
62. Rauck RL, Wallace MS, Leong MS, Minehart M, Webster LR, Charapata SG, et al; Ziconotide 301 Study Group. A randomized, double-blind, placebo-controlled study of intrathecal ziconotide in adults with severe chronic pain. J Pain Symptom Manage 2006;31:393-406.
63. Shields D, Montenegro R, Ragusa M. Chemical stability of admixtures combining ziconotide with morphine or hydromorphone during simulated intrathecal administration. Neuromodulation 2005;8:257-63.
64. Shields D, Montenegro R. Chemical stability of ziconotide-clonidine hydrochloride admixtures with and without morphine sulfate during simulated intrathecal administration. Neuromodulation 2007;10[suppl 1]:6-11.
65. Candido K, Stevens R. Intrathecal neurolytic blocks for the relief of cancer pain. Best Pract Res Clin Anaesthesiol 2003;17:407-28.
66. Gerbershagen HU. Neurolysis. Subarachnoid neurolytic blockade. Acta Anaesthesiol Belg 1981;32:45-57.
67. Ischia S, Ischia A, Polati E, Finco G. Three posterior percutaneous coeliac plexus block techniques: a prospective randomized study in 61 patients with pancreatic cancer pain. Anesthesiology 1992;76:534-40.
68. Mercadante S. Coeliac plexus block versus analgesics in pancreatic cancer pain. Pain 1993;52:187-92.
69. Wong G, Schroeder DR, Carns PE, Wilson JL, Martin DP, Kinney MO, et al. Effect of neurolytic coeliac plexus block on pain relief, quality of life, and survival in patients with unresectable pancreatic cancer: a randomized controlled trial. JAMA 2004;291:1092-9.
70. De Cicco M, Matovic M, Bortolussi R, Coran F, Fantin D, Fabiani F, et al. Coeliac plexus block: injectate spread and pain relief in patients with regional anatomic distortions. Anesthesiology 2001;94:561-5.
71. Eisenberg E, Carr DB, Chalmers TC. Neurolytic coeliac plexus block for treatment of cancer pain: a meta-analysis. Anesth Analg 1995;80:290-5.
72. Hayakawa J, Kobayashi O, Murayama H. Paraplegia after intraoperative coeliac plexus block. Anesth Analg 1997;84:447-8.
73. Wong GY, Brown DL. Transient paraplegia following alcohol coeliac plexus block. Reg Anesth 1995;20:352-5.
74. Teng J. Cancer pain and neurolysis. Semin Anesth 2003;22:175-85.
75. de Leon-Casasola OA. Critical evaluation of chemical neurolysis of the sympathetic axis for cancer pain. Cancer Control 2000;7:142-8.
76. Plancarte R, Amescua C, Patt RB, Aldrete JA. Superior hypogastric plexus block for pelvic cancer pain. Anesthesiology 1990;73:236-9.
77. de Leon-Casasola OA, Kent E, Lema MJ. Neurolytic superior hypogastric plexus block for chronic pelvic pain associated with cancer. Pain 1993;54:145-51.
78. Plancarte R, de Leon-Casasola OA, El-Helaly M, Allende S, Lema MJ. Neurolytic superior hypogastric plexus block for chronic pelvic pain associated with cancer. Reg Anesth 1997;22:562-8.
79. Nebab EG, Florence IM. An alternative needle geometry for interruption of the ganglion impar. Anesthesiology 1997;86:1213-4.
80. Munir MA, Zhang J, Ahmad M. A modified needle-inside-needle technique for the ganglion impar block. Can J Anaesth 2004;51:915-7.
81. Foye PM. New approaches to ganglion impar blocks via coccygeal joints. Reg Anesth Pain Med 2007;32:269.
82. Ho KY, Nagi PA, Gray L, Huh BK. An alternative approach to ganglion impar neurolysis under computed tomography guidance for recurrent vulva cancer. Anesthesiology 2006;105:861-2.
83. Gupta D, Jain R, Mishra S, Kumar S, Thulkar S, Bhatnagar S. Ultrasonography reinvents the originally described technique for ganglion impar neurolysis in perianal cancer pain. Anesth Analg 2008;107:1390-2.
84. Khor KE, Ditton JN. Femoral nerve blockade in the multidisciplinary management of intractable localized pain due to metastatic tumor: a case report. J Pain Symptom Manage 1996;11:57-61.
85. Fischer HB, Peters TM, Fleming IM, Else TA. Peripheral nerve catheterization in the management of terminal cancer pain. Reg Anesth 1996;21:482-5.
86. Vranken JH, Zuurmond WW, de Lange JJ. Continuous brachial plexus block as treatment for the Pancoast Syndrome. Clin J Pain 2000;16:327-33.
87. Mercadante S, Sapio M, Vilari P. Suprascapular nerve block by catheter for breakthrough shoulder cancer pain. Reg Anesth 1995;20:343-6.
88. Calava JM, Patt RB, Reddy S, Varma DG, Chiang J. Psoas sheath chemical neurolysis for management of intractable leg pain from metastatic liposarcoma. Clin J Pain 1996;12:69-75.
89. Kaki AM, Lewis GW. Inguinal paravascular (lumbar plexus) neurolytic block – description of a catheter technique: case report. Reg Anesth Pain Med 1998;23:214-8.
90. Antila H, Kirvela O. Neurolytic thoracic paravertebral block in cancer pain. A clinical report. Acta Anaesthesiol Scand 1998;42:581-5.
91. Fineman SP. Long-term post-thoracotomy cancer pain management with interpleural bupivacaine. Anesth Analg 1989;68:694-7.
92. Myers DP, Lema MJ, de Leon-Casasola OA, Bacon DR. Interpleural analgesia for the treatment of severe cancer pain in terminally ill patients. J Pain Symptom Manage 1993;8:505-10.
93. Dravid RM, Paul RE. Interpleural block – part 1. Anaesthesia 2007; 62:1039-49.
94. Giller CA. The neurosurgical treatment of pain. Arch Neurol 2003;60:1537-40.
95. Sanders M, Zuurmond W. Safety of unilateral and bilateral percutaneous cervical cordotomy in 80 terminally ill cancer patients. J Clin Oncol 1995;13:1509-12.
96. Wong ET, Gunes S, Gaughan E, Patt RB, Ginsberg LE, Hassenbusch S, et al. Palliation of intractable cancer pain by MRI-guided cingulotomy. Clin J Pain 1997;13:260-3.
97. Burton AW, Mendel E. Vertebroplasty and kyphoplasty. Pain Physician 2003;6:335-41.