Interventional treatment of cancer pain

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Introduction

Cancer pain is one of the most witnessed pain syndromes all over the world [1]. The three-step analgesic ladder developed by WHO is an important development since the 1980s to relieve cancer-related pain syndromes including pain related to cancer therapy [2,3]. The WHO analgesic ladder has been reported to be efficacious in controlling pain in approximately 70–90% of patients [4–7]. This means that there remain a number of patients who are candidates for interventional treatment of cancer pain. There is a wide range of interventional procedures when pain has not been controlled by using the combination of drugs included in the "ladder".

The use of interventional techniques for the control of cancer pain needs trained pain physicians, development of facilities for applying these techniques and follow-up of the patients. Patients who are candidates for interventional therapies need special care and follow-up. Although most of the procedures are performed by anesthesiology or neurosurgery departments, interventional pain procedures require special training and facilities which will maintain proper and continuous follow-up. That is one of the main reasons for the development of pain medicine all over the world.

Patient selection for interventional pain treatment

Patient selection criteria are very important prior to the interventional pain treatment. A thorough history of the patient related to his disease and pain including the onset, duration, intensity, localization and course of the pain, should be evaluated. Besides the disease itself, a complete evaluation of the patient related to pain should be carried out. This should include a general medical and neurological evaluation, along with laboratory tests and radiographic evaluation. Most of the interventional techniques target the nervous system, thus a recent radiological evaluation is essential in order to identify the cause of the pain, as well as to prevent complications related to the technique. It is also important to verify the objective findings of pain which will aid the choice of what kind of intervention has to be used. The emotional and psychological status of the patient should be assessed prior to the intervention. This assessment of the patient will guide the physician' s decision as to whether the patient is suitable for an intervention and the type of intervention. The mechanism of pain, either nociceptive or neuropathic, should also be identified while selecting the technique to be used. Most cancer pain syndromes are nociceptive, but neuropathic pain may also develop either due to the development of the disease itself or due to the treatment, like radiation myelopathy, polyneuropathies due to chemotherapy, or surgery-related painful conditions (e.g. post-mastectomy or post-thoracotomy syndromes) [8,9]. The life expectancy of the patient is another important criterion for selection of the interventional technique. Most of the cancer patients referred for interventional treatment are at the terminal stage with short life expectancy. The interventional technique to be applied should sustain a better quality of life with the least complications or side effects. Interventional techniques should only be applied when more conservative pain relief modalities fail. Generally the WHO ladder is applied and when all the drugs included in the ladder are inadequate, interventional techniques are considered. However in some cases interventional techniques may be applied earlier, as will be discussed later in this chapter. There should be no general contraindications such as sepsis or coagulopathy while performing the interventional techniques.

Types of interventional pain treatment, definitions

Interventional techniques are divided into two categories: neuroablative and neuromodulatory procedures [10]. Neuroablation is the physical interruption

of pain pathways, surgically, chemically or thermally. Neuromodulation is the dynamic and functional inhibition of pain pathways either by administration of opioids and other drugs intraspinally or intraventricularly, or by stimulation. It is not appropriate to compare neuroablation versus neuromodulation. In an algorithm of interventional pain treatment all techniques have their own indications and are part of a multidisciplinary approach.

Neuroablative techniques for cancer pain treatment

Neuroablative techniques for cancer pain treatment have been used for more than a century. With the development of imaging facilities such as fluoroscopy neuroablative techniques are performed more precisely and efficiently. Neuroablative techniques are used less frequently now with the use of new drugs, new routes, such as transdermal application of opioids, as well as long-acting opioids and adjuvant drugs. Although more limited than before, neuroablative techniques still have a certain role in the treatment of intractable cancer pain. These techniques are indicated when administration of analgesics according to the "ladder" are inadequate. Life expectancy of the patient should be limited and the pain should be localized to one part of the body. Neuroablative techniques can be used for somatic or visceral pain. In neuropathic pain syndromes, besides sympathetic blocks they do not have a real place. Although neuroablative techniques should be performed when the "ladder" is inadequate, in certain cancer pain syndromes they may be performed at an earlier stage. Localized pain at the innervation of the trigeminal nerve may be interrupted either by the neurolytic block or radiofrequency thermocoagulation of the Gasserian ganglion. Celiac and splanchnic blocks may also be performed at an earlier stage before the anatomy of the region is distorted. The advantages of neuroablative techniques are: less follow-up of the patient is required when compared with neuromodulatory techniques; more cost effective, they may also have a place in patients with short life expectancy. The disadvantages are: potential risks such as permanent motor loss; paresthesia and dysesthesia, which are more common; the necessity of performance by only very well trained physicians, performance only for localized pain.

Neurolytic nerve blocks

Neurolytic agents are chemical substances which destroy the nerve: including 50–100% alcohol, 5–15% phenol, glycerol, and hypertonic saline. Alcohol is the oldest agent, generally used for celiac plexus, Gasserian ganglion, sympathetic chain, or intrathecally. Several concentrations, varying between 50–100%, are used. It damages the nerve in a non-selective way. Phenol is more frequently used in glycerin solutions as a hyperbaric solution in concentrations between 5% and 15%. It also damages the nerve in a non-selective way but more reversible than alcohol. Glycerol is only used for peripheral nerves, but the duration of effect is much shorter.

Trigeminal ganglion neurolysis

The percutaneous trans-foramen ovale approach for the trigeminal (Gasserian) ganglion using absolute alcohol was first described by Hartel in 1912 [11]. In the evolution of the treatment, radiofrequency lesioning for this ganglion was described by Sweet and Wepsic in 1974 [12], retrogasserian glycerol injection by Hakanson in 1981 [13]. Trigeminal ganglion block is generally used for the treatment of idiopathic trigeminal neuralgia but it has a place in the treatment of secondary pain due to cancer of the region. To get a better result, before the anatomy of the region is distorted by the growth of the cancer, it should be performed at an earlier stage. It lasts for months to years. It should be performed under fluoroscopy. The foramen ovale is easily seen under the fluoroscope and the neurolytic solution, either alcohol or phenol, which should not exceed 1 ml is given in smaller aliquots. Otherwise it may spread to the brain stem and cause severe complications. Currently, the use of radiofrequency lesioning is preferred to neurolytic agents. More precise location of the nerve is possible with radiofrequency lesioning and there is no risk of spread of neurolytic solution to the brain stem. Trigeminal ganglion neurolysis is not free of complication [14]. In all cases facial numbness develops as a result of the neurolysis. Patients should be well informed in advance of this outcome. In fact it may not be accepted as a complication but a result of neurolysis. Loss of corneal reflex may occur as a result of the destruction of the ophthalmic branch of the trigeminal nerve. Carotid artery puncture occurs when radiographic landmarks are not employed and the needle is too inferior and medial. If the needle is advanced to the retrobulbar space retrobulbar hematoma may develop. Anesthesia dolorosa is the most severe complication. The pain is relieved but burning pain and dysesthesia in the region develop, which is difficult to control.

Intercostal nerve block

By 1922, Labats textbook contained an elaborate description of the intercostal nerve block that is quite similar to our present day conceptions [15]. Intercostal nerve block is one of the most effective blocks in the treatment of pain. It may be used in the treatment of pain due to fractured ribs and metastasis of the cancer [16]. It is generally performed in prone position where rib identification by posterior palpation of the intercostal spaces is optimal. In the classic approach, intercostal nerve block is performed posteriorly at the angle of the ribs and just lateral to the sacrospinalis group of muscles [17]. It is much better to perform the block under fluoroscopy. The needle touches the lower edge of the rib and slips down the rib adjacent to the rib. It is better to perform the block first with a local anesthetic, e.g. 2% lidocaine solution. If it is helpful then 6–8% phenol, 3–5 ml may be administered. Pneumothorax and intravascular injection are the main risks. However, careful performance of the block reduces the risk of development of pneumothorax.

Intrathecal and epidural neurolytic blocks

Intrathecal neurolysis has been used since 1931, first performed by Dogliotti [18]. The use of intrathecal alcohol and phenol is has become less frequent in recent years because of the fear of complications such as motor, autonomic and sensorial loss. The intention of the procedure is to bathe the posterior, sensory nerve root, with the neurolytic solution; either alcohol or phenol. Very small amounts of the neurolytic solution are delivered according to the position of the patient, if hypobaric alcohol is used, the painful side up [19], if phenol is used, the painful side down [20]. It should be performed by very experienced physicians in order to prevent dreadful complications. Phenol may also be delivered epidurally to the affected route [21]. It should be performed under fluoroscopy, the catheter tip should be visible in order to advance to the root, and then 6% aqueous phenol may be injected. The risk of complications, such as sensorial or motor loss, is less frequent than intrathecal neurolysis.

Neuroadenolysis of the pituitary gland

In hormone-related cancers such as thyroid or breast cancer, with several metastases throughout the body, neuroadenolysis of the pituitary gland may be considered. It was first performed by Morrica in the 1970s [22]. The technique is performed under fluoroscopy, the patient lying in the supine position; the needle is advanced transnasally, transsphenoidally to the pituitary gland. Following the verification of the position, 0.5–6 ml of absolute alcohol is injected to destroy the pituitary gland [23]. Cephalalgia, hypothyroidia, hypoadrenalism and diabetes insipidus are the most frequently seen complications. Currently the technique has lost popularity.

Neurolytic sympathetic blocks

The relationship of the sympathetic nervous system and several chronic pain syndromes including cancer pain has long been recognized [24,25]. Sympathetic blocks may have a place in cancer pain patients if they have neuropathic pain syndromes due to surgery, chemotherapy, radiotherapy or infiltration of the brachial or lumbosacral plexus or in visceral pain arising from the upper or lower abdominal organs. Stellate and thoracic and lumbar sympathetic blocks are used in the treatment of neuropathic pain syndromes related to the cancer, while splanchnic, celiac, hypogastric and impar ganglion blocks are used for the treatment of visceral pain arising from the upper or lower abdominal organs.

Stellate ganglion block

Selective block of the stellate ganglion was first described by Sellheim and, shortly after, by Kappis in 1923 [25], and Brumm and Mandl in 1924 [26]. Stellate ganglion block is useful in cancer patients if the patient has a burning pain radiating to the upper extremity. It is much better to combine it with the thoracic sympathetic block. It is also effective in patients with postherpetic neuralgia. It is contraindicated if the patient had a pneumonectomy on the contralateral side because of the danger of additional pneumothorax on the ipsilateral side. It is also contraindicated if the patient had a recent cardiac infarction. There are several techniques described, in both supine and prone position [27]. Previously it was performed (and still is in some centers) using a blind approach but this is not appropriate and it should be performed under fluoroscopy. The ganglion lies at the junction of the vertebral body and the transverse process of C7. The needle is advanced to that point. It should first be performed by a local anesthetic solution and, if effective, then neurolytic solution should be given. Currently, stellate gangliolysis may be performed by radiofrequency thermocoagulation. The two principal complications of stellate ganglion block are pneumothorax and intraspinal injection. A third risk is the possibility of persistent Horner' s syndrome. If the neurolysis is performed under fluoroscopy the potential risk becomes minimal.

T2–T3 sympathetic neurolysis

Previously T2–T3 sympathectomy was performed surgically. With the development of imaging techniques, neurolysis is performed more often. In 1979 Wilkinson devised the technique for radiofrequency thermocoagulation with minimal complications [28]. T2–T3 sympathetic block is considered for patients who have sympathetically maintained pain. In respiratory insufficiency or thoracic aortic aneurysm it is contraindicated. It is performed in a prone position under fluoroscopy. 2–3 ml of phenol may be delivered to the sympathetic chain or radiofrequency thermocoagulation is performed. Pneumothorax is the principal complication. Another side effect of this procedure is intercostal neuritis. This problem can be minimized by meticulously performing sensory and motor stimulation prior to lesioning [27].

Splanchnic nerve block

The first anterior percutaneous approach to splanchnic nerve block was described by Kappis in 1914 [29].The recognition that splanchnic nerve block may provide relief of pain in a subset of patients who fail to obtain relief from celiac plexus block has led to a renewed interest in this technique. It was recently advised by P. Raj for radiofrequency thermocoagulation [27]. Splanchnic block is effective in relieving cancer pain due to upper abdominal organs, including stomach and pancreas. It should be performed with the patient in a prone position under fluoroscopy. If the pain is unilateral the splanchnic nerve on the same side is blocked, however it is generally bilateral and the block should be performed for both sides. Smaller volumes (5–8–ml) of absolute alcohol are recommended for single-needle procedures [30]. Many investigators believe that alcohol as a neurolytic agent is superior to phenol in duration of neural blockade [31]. 6–10% phenol may also be used. Because splanchnic nerves are contained in a narrow compartment, they are accessible for RF lesioning. To produce a lesion of the splanchnic nerve, the needle needs to lie on the mid third portion of the lateral side of the T11–T12 vertebral body. After a sensorial test stimulation, during which the patient should report a stimulation in the epigastric region, RF lesion is created [27]. Complications of splancnic block can be minor, moderate or severe. Those relatively minor are hypotension and diarrhea, and they are readily reversible. Moderate complications like pneumothorax should not occur if performed under fluoroscopy, but again are transient. Major complications such as paraplegia are rare.

Celiac plexus block

In 1914 Kappis introduced the percutaneous techniqe for the celiac plexus block [29]. Since then several other techniques, like posterior approach, transaortic approach, intradiscal approach and anterior approach have been introduced. Innervation of the abdominal viscera originates in the anterolateral horn of the spinal cord with the ventral spinal routes to join the white communicating rami en route to the sympathetic chain. Nociception from the abdominal viscera is carried by afferent nerves that are part of the spinal nerves but accompany sympathetic nerves. The celiac plexus lies anterior to the aorta and epigastrium, just anterior to the crus of the diaphragm. Fibers within the plexus arise from preganglionic splanchnic nerves, parasympathetic preganglionic nerves from the vagus, some sensory nerves from the phrenic and vagus nerves and sympathetic postganglionic fibers. Postganglionic nerves from these ganglia innervate all abdominal viscera, with the exception of part of the transverse colon, the left colon, the rectum and pelvic viscera. Any pain originating from the visceral structures and innervated by the celiac plexus can be effectively relieved by the block of the plexus. These structures include the pancreas, liver, gallbladder, omentum, mesentery and alimentary tract from the stomach to the transverse portion of the large colon. Celiac plexus block increases the gastric motility. This may be a benefit in patients with chronic constipation due to analgesics. Diarrhea has been reported in a few patients as well as concomitant decrease in the incidence of nausea and vomiting. However the celiac plexus block should be avoided in patients with bowel obstruction [32]. 50–100% alcohol is the agent generally used for the neurolysis. Although it was performed with the blind technique in the past and currently in some centers, it should be performed under fluoroscopy to prevent any complication. It may either be performed by single-needle technique by transaortic approach or by double-needle technique. In the hands of an experienced physician serious complications rarely occur. Because of the proximity of other vital structures, coupled with large volumes of neurolytic drugs side effects and complications may be seen. Minor complications are hypotension, diarrhea, and back pain. Minor complications fade within days. Moderate complications are mechanical or chemical disturbance of the organs in the proximity of the ganglion and irritation of the genitofemoral nerve. Major complications are paraplegia, with the incorrect placement of the needle near to the spinal nerves, or subarachnoid injection, vascular injection of the neurolytic solution, renal injury, perforation of

cysts of tumors or peritonitis [27]. In spite of the risks and complications, celiac plexus block is one of the most effective neurolytic blocks if performed properly. Time to maximal pain relief is variable. In most patients, relief is immediate and complete, in others it will accrue over a few days. In addition pain relief is re-established with repetition. Its effect lasts for months [33,34].

Hypogastric plexus neurolysis

The first attempts to interrupt the sympathetic pathways in the pelvic region took place at the end of the 19th century, by Jaboulay in France [35] and Ruggi in Italy in 1899 [36]. In 1990 Plancarte described the technique for hypogastric plexus block [37]. The superior hypogastric plexus is the extension of the aortic plexus in the retroperitoneal space below the aortic bifurcation. It contains almost exclusively sympathetic fibers. The anatomic location of the superior hypogastric plexus and the sympathetic predominance of the fibers of the plexus and its role in the transmission of most of the pain signals from the pelvic viscera make these structures an ideal target for neurolysis in cancer pain arising from the pelvic viscera. It may be performed by lateral approach by double needle technique trying to reach the L5–S1 level. It may also be performed with the intradiscal approach under fluoroscopy. Hypogastric plexus block is not free of complications. There is a risk of intravascular injections in all approaches. A potential risk of discitis may occur with the intradiscal approach [27]. Long-lasting pain relief with this procedure has been achieved in patients with pelvic cancer pain [38].

Ganglion impar block

The first report of interruption of the ganglion impar for the relief of perineal pain came from Plancarte in 1990 [39]. Ganglion impar, also known as ganglion of Walther or the sacrococcygeal ganglion is the most caudal ganglion of the sympathetic trunk. Visceral pain or sympathetically maintained pain in the perineal area associated with malignancies of the pelvis may be treated with the neurolysis of the ganglion impar. Tenesm like pain in patients with colostomy, patients with a clinical picture of vague, burning localized pain may benefit from this block, but the duration is shorter than other sympathetic blocks. There are multiple approaches to this block such as lateral approach and transdiscal approach. All approaches should be performed under fluoroscopy. Rectum puncture, neurolytic injection into the nerve roots and rectal cavity and neuritis due to nerve root injection are the potential complications [27].

Radiofrequency thermocoagulation for the treatment of cancer pain

The use of current lesions for the treatment of pain is not new. Kirschner was the first to describe the use of percutaneous current lesions for the treatment of trigeminal neuralgia using direct current delivered to a needle placed in the Gasserian ganglion [40]. Since then, technique and equipment have developed. In 1965 Mullan and Rosomoff described the percutaneous lateral cordotomy for unilateral malignant pain [41,42]. A few years later in 1974 Sweet used radiofrequency lesions for the treatment of trigeminal neuralgia [12]. Shealy in 1975 used a radiofrequency probe to interrupt the posterior primary ramus of segmental nerves [43]. Uematsu in 1977 described the technique for the radiofrequency of the dorsal root ganglion [44]. The development of a small diameter (22 gauge) electrode system made the use of the RF procedures safer. In recent years Sluijter is a pioneer of developing newer techniques like pulsed radiofrequency.

What is radiofrequency treatment?

Radiofrequency is an alternating current with an oscillating frequency of 500,000 Hz. When the lesion generator produces an output, current starts flowing in the circuit and the current flows through the body tissue which acts as a resistor. Current flowing through the resistor produces heat. The production of heat will be the highest where the current density is highest at the electrode tip. The heat produced by radiofrequency creates circumscriptive lesions by which selective nerve lesioning is possible. The effect of heat on neural tissue becomes destructive above 45°C. Generally, lesions are created with heat over 60°C. Currently, radiofrequency thermocoagulation is used for the treatment of various non-malign and malign pain syndromes. In fact, radiofrequency treatment began with the development of percutaneous lateral cordotomy by Mullan and Rosomoff [41,42]. The main procedures of radiofrequency lesioning used in the treatment of cancer pain are:

(a) Percutaneous cordotomy.
(b) Radiofrequency thermocoagulation of the Gasserian ganglion.
(c) Percutaneous rhizotomy.
(d) Percutaneous RF sympathectomy.

a. Percutaneous cordotomy. At present, percutaneous cervical cordotomy is one of the most important

neuroablative techniques in the treatment of cancer pain. In recent years, however, the technique is less frequently used. The number of patients referred for cordotomy has decreased dramatically since the introduction of intraspinal techniques. There are only very few experts in the world performing cordotomy. But it still has a place in the treatment of severe cancer pain. The aim of percutaneous cordotomy is to interrupt the spinothalamic tract in the anterolateral quadrant, the most prominent ascending nociceptive pathway in the spinal cord. The cordotomy is performed at the cervical level between C1–C2 where the fibers of the lateral spino-thalamic tract are closely compact in the anterolateral quadrant and present a precise somatotropy: the fibers coming from the lumbosacral segments lay in the dorsolateral position, whereas those of thoracic–cervical origin are more ventral. The cordotomy is performed with the patient awake and able to collaborate, in order to have continuous control of the precise positioning of the electrode in the spinal cord. It may be performed under fluoroscopy, by first introducing contrast material to the subarachnoid space to visualize the upper and lower margins of the subarachnoid space, as well as the ligamentum dentatum. Recently several experts have come to prefer the CT-guided technique. Percutaneous cordotomy is indicated for strictly unilateral pain of malignant origin. It is contraindicated in bilateral pain, pain extending to levels cranial to C5, if the patient has a life expectancy more than one year, in patients with poor lung function, and in vertebral and epidural metastasis. There are very serious complications of percutaneous cordotomy. There is risk of motor loss if the lesion has been made too close to the pyramidal tract. Paraplegia may also develop. Transient urinary retention may develop for the first 48 hours following the procedure. Ondine syndrome, which means that the patient can breathe voluntarily but that respiration stops when the patient falls asleep may develop. Dysesthesia is the most unpleasant complication, that the patient defines an unpleasant sensation in the originally painful side of the body. This usually develops after several months. Percutaneous cordotomy is the most dangerous of all percutaneous neuroablative techniques. It should be performed only by very well experienced experts.

b. Percutaneus radiofrequency lesioning of the trigeminal ganglion. Generally, neurolysis of the Gasserian ganglion is used for the treatment of cancer pain related to the trigeminal nerve. However, radiofrequency lesioning is less risky than neurolysis. If phenol or glycerol is used, the solution may spread to the brain stem resulting in serious side effects, like nausea and vomiting for several days. Lesioning of the nerve is more precise with thermocoagulation. In cancer pain generally, all three branches of the trigeminal nerve are affected. Thus all branches should be thermocoagulated. The same approach as for the neurolysis is used. The patient should be able to respond to sensorial stimulation prior to lesioning of the nerve. Sensorial stimulation at 50 Hz is applied to find the branches of the nerve. Then the patient is heavily sedated and all three branches are lesioned. The complications are the same as with neurolysis.

c. Percutaneous dorsal root ganglion rhizotomy. Only after a successful diagnostic block should a partial rhizotomy of the dorsal ganglion be attempted. In the past, neurolytic agents were used but now they are used infrequently. One of the biggest concerns is damage to the nerve root while positioning the needle and radiofrequency lesioning. Thus it should be only considered when other techniques are not effective.

d. Lumbar and thoracic sympathetic radiofrequency lesioning. Lumbar and thoracic sympathetic radiofrequency is infrequently used for cancer pain treatment. Generally, neurolytic agents are used if the patient has sympathetically maintained pain, generally due to chemotherapy or radiotherapy.

Neuromodulation

In 1979 Wang first demonstrated that intrathecal bolus injections of morphine produced pain relief in cancer patients [45]. Yaksh and Rudy [46] documented the physiologic basis of the pain relief produced by the intraspinal administration of opioids as the modulation of inhibitory mechanisms occurring at the spinal cord. Since the introduction of spinal opioids, techniques and delivery systems have been developed for catheter applications. The two intraspinal routes commonly used are the epidural and the intrathecal. The administration of spinal opioids by drug delivery systems has several potential advantages; with very low doses of opioids adequate analgesia is maintained and the duration of analgesia is increased. Also, when the spinal route for administration is used, potential side effects as seen with oral or parenteral opioids are greatly reduced. The sedation due to opioids is less, so patients may exhibit a more alert and manageable status. A careful clinical evaluation and analysis of the pain is necessary before selecting the route of administration. This is also important regarding the development of complications, several of which can arise due to the wrong choice of route or system. During patient selection, the general and mental status, life expectancy, nature and origin of pain, skin over the

implantation area, patient' s environment and support system should be considered. The success of spinal opioid delivery depends mainly on proper patient selection.

Spinal drug delivery systems should be used as follows:

- when the oral route or other less invasive methods are excessive and inadequate;
- when intraspinal analgesia will sustain better pain relief and quality of life than other methods;
- when the patient' s general and psychological status is stable and favorable;
- when the drug delivery system is cost-effective.

Contraindications for intraspinal analgesia are low platelet count, blood coagulation disorders, local infection, psychological abnormalities that interfere with the pain assessment such as metabolic encephalopathy, pre-existing structural abnormalities and neurodegenerative disorders and behavioral abnormalities such as drug dependence, psychiatric disorders and use of pain for more medication, attention seeking or punishing caregivers.

The life expectancy of the patient is very important when selecting the appropriate system. For a patient with short life expectancy sophisticated programmable pumps are not appropriate. Catheters or access ports will be adequate. Pumps should be considered for a patient with a life expectancy of months to years. Many factors determine the clinical efficacy of spinal opioid delivery:

- the patient' s characteristics, including life expectancy, the origin of the pain, age, weight, spinal canal;
- route used, intrathecal or epidural;
- physical and chemical properties of the drugs used;
- injection technique, bolus or continuous infusion;
- characteristics of the delivery system used, internal or external;
- cost of the system.

Not all pain responds to spinal opioids. The route of administration and choice of drugs differ according to the response to opioids. Neuropathic pain, incident pain as observed on weight bearing, bone pain and pressure sore pain are all unlikely to respond to opioids alone. However no patient should lightly be called opioid resistant. Many patients with neuropathic pain respond to intraspinal opioids. Also there is no correlation between specific pain source and the degree of pain relief. A complete assessment of the spinal canal is mandatory. A space occupying lesion in the epidural space or compression of the spinal cord or nerves may be seen. The patient' s and the caregiver' s ability to cope with the equipment and perform tasks associated with drug administration should be considered.

Intraspinal analgesia may be accomplished either by epidural or by intrathecal route. The potential advantages of the epidural route are placement at the dermatomal level, no risk of spinal fluid leakage and related spinal headache. There is greater flexibility for the preference of drugs, so that drugs other than opioids can be selected, either together or alone to potentiate the analgesia. However the number of catheter dysfunctions is much higher in the epidural space than in the intrathecal space. In quite a number of patients fibrosis develops in the epidural space around the tip of the catheter and may occlude the catheter. Epidural fibrosis develops generally within 2–3 months. Dose escalation, which may be considered as pseudotolerance, is caused by the dural thickening and fibrotic reactions in the epidural space that affects the dural kinetics. Burning pain on epidural injection is observed in a number of patients. Fibrosis, inflammation or infection in the epidural space may be the cause. This type of pain is sometimes so intractable that patients prefer the pain of their disease and desire removal of the system. Injection-related burning pain and fibrous tissue development are the main reasons for preferring the intrathecal route in patients whose pain responds to opioids. The advantages of intrathecal route are: less risk of catheter obstruction; no risk of fibrosis or injection-related burning pain; less risk of catheter migration; longer and stronger analgesia, and lower dose of opioids. Generally the intrathecal dose is 10% of the epidural dose. Complications due to the spinal delivery systems seem to be less in the intrathecal route. However, side effects including nausea, vomiting, and urine retention are more severe at the beginning with the intrathecal route. Originally only opioids were used with the intrathecal route, but now bupivacaine and other drugs are also administered. There are some disadvantages of intrathecal delivery. Cerebrospinal fluid leakage and postspinal headache may be seen. If a system inserted intrathecally has to be removed for any reason, a cerebrospinal fistula may develop. This is a rare complication that requires careful treatment.

Drugs used intraspinally

The ideal agent for intraspinal use should have a long duration effect, no or minimal side effects, no toxic effect on the spinal cord during long-term delivery, no pain on injection, and should have a compatibility with the available drug delivery system. Morphine is still the drug of first choice because of its long duration of action, excellent analgesia, accessibility and relatively

low cost. Several other agents, such as bupivacaine, clonidine, midazolam and droperidol are also used for intraspinal delivery. Several drug delivery systems are now in use. These may be categorized as follows:

- Percutaneously inserted epidural catheters.
- Subcutaneously tunneled epidural or intrathecal catheters.
- Implanted epidural or intrathecal catheters connected to access ports.
- Implanted intrathecal manual pumps.
- Implanted intrathecal or epidural infusion pumps.
- External pumps.

Percutaneous epidural catheters are generally used in acute intraoperative, postoperative and obstetric pain. They may also be used for the preimplantation trial period, to observe the efficacy of the method and the route of administration, and for patients with a life expectancy of days. However, prolonged use of a percutaneous catheter has been reported to be reliable and safe. If the percutaneous catheter is going to be used for a preimplantation trial, it should be inserted under fluoroscopy. It can be attached to an external infusion pump. It can easily be placed and removed, which is both an advantage and disadvantage. The subcutaneous epidural or intrathecal catheter has the advantages of easy placement in patients with poor general status and short life expectancy, less risk of infection than percutaneous catheters, ease of injection by a non-medical caregiver and attachment to an external pump. The disadvantages of subcutaneously tunneled epidural or intrathecal catheters are dislodgement or migration of the catheter, kinking or obstruction, infection, irritation of the skin by bandages and difficulty with skin cleaning. Totally implanted epidural or intrathecal catheters connected to access ports may be stable for longer periods and the risk of infection is less. However, they have the disadvantages of multiple punctures of the skin, kinking and obstruction of the catheter. Removal or replacement of the port system requires further surgery. Special needles are necessary for the puncture of the port and the number of injections possible through the port is limited. Totally implantable infusion pumps have the advantages of lower peak cerebrospinal fluid and plasma morphine levels than the mechanical pumps, which can be used only for bolus injection. These are stable for very long periods and can be used in patients with non-malignant pain. Implanted infusion pumps also vary widely from fixed rate to programmable pumps. Programmable pumps are more favorable for non-malignant patients, as they can be assessed easily. However, for cancer patients with limited life expectancy, they may be considered too expensive, although some studies claim that these are cost-effective, even in cancer patients after 3 months. An increasing number of externally portable infusion devices is available, ranging from a relatively inexpensive syringe driver with a simple on-demand system, to more expensive programmable devices containing exchangeable plastic reservoirs. The patient or caregiver should successfully manage external systems at home, including changing catheter dressings, changing medication reservoirs, operating the pump and monitoring side effects. These requirements may cause some difficulties during long-term delivery.

Side effects and complications of spinal drug delivery systems

We believe that the complications due to the system and the side effects of the opioids should be discussed separately. Side effects that develop with other routes of opioid administration may also be observed as side effects of spinal opioid delivery. They are either dose independent (these, which may occur irrespective of the opioid dose, include urinary retention, pruritus, perspiration and sedation) or dose dependent (such as nausea, emesis, dysphoria, euphoria and central depression, including major sedation, respiratory depression, hypotension and tachyphylaxis). Dose escalation does occur during long-term delivery. It is not appropriate to address every dose escalation as tolerance. True tolerance and pseudotolerance should be differentiated. In cancer pain there may be a continuous increase in nociceptive stimulus. Dose increase during long-term delivery may be due to disease progression, development of opioid-resistant pain during the time course, or changes in the epidural or subarachnoid space as dural thickening and fibrotic reactions. This is generally called pseudotolerance. In fact, various studies suggest that tolerance to the pharmacological effects of opioids other than analgesia develop; this selective tolerance is beneficial for the patient. If morphine tolerance develops, substances such as DADL, metenkephalin, β-endorphin, clonidine, labetalol, lysine acetylsalicylate, calcitonin, somatostatin, octreotide or droperidol may be used. Accidental overdose through the injection port may cause respiratory depression. Pruritus is a side effect observed only during intraspinal delivery. The incidence of nausea and vomiting is not as high in opioid-experienced patients as it is in opioid-naive ones. Generally these symptoms subside during the delivery. Urinary retention has been observed in 20–40% of the patients, especially in men. It occurs within the first 2 days, and intermittent bladder catheterization

may be necessary. These side effects are not generally a reason for ceasing the treatment. They generally subside within days. It has been suggested that the side effects and tolerance have been overemphasized.

Complications may be due to several factors independent of the choice of the system, route and application. Complications of the drug delivery systems may be categorized as time-related, related to the site of the catheter, related to parts of the system and rare complications. Time-related complications are either immediate or late. Immediate complications are bleeding at the site of surgery, hematoma along the course of the subcutaneous tunneling device, epidural hematoma, early infection, cerebrospinal fluid leakage, post-spinal headache, edema, pump pocket seroma, and improper placement of the system. Late complications are obstruction of the catheter, obstruction of the port or the pump, catheter kinking, catheter dislodgment, pump malfunction or failure, late infection, fibrosis and injection-related burning pain. Complications related to the site of the catheter are either epidural or intrathecal. Complications related to the epidural space are fibrosis in the epidural space, injection-related burning pain, epidural hematoma, epidural abscess and fibrous sheath formation around the catheter. Complications related to the intrathecal space are leakage of the cerebrospinal fluid, fistula of the dura, cerebrospinal hygroma, spinal headache and meningitis. Complications related to parts of the system are related to the catheter, to the port or to the pump. Complications related to the catheter are clot formation, kinking, curling, and knotting, misplacement, displacement, occlusion or migration of the catheter and removal difficulties. Complications related to the port or pump are obstruction of the port, leakage from the port membrane, mechanical pump failure, pump malfunction, disconnection of the catheter and seroma formation around the port or the pump. Rare complications are skin necrosis and skin reaction to the percutaneous or subcutaneously tunneled devices.

Some of the complications may be resolved without replacing the system. However, complications such as infection, occlusion or displacement of the catheter and port or pump malfunction have to be taken into consideration seriously. Infections related to the drug delivery systems mostly occur at the exit site of the catheter or where the port or pump is inserted. Superficial infections at the exit site occur in 6% of patients. Epidural abscess or meningitis is related to the space of insertion. Epidural infection or abscess formation may be due to hematogenous spread or extension of the superficial infection at the port site during injection. Meningitis is mostly observed when the catheter is inserted intrathecally. It has been shown in several studies that the incidence of infection if the catheter is inserted intrathecally is 4%, while it is approximately 9% for the epidural route. Occlusion of the system may be due to the port, pump, or catheter. The catheter may be occluded by clot, fibrosis around the tip of the catheter, foreign particles in the injected solution, or kinking. Dislodgment of the catheter is also an important problem. In patients with fully inserted systems, catheter dislodgement necessitates removal of the system. Although several measures can be taken, it is still a problem in drug delivery systems. When evaluated retrospectively, the frequency of dislodgement has been shown to be approximately 8%. Valve failure in manual pumps or pump malfunction in infusion pumps may also occur. In such cases the pump has to be replaced.

Future aspects

The appropriate use of spinal drug delivery systems should be based upon the principle of optimum benefit and minimal harm both for the patient and the health system as a whole. The analgesic ladder described by WHO may be effective in 90% of cancer pain patients, but it also means that there are still 10% of the patients needing other interventions for pain control. Developing algorithms and guidelines is crucially important for the appropriate use of interventional treatment of cancer pain.

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