Neuraxial (epidural and intrathecal) opioids for intractable pain

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Summary Points

1. Neuraxial opioids are considered for use in patients who have resistant intractable pain that fails to respond to other treatment options or pain that responds to analgesia but for which the doses required result in unacceptable side-effects.
2. Neuraxial opioids can be considered for both chronic non-malignant pain and chronic cancer-related pain.
3. Effectiveness in chronic non-malignant pain and cancer pain is exerted through the use of either single-agent drugs (opioids) or a combination of drugs: opioids, local anaesthetics and other drugs such as clonidine and ziconotide.
4. Complications of long-term continuous infusion therapy are related to the insertion process (haematoma), the mechanical device (both pump and catheter) and the long-term effects of the drugs.
5. Patients will require ongoing ambulatory monitoring and supportive care.

Keywords

Analgesics, opioid/administration and dosage, pain/drug therapy, analgesia, infusions spinal, injections epidural

There is an increasing evidence base for the use of neuraxial analgesia for chronic non-malignant pain (CNMP), cancer-related intractable pain and spasticity. Several drugs are available for use including opioids, local anaesthetics and adjuvant drugs such as clonidine and ziconotide. This review will focus mainly on the use of neuraxial opioids for CNMP and cancer-related pain; a brief description of the action of the other drugs will be provided but not discussed in full.

Patient selection

Neuraxial analgesia is considered for use in patients who have resistant intractable pain that fails to respond to other treatment options or pain that responds to analgesia but for which the doses required result in unacceptable side-effects. In rare circumstances it may be used for rapid, effective analgesia when there is limited time available for titration of oral or subcutaneous analgesia (e.g. end-of-life palliative care).

Exclusion criteria relate specifically to psychological and psychiatric illness, allergy and certain physiological conditions which may be relative or absolute contraindications. If a significant psychological disorder, personality disorder, addictive personality or frank psychiatric illness is detected during the assessment and history-taking process then the patient is not considered suitable. Other exclusion criteria include depression, senility, suspected pain behaviour, alcohol or opioid abuse and poor physical condition. True allergy to any of the proposed analgesic or adjuvant drugs will preclude their use. Absolute contraindications include coagulation defects, local sepsis at the proposed

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epidural or intrathecal injection site, unstable spinal fracture, spinal cord compression and raised intracranial pressure.¹ Relative contraindications will be assessed by the person undertaking the procedure with the patient and include co-morbid conditions, concomitant medication (anticoagulants, steroids) and lack of capacity to make an informed choice.¹ In addition, the life expectancy of the patient should be considered, particularly for cancer patients, so that the quality-of-life–benefit and the cost–benefit aspects can be assessed.

Other considerations prior to neuraxial therapy include the environment in which the patient will continue to be managed after insertion. This will depend on the type of device used to deliver the neuraxial analgesia (fully implantable system or external pump). The patient needs to be able to comply with ambulatory surveillance, and there should also be evidence of family/caregiver support to administer and monitor the therapy at home. In cancer patients, the use of neuraxial analgesia therapy devices may change their preferred place of death (necessitating hospital or hospice inpatient stay) if the support structure cannot be provided in the home.²

Anatomy and physiology

The spinal cord rests in a medium of cerebrospinal fluid (CSF) and is contained by a series of protective membranes, known as the meninges: the pia mater, arachnoid mater and dura mater.

The pia mater covers the spinal cord and the arachnoid mater lies closely adherent to the outer, tough, dura mater.³ The epidural space lies outside all three membranes. The contents of the epidural space include a rich venous plexus, spinal arterioles, lymphatics and extradural fat.² The intrathecal space lies between the arachnoid mater and pia mater and contains the CSF (Figure 1).⁴

The 31 pairs of spinal nerves pass out through the intervertebral foramina between each vertebra, and are composed of a posterior and anterior root.⁴ Specific skin surface areas are supplied/innervated by each of the spinal nerves and these areas are known as dermatomes.

Outside the dura mater is termed the epidural space. Epidural analgesia is the administration of analgesics into the epidural space.⁵ Analgesics can be given either as a single injection or as a continuous infusion via an indwelling catheter.

Intrathecal analgesia is the administration of analgesic drugs (as listed above) directly into the CSF in the intrathecal space.⁶ The intrathecal space may also be referred to as the subarachnoid space. Analgesic drugs given via this route are approximately 10 times as

potent as those given into the epidural space, so doses and volumes required are potentially much smaller.

In palliative cancer patients there are some specific anatomical considerations:⁷

- The tumour may narrow the exit foramina and reduce the flow of the injected solution.
- Vertebral metastases, spinal stenosis, loss of epidural fat in cachexia and epidural invasion by tumour may complicate administration of the drugs and drug distribution.
- Tumour-related obstruction to CSF circulation may compromise intrathecal drug delivery.
- If patients have impending cord compression from spinal disease, intrathecal or epidural injection can precipitate complete cord compression.

Evidence base for effectiveness in cancer pain and chronic non-malignant pain

Chronic non-malignant pain

Chronic or persistent non-malignant pain may be managed with neuraxial interventions. Clinical indications for intrathecal therapy in CNMP include neuropathy (post-herpetic neuralgia and peripheral neuropathy), mixed neuropathic–nociceptive pain, radicular pain from failed back syndrome and complex regional pain syndrome (CRPS). Patients selected for this form of analgesia must have a favourable psychosocial assessment, as discussed in the patient selection section, and a positive response to a screening trial.

The evidence supporting intrathecal opioids in CNMP is less robust than that for cancer pain. There are few randomised controlled trials (RCTs) for intrathecal drug delivery in CNMP, but there is supportive evidence from prospective open studies and retrospective case series reviews. Long-term outcomes of intrathecal opioid therapy were studied by Kumar et al.⁸ and Thimeneur et al.⁹ and both reported improvements in pain, mood and function from the baseline. Kumar et al.⁸ reported an average pain reduction after 6 months of 67.5% and at the last follow-up (range 13–49 months) of 57.5%. However, Thimeneur et al.⁹ also reported that although refractory pain improved with intrathecal therapy, overall pain and symptom severity remained high.

A multicentre retrospective study in France¹⁰ in CNMP analysed data from 19 patients receiving intrathecal morphine via implanted pumps. The patients reported high (90%) satisfaction and an analgesic effect of 67.8% with a visual analogue scale decrease of 49.2%. Physical activity improved but only

Figure 1. Gross anatomy of the spinal cord. Cox F (2009), *Perioperative Pain Management*, Wiley-Blackwell. Reproduced with permission.

26.3% of patients returned to their initial functional status. Raphael et al.,¹¹ in a prospective controlled study looking at short-term efficacy, demonstrated spinal morphine to be of use in CNMP patients in whom systemic morphine therapy had become intolerable.

The effectiveness of intrathecal pump systems was reported as a reduction in visual analogue scores from

7.6/10 to 3/10 over a variable period of up to 2 years; other indicators, such as quality of life, are also reported positively.¹² However, this was based on data from 53 studies, such as case reports or case series information, as no RCTs were available.

In all review and guideline publications a trial of either epidural or intrathecal analgesia is considered of

paramount importance. This will establish the likely effectiveness of the proposed intrathecal implantable system. It may also help to determine the best drug or drug combination. It does not predict the long-term outcome, however, and concerns remain on the long-term effects of intrathecal opioids, including tolerance, hyperalgesia, dependency and addiction.

Most studies evaluating intrathecal opioids in CNMP show a significant improvement in the short and medium term for both nociceptive and neuropathic pain, but pain is rarely eradicated and there are fewer long-term benefits on other parameters such as mood and functional capacity. Intrathecal therapy demonstrated a better improvement in patients with nociceptive pain than with neuropathic pain or deafferentation pain syndromes.¹³

Cancer pain

Neuraxial approaches are used in only a small percentage of cancer patients with refractory pain. Consequently, there is limited high-quality controlled study evidence available evaluating their effectiveness. The evidence for the use of epidural versus intrathecal routes is also limited. Systematic reviews tend to include studies for either route and the data are often presented as combined for both approaches under the umbrella term 'spinal' or 'intraspinal' analgesia.

A review undertaken on behalf of the European Palliative Care Research Collaborative (EPCRC) analysed analgesic efficacy and side-effects of spinal opioids in adult patients with cancer who had previously been treated with systemic opioids.¹⁴ The review concluded that there are few RCTs and that these are of low quality, generally due to small sample size, variable study design and methodological limitations thus producing weak evidence. They analysed the accumulated incidence data from the uncontrolled trials, and concluded that spinal opioid therapy may be effective for treating cancer pain that has not been adequately controlled by systemic treatment. These findings are similar to those reported in another systematic review by Myers et al.,¹⁵ who also identified unacceptable side-effects as a second clinical indication.

A review article comparing epidural, subarachnoid (intrathecal) and intracerebroventricular opioids in patients with pain due to cancer concluded that neuraxial opioid therapy is often effective for treating cancer patients with pain that has failed to respond to systemic treatment.¹⁶ This review of uncontrolled studies reported excellent or good pain relief in 87% of patients from epidural opioids and 84% of patients for intrathecal opioids.

A multicenter, multinational RCT of an intrathecal implantable drug delivery system (IDDS) supplemented

with comprehensive medical management (CMM) versus CMM alone concluded that IDDS improved clinical success in pain control, reduced pain scores, relieved most toxicity of pain-control drugs (depressed level of consciousness and fatigue) and was associated with increased survival for the duration of this 6-month trial (53.9% alive at 6 months compared with 37.2% in the CMM-only group).¹⁷

Both epidural and intrathecal analgesia have been shown to be effective in uncontrolled studies and case series reviews, but there are few studies that directly compare the two routes in the management of cancer pain. Data are scarce, making it difficult to recommend one route over the other. Individual patient assessment of analgesic requirement, the technique that is appropriate for the patient and local practice and training will guide this choice.¹⁸

Medicines used in epidural and intrathecal analgesia

The effectiveness of neuraxial medicines in cancer pain and CNMP is exerted through the use of either single-agent drugs or a combination of medicines: opioids, local anaesthetics and adjuvant medicines such as clonidine and ziconotide. This section will focus mainly on opioids and the evidence for their use in neuraxial analgesia. A short description of other drugs and their actions is also provided.

Opioids

Opioids given by the neuraxial routes have a significant analgesic effect due to the direct uptake of the opioid into the spinal cord and CSF. The opioids block the transmission of pain signals by binding at pre- and postsynaptic receptors in the spinal cord and also at brainstem sites (which they reach by cephalad CSF spread). The spinal cord is composed of white and grey matter surrounding a small central canal. White matter is made of approximately 80% lipids, attributable to the myelinated nerves that comprise the ascending and descending neuronal tracts for communication with the brain. Lipophilic opioids, such as fentanyl and sufentanil, preferentially move into the white matter. Grey matter is host to the spinal cord through neuronal axons and dendrites. The dorsal horn, rich with opioid receptors, is part of the grey matter. Hydrophilic opioids, such as morphine and hydromorphone, preferentially move into the grey matter. The presynaptic effects of opioids include a reduction in the nerve transmitters such as substance P and glutamate; postsynaptic effects induce the release of spinal adenosine.¹⁹

Several opioids, including morphine, diamorphine, hydromorphone, fentanyl, sufentanil and methadone,

have been administered by the neuraxial route to manage pain. Morphine remains the most studied of the opioids used and is recommended due to its stability, receptor affinity and extensive experience in clinical practice via this route.^{20,21} Neuraxial opioid dose varies considerably for the different opioids and individual patients. Factors involved in the effectiveness of neuraxial opioids are the lipophilicity of the drugs, which determines the onset, spread and duration of analgesia. Higher lipid-soluble drugs such as fentanyl and sufentanil are associated with a more rapid onset of analgesia and a shorter duration of action. They are more rapidly cleared from the CSF. Because of the shorter duration of action, these drugs are more effective when administered by continuous infusion. Hydrophilic drugs (which have a lower lipid solubility), such as morphine and hydromorphone, have a more prolonged half-life in the CSF and a delayed or slow onset of analgesic action, mainly due to the rostral migration of the drugs, and a longer duration of analgesia.¹⁸ Potencies of epidural opioids are inversely related to their lipophilicity. Epidural morphine is about 5–10 times more potent than intravenous morphine, whereas epidural doses of lipophilic opioids are only twice as potent as the intravenous administration of these drugs.

The choice of drug may be based on evidence of effectiveness, the practitioner's familiarity with a specific drug and local availability. Opioids delivered by both routes can show tolerance and may need dose escalation over time; side-effects and complication rates are variable, but even at lower doses patients can experience significant opioid-induced problems (pruritis, nausea and vomiting and urinary retention are cited as the most common).¹⁸

Local anaesthetics

Local anaesthetic drugs are often used in combination with opioids to improve the analgesic effectiveness of neuraxial analgesia and also to reduce the opioid requirement. Local anaesthetic drugs exert their effect by sodium channel blockade, inhibiting the action potential in the dorsal horn. However, they are not specific to pain transmission action potentials and can cause adverse effects, including sensory deficits, motor weakness/paresis, signs of autonomic dysfunction (orthostatic hypotension) and neurotoxicity.¹⁸ Alteration of the local anaesthetic drug concentration and/or a reduction in the infusion rate may reduce these effects.¹⁸ Intrathecal administration is delivered directly into the CSF and into the superficial spinal cord; epidural administration diffuses through the dura into the CSF, and thus has a slower onset of action.¹⁸

The most commonly used local anaesthetic drugs are the amide types, such as bupivacaine/levobupivacaine, lidocaine and ropivacaine.

Adjuvant drugs

Clonidine is a centrally acting α -2 agonist that modulates pain transmission by the depression of the release of neurotransmitters, and is used in conjunction with opioids for the treatment of neuropathic pain. An RCT of patients with advanced cancer pain demonstrated an improvement of 56% in patients with cancer-related neuropathic pain in the clonidine group compared with 5% in the placebo group.²²

Ziconotide is a calcium channel antagonist thought to produce its effect by blocking neurotransmitter release in the primary nociceptive afferent fibres.²⁰ Ziconotide may have a role in the treatment of cancer pain refractory to neuraxial treatment, but the evidence for this is limited, with only one study of cancer and patients with human immunodeficiency virus reporting a reduction in pain (53% of patients) but significant side-effects (dizziness and confusion) in 30% of the treatment group.²³

Mechanisms of drug delivery

Drugs can be delivered as a continuous infusion using either an external pump system or a fully implantable reservoir system. Both the epidural and intrathecal route can use an external infusion pump with a percutaneous catheter (see Figure 2), and this type of infusion device is more often utilised in palliative care. An external pump system is suitable for patients requiring therapy of less than 3–6 months' duration. In CNMP this is not suitable for long-term management and is only considered for a trial infusion before considering a fully implantable device.

A fully implantable reservoir system can be used for intrathecal infusions as the volume of drug required is much less than the epidural route, and therefore more suitable for these systems. The latter is more often used for chronic non-cancer pain management.²⁴

Intrathecal Drug Delivery Systems consist of an implantable pump and an intrathecal catheter. The pump is a round metal device that stores and automatically releases prescribed amounts of analgesia through the catheter directly into the intrathecal space. It has a refill port to enable the reservoir to be refilled with medication. An IDDS can deliver analgesia with either a fixed-rate or programmable delivery schedule. Fixed-rate machines cannot be controlled by the practitioner once implanted and the drug dose has to be altered by changing the medication concentration in the pump reservoir.

Figure 2. Bodyguard 545 epidural external infusion pump. Image sourced from www.cmemedical.co.uk/products/body-guard-545-epidural-infusion-pump/index.asp. Reproduced with the permission from CME Medical.

Figure 4. Example of placement of intrathecal drug delivery system pump. Images from wwwp.medtronic.com/UK/physicians/pain/idd_equipment.html. Reproduced with permission from Medtronic.

Figure 3. Implantable intrathecal drug delivery system. Images from www.medtronic.com/uk/physicians/pain/idd_equipment.html. Reproduced with permission from Medtronic.

An example of this type of pump is the Medtronic Isomed pump (Medtronic Limited). Programmable pumps allow for more complex schedules and changes to doses by use

of an external programmer, an external computer-type device that controls the pump's memory. Examples of this type of pump are the Synchromed II IDDS (Medtronic Limited), which is available with a 20-mL or 40-mL reservoir (see Figure 3).

Fixed-rate pumps are most appropriate for patients who experience stable pain that is not expected to change over time. Advantages of the programmable intrathecal pumps lie in their adaptability. Pain is dynamic and may change over time – progressing, decreasing or developing new pathology. The clinician can alter the dose of medication delivered to the patient without making any changes to the medication within the pump reservoir. The continuous infusion systems may also be programmed to allow the patient to deliver a bolus dose within preset controlled limits.

Surgical placement of an intrathecal catheter and pump system in a patient requires consideration of the location for the pump. Anatomically, the site that can accommodate the size of the pump is the lower quadrant of the left or right abdomen. In a small number of patients

where this is not feasible the pump may be implanted in the posterior flank, for example in obese patients where abdominal anchoring of the pump may be more difficult. Figure 4 shows an example of IDDS placement.

The choice of system should be based on the following considerations:

- expertise at each institution and practical consideration for ongoing care;
- expected length of treatment; and
- quality-of-life–benefit versus cost–benefit.

Jones and Rawlings²⁵ reviewed the causes of implanted intrathecal pump system failure. These included:

- change in performance or failure of the catheter (e.g. microfracture, pinhole leak, disconnection, breakage, migration, partial occlusion, tip fibrosis/granuloma, inflammatory mass);
- unexpected battery depletion;
- component or motor failure; and
- catheter access port failure.

External pumps are prone to similar problems.

Complications relating to the insertion process and long-term therapy

Thromboprophylaxis

Haematomas can arise as a result of trauma to an epidural blood vessel during catheter insertion or removal. Although the incidence of this is extremely rare, care must be taken, particularly in those patients who are receiving thromboprophylaxis such as anticoagulants, antifibrinolytics and antiplatelet medications. Initial symptoms, such as back pain and tenderness, must be investigated immediately. As the haematoma expands to compress the nerve roots or the spinal cord, the patient develops sensory–motor weakness.⁴ The risk of developing a haematoma is greatest during the insertion and removal procedures, but should be considered at other times if the patient develops symptoms.

If a patient with an external pump and catheter system is fully anticoagulated, a clotting profile must be performed and advice sought from the anaesthetists as to when the epidural/intrathecal catheter can be removed. The final decision to perform neuraxial techniques in a fully anticoagulated patient has to be taken after careful assessment of individual risks and benefits.

There are recommended guidelines for patients who are receiving a prophylactic anticoagulant.^{26–28} In addition, hospitals should have local evidence-based guidelines to follow.²⁹

If low-dose low-molecular-weight heparin is given once daily, the epidural/intrathecal catheter should be removed at least 12 hours after the last injection and several hours prior to the next dose. The timing will depend on the manufacturer's recommended guidelines; for example, for Tinzaparin (Leo Laboratories Ltd) it is recommended that epidural or spinal catheters are removed a minimum of 4 hours before the next dose.

For unfractionated heparin, the epidural/intrathecal catheter should be removed following local guidelines and the advice of the anaesthetist or pain management team. This will involve checking the patient's clotting results and suspending the heparin infusion for a period of time before and after the removal of the catheter.

Clopidogrel is a thienopyridine derivative that exerts its antiplatelet effect by binding irreversibly to the adenosine diphosphate receptors on platelets. It is increasingly used as secondary prevention of vascular events in patients with established atherosclerotic disease. In patients treated with clopidogrel the manufacturer's recommendation is to stop clopidogrel 7–10 days before surgery or neuraxial blockade.

Aspirin (acetylsalicylic acid) also has an antiplatelet effect by inhibiting the production of thromboxane. It is used at low doses to prevent myocardial infarction and stroke in people at high risk of developing blood clots. In patients treated with aspirin it is recommended it is stopped 7 days before major surgery or neuraxial blockade.

There is an increased risk of neuraxial haematoma in patients on warfarin (a coumarin derivative anticoagulant). It is recommended that it is stopped and replaced with a different form of anticoagulation, such as low-dose low-molecular-weight heparin. Expert haematological advice may be sought.

Infection

Infection around the catheter, epidural abscess and meningitis are serious risks. Infections can occur at the entry site, in deeper tissues along the course of the tunnelled epidural catheter and within the epidural space. Infection can be introduced into the epidural space from an exogenous source, such as contaminated drugs or equipment, or an endogenous source, i.e. from the patient, leading to bacteraemia, which seeds to the insertion or catheter tip.³⁰ The catheter may also act as a wick through which the infection tracks down from the entry site on the skin to the epidural/intrathecal space. This is the rationale for tunnelling the epidural/intrathecal catheter during the insertion process to minimise the risk of infection in long-term therapy.

Rathmell et al.³¹ reported the risk of infection (entry-site infection and deep infections along the subcutaneous catheter track) as 15% in patients receiving epidural therapy for more than 70 days, whereas the risk for infection extending to the epidural space is about 1%.

Meningitis incidence after intrathecal pump implantation is reported as 3%.¹² Epidural placement has been suggested to reduce the incidence of meningitis, but infection rates have been shown to be similar.³² Follett et al.³³ analysed four prospective trials using various implanted drug delivery systems. They reported a total of 36 infections involving 35 separate patients in a total of 700 patients – an overall infection rate of 5%. The analysis reported a infection rate at the pump pocket of 57–80% at the lumbar site in 13–33% of patients and meningitis in 0–14% of patients. The aggregate total period at risk for the occurrence and detection of infection in those studies was 7620 device months. However, the authors acknowledge the limitations in the different data collection periods and that the investigation of device-related infections was not specifically in the study designs. A systematic review of intrathecal catheters and external pumps in a total of 821 patients (from 10 articles reviewed) by Aprili et al.³⁴ reports 20 catheter-related infections of which 10 were superficial and 10 were deep. The authors reported that every 71st patient had a deep infection after an average catheter duration of 54 days.

Effects of long-term therapy

Problems can occur at the catheter tip with both routes. Hicks and Simpson⁷ report that during the first 20 days it is more likely that catheters placed in the epidural space will become blocked by fibrosis. This may lead to loss of analgesia and local pain during the epidural infusion.

However, in long-term therapy with intrathecal catheters, granulomas/inflammatory masses may develop due to the use of multiple drugs or concentrated doses of opioids.⁷ The infusion of opioids leads to the organised collection of inflammatory cells in the intrathecal space adjacent to the catheter tip. These inflammatory masses consist of granulation tissue and are termed granulomas.³⁵ In large animal preclinical studies these masses, arising from the meninges and leading to spinal cord compression, reflect a dose-dependent effect of the opioid leading to the intrathecal accumulation of these inflammatory cells.³⁵ The incidence for intrathecal catheters is estimated as 0.5% for a patient.²⁰ This may be more of an issue in patients with chronic non-cancer pain, owing to their longer life expectancy, longer exposure to intrathecal drugs and

higher daily doses than patients with cancer pain.³⁶ Granuloma formation is a serious complication that can potentially cause spinal cord compression and neurological dysfunction, such as urinary incontinence, and paralysis distal to the mass.³⁷ Granuloma formation therefore appears to be a result of a combination of factors: drug concentration, daily dose and duration of therapy (although some were noted within 1 month of therapy).³⁸

Pharmacological side-effects of opioids reported with intrathecal therapy include:¹²

- nausea and vomiting (25%);
- sedation and somnolence (17%);
- urinary retention (19%);
- pruritis (17%);
- myoclonic activity (18%); and
- respiratory depression (3%).

In patients with cancer who are receiving long-term intrathecal morphine infusions, Aprili et al.³⁴ found an overall infection risk rate of 1.4% for deep infections (one infection after 4716 catheter days), 2.3% for superficial infections (one infection after 2427 catheter days) and 2.9% for any catheter-related infection. Patients with implanted pumps had fewer deep infections per time unit. A 0.9% risk of bleeding or epidural haematoma with serious neurological consequences seemed to be less common, and no catheter-related deaths were found.³⁴

Although neuraxial opioid doses are lower than those required for other routes of administration, theoretically long-term neuraxial blockade can risk opioid-induced androgen deficiency in men.³⁹ This may result in symptoms such as fatigue, lowered libido, erectile dysfunction and weight gain. The hypothalamic–pituitary axis should be monitored in any patient who is receiving long-term opioids.

Legal and professional issues

There should be a formal induction course and regular updates for doctors, nurses, theatre and recovery staff who will be responsible for supervising patients receiving continuous epidural analgesia.²⁹ A clearly designated consultant anaesthetist will be responsible for the immediate supervision of patients receiving epidural or intrathecal infusions. The National Patient Safety Agency⁴⁰ recommends that in addition to routine training and regular updates, additional training should occur when changes are made to protocols, medicine products or medical devices. Routine training should include a programme to help healthcare staff gain competence and confidence in using infusion devices used to deliver epidural or intrathecal

analgesia. Clear guidelines and policies should be developed by all stakeholders involved in the ongoing care for the patient and the infusion. There should be clear agreement between clinicians and nursing staff on who is responsible for which aspects of care.⁴¹ Other key healthcare professionals involved in the delivery and care of neuraxial opioid analgesia are ward-based healthcare professionals, community and hospice staff and pharmacists.

Availability of neuraxial interventions may be compromised by the lack of anaesthetic and pain specialist input into patients with advanced disease (more likely to have more severe and refractory pain) under palliative care. A postal questionnaire survey of UK pain specialists (62% response rate) demonstrates evidence of under-referral of cancer patients for advanced pain management procedures; joint consulting arrangements between pain specialists and palliative medicine were rare, and only 25% of anaesthetists' job plans had time allocated for palliative medicine referrals.⁴² More integration of pain services with palliative care would increase the availability of these beneficial interventions.

Patient and carer experience

Hawley et al.⁴¹ undertook a qualitative study of the impact of implanted intrathecal pumps for intractable cancer-related pain. A series of three semi-structured interviews were undertaken with six patients who also completed daily written questionnaires on pain and symptom management and perceived quality of life. Nurses and physicians directly involved in the care of the patients were also interviewed to establish the impact that caring for these patients had on the staff in a palliative care unit. Patients reported a significant reduction in their pain with a profound positive effect on quality of life, even though their hopes and expectations were not always fully met. Patients also expressed high anxiety about being dependent on the device and a small number of highly skilled individuals. The palliative care unit staff revealed a significant impact on the 'culture' of the unit. Clear communication regarding the rationale for the infusion and ongoing education regarding infusion management were very important. Patients also required ongoing palliative care afterwards to address the emotional, psychosocial, spiritual and intellectual aspects of their pain that are not managed by the intrathecal infusion.

Ongoing care and support

If the patient is to go home with an epidural/intrathecal infusion using an external pump, discharge planning

should begin prior to insertion of the spinal catheter. Primary care teams, patients and their families will need to be trained and supplied with the appropriate equipment, drugs, catheter filters, and information about the infusion pump, how to identify a catheter-related or systemic infection and what to do if pain occurs or complications arise. For the implanted reservoir systems ambulatory surveillance arrangements are required to refill the reservoir within the system, adjust infusion rates or bolus doses in response to changes in pain and analgesic effect, check the site and monitor for evidence of infection. Clear instructions on how to manage the incidence of analgesic failure are also required.

Contact numbers must be available in case specialist advice is needed.

Conclusion

Neuraxial analgesia is a valuable analgesic approach in patients with cancer or CNMP refractory to systemic analgesic therapy or with severe side-effects that prevent the escalation of analgesia. Drug side-effects, procedure-related complications and mechanical device problems may occur but often can be managed without the need to remove the catheter or the implanted device. Patients will require ongoing ambulatory monitoring and supportive care if discharged, and this requires a team approach to care. In patients with cancer the use of neuraxial analgesia may change the patient's place of death and this needs to be discussed with the patient. More controlled studies are required to compare the different routes and different analgesic drugs available.

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Conflict of interest

The authors declare that they do not have any conflict of interest.

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Multiple-choice questions

More than one answer may be correct. Select all that apply.

1. **Neuraxial opioid analgesia is considered for use when:**
 - a) patients find it difficult or are unwilling to take oral medication
 - b) pain fails to respond to other treatment options
 - c) pain responds to other treatment options but the patient experiences unacceptable side effects
 - d) patients require short term relief of acute pain not achieved by other methods
 - e) there is limited time to titrate oral or subcutaneous analgesia in end-of-life palliative care
2. **Exclusion criteria for neuraxial analgesia include:**
 - a) coagulation abnormalities
 - b) obesity

- c) significant psychological or psychiatric illness
- d) true allergy to proposed medication
- e) lack of capacity to make an informed choice

3. **Patients with chronic non-malignant pain (CNMP) who may be considered for intrathecal therapy may have:**

- a) radicular pain from failed back surgery
- b) chronic visceral pain
- c) neuropathic pain such as peripheral neuropathy
- d) complex regional pain syndrome
- e) chronic ischaemic pain

4. **Neuraxial opioids:**

- a) exert their effect on NMDA receptors
- b) exert their effect due to direct uptake into the spinal cord and cerebrospinal fluid (CSF)
- c) exert their effect by an anti-inflammatory action
- d) block transmission of pain signals by binding at presynaptic and postsynaptic receptors in the spinal cord and also at the brainstem sites
- e) presynaptic effects of opioids include a reduction in the nerve transmitters such as substance P and glutamate

5. **Intrathecal drug delivery systems:**

- a) are always a fully implantable system
- b) can be a percutaneous catheter with an external pump
- c) can be a fully implanted pump with a reservoir system that can be refilled
- d) can be fixed rate or programmable
- e) can allow the patient to deliver a bolus dose within pre-set controlled limits.

6. **Causes of implanted intrathecal pump system failure include:**

- a) pump alarming and causing distress to the patient
- b) change in performance or failure of the catheter
- c) component or motor failure
- d) catheter access port failure
- e) unexpected battery depletion

Answers

- 1: b, c, e; 2: a, c, d, e; 3: a, c, d; 4: b, d, e; 5: b, c, d, e; 6: b, c, d, e.