19: SPINAL ANALGESIA

Indications

Spinal analgesia is commonly used for obstetric or peri-operative pain relief. In the case of cancer patients receiving specialist palliative care, about 2–4% proceed to spinal analgesia because of unsatisfactory pain relief with more standard systemic analgesia.[1–7]

Typical indications include:

- systemic opioid intolerance
- pathological fracture in a patient close to death
- refractory neuropathic pain (e.g. visceral neuropathic pain, lumbosacral plexopathy).

Spinal analgesia is effective in $\geqslant$50% of patients.[3,4,8–13] Good communication between palliative, pain and primary care teams is essential.

Contra-indications: Uncorrected coagulopathy, systemic or local infection, raised intracranial pressure.

Circumstances in which extra caution should be used include:

- spinal deformity
- incipient spinal cord compression
- myelosuppressive chemotherapy.

Route, placement and delivery device considerations

Analgesics are delivered to the intrathecal (IT) or epidural (ED) space via a small indwelling catheter placed by an anesthetist. The tube is generally tunnelled subcutaneously to emerge at a distant site, e.g. the supraclavicular fossa or flank, to reduce the risk of displacement and infection. This can be done using local anesthesia$\pm$sedation, but general anesthesia is more comfortable for the patient.[4] The preferred route and delivery device are influenced by local experience and the likely duration of use (Table 19.1). Devices vary in allowing fixed vs. variable delivery rates, patient-controlled boluses, and cost.

Table 19.1 Preferred route and delivery device

Likely duration of use	*Route and device*	*Comments*
$\leqslant$3 weeks	External ED device (re-usable)	Fewer initial complications than IT (8% vs. 25%); less headache from CSF leakage (Crul and Delhaas 1991)[14]
3 weeks–3 months	External IT device (re-usable)	Fewer later complications than ED (5% vs. 55%); less catheter occlusion[14]
$\geqslant$3 months	Implantable IT device	More expensive initially, lower running costs; more cost–effective long-term[15]

Drugs delivered to the ED space diffuse through the meninges to reach the spinal cord and adjacent nerve roots. The level of the spinal cord at which the catheter is sited influences the area over which maximal analgesia is obtained. Migration or misplacement of ED catheters into the IT space (a rare event) will deliver an excessive dose resulting in significant toxicity, and may cause death secondary to respiratory arrest, unless recognized and treated urgently.

The IT route delivers drugs directly to the cerebrospinal fluid (CSF). Compared with the ED route, lower doses are required, thereby permitting the use of smaller devices and/or reducing the frequency of refilling (see below). IT administration generally provides better pain relief than

the ED route.[3,14,16,17] IT is also the preferred route for long-term spinal analgesia, i.e. >3 weeks.[3] The area of analgesia is less dependent on the site of the catheter because drugs in the CSF automatically diffuse rostrally.

Although the same delivery devices can theoretically be used for SC, IV and spinal infusion, for maximum safety it is best to use a device specifically designed for spinal delivery.[5] Distinct pumps and connectors will reduce the potential for confusion in a patient receiving concurrent spinal and SC/IV infusions.[3] However, such recommendations must be weighed against the considerable advantage of staff using a delivery device with which they are familiar from frequent SC/IV use.

Clinical services caring for patients receiving spinal analgesia require clear procedures to be in place to minimize risk at all stages of treatment. An added problem is maintaining staff competence where such approaches are required infrequently: clear clinical guidelines and 'refresher' training can be helpful.

Choice of drugs

Morphine, **bupivacaine** and **clonidine** are the most commonly used (see below). In cancer pain, particularly neuropathic pain, opioids are generally combined with **bupivacaine** (or alternative local anesthetic) from the outset, and **clonidine** added subsequently. **Hydromorphone** is an alternative where morphine is poorly tolerated.[3,5,6,18,19]

Opioids

Spinally administered opioids act locally and/or in the brain stem. The latter occurs through CSF diffusion and/or systemic redistribution. The advantages of spinal administration are greatest with hydrophilic opioids, e.g. **morphine** and **hydromorphone** which penetrate the spine effectively and are slowly redistributed. **Fentanyl** and other hydrophobic opioids are rapidly redistributed: their spinal administration thus has fewer advantages over their systemic use,[20] although the lower risk of catheter tip granuloma is an advantage in specific patients (see below).

There is considerable uncertainty about dose equivalences between routes.[3,21,22] However, the following conversion factors for **morphine** can be used when deciding the initial spinal dose and an appropriate p.r.n. dose:

- SC → ED, divide SC 24h dose by 10
- SC → IT, divide SC 24h dose by 100.

Thus, **morphine** 300mg/24h SC is replaced by 3mg/24h IT. The appropriate p.r.n. dose of SC **morphine** for this will be (as usual) 1/10–1/6 of the SC equivalent of the IT dose, i.e. 30–50mg SC.[3,19,22]

Maximum opioid concentrations and daily doses have been proposed to minimize the risk of catheter tip granuloma formation (Table 19.2).[6] These are less applicable if short-term use is anticipated, although granulomas have been reported after just 27 days.[23]

Table 19.2 Recommended maximum long-term IT drug concentrations and doses[6]

Drug	*Maximum concentration (mg/mL)*	*Maximum daily dose (mg)*
Morphine	20	15
Hydromorphone	10	4
Bupivacaine	40	30
Clonidine	2	1

Local anesthetic

Bupivacaine is the most widely used local anesthetic for spinal analgesia.[3,5,6,19] Inherent antimicrobial properties may decrease the probability of infection.[19] Undesirable effects include dose-dependent motor and sensory impairment, affecting 4–13% and ⩽7% of patients respectively, generally at doses >15mg/day.[3,5,8–10,12]

Ropivacaine is used at some centres.[24] This has similar efficacy and tolerability to **bupivacaine**.[25,26]

Clonidine

Clonidine 15–30microgram/24h (IT) or 150–300microgram/24h (ED) is generally given with an opioid and a local anesthetic. Benefit is seen particularly in neuropathic pain. Undesirable effects

include dose-dependent hypotension and bradycardia (see p.000).[3,5,19] Abrupt cessation (e.g. because of pump failure) may cause severe rebound hypertension. Administer oral **clonidine** whilst seeking specialist advice.[6]

Other drugs

Baclofen is used for pain related to spasticity. A life-threatening withdrawal syndrome can occur if IT baclofen is abruptly discontinued (Box 19.A).

Ketamine's spinal use is associated with histological changes of uncertain significance within the cord.[6,27–30]

The spinal use of various other drugs is described or under investigation, including **adenosine**, **gabapentin**, **midazolam**, **ketorolac**, **ziconotide** (not available in Canada) and **octreotide**.[6,31]

Box 19.A IT baclofen withdrawal syndrome[32]

Cause
Sudden cessation of IT baclofen (e.g. delivery device failure).
Reported with a wide range of doses (50–1500microgram/24h).

Clinical features
Symptoms evolve over 1–3 days:
- tachycardia, hypotension or labile blood pressure
- fever
- dysphoria and malaise → unconsciousness → seizures
- spasticity and rigidity → rhabdomyolysis → acute renal failure
- pruritus, paresthesia
- priapism.

Differential diagnosis
Other drug-related cardiovascular-neuromuscular syndromes:
- Neuroleptic (antipsychotic) malignant syndrome (see p.000)
- Malignant hyperpyrexia
- Serotonin toxicity (see p.000).

Autonomic dysreflexia.
Sepsis.
Undesirable effects of spinal medication (e.g. hypotension caused by clonidine or bupivacaine).

Management
Restart the IT baclofen infusion as soon as possible.
Cardiopulmonary support as indicated.
High-dose baclofen PO or by enteral feeding tube (up to 120mg/24h).
If necessary, give a benzodiazepine by CSCI/CIVI (e.g. midazolam) titrated to achieve muscle relaxation, normothermia, stabilization of blood pressure and cessation of seizures.[a]

a. Dantrolene is reported to improve spasticity but not other symptoms. Its use in this setting has been superseded by the benzodiazepines.

Drug compatibility

Unlike acute pain, with chronic intractable pain, single drug spinal analgesia is often inadequate. Combinations of **morphine** with **bupivacaine** ± **clonidine** are widely used, particularly with external devices.[8–10,16] Long-term compatibility data for drug combinations in both external devices (at room temperature) and implanted pump reservoirs (at body temperature) are limited.[5] Several factors can affect drug stability and compatibility (see Box 18.C, p.000). It is important to ascertain if the compatibility data are relevant to the situation of intended use, and confirm what is the appropriate diluent, i.e. discuss with a pharmacist.

Compatibility data at room temperature

There are compatibility data on the following combinations at room temperature:

- **morphine sulfate** with **bupivacaine** or **clonidine** 2 months[33,34]
- **morphine sulfate** with **ropivacaine** 1 month[26]
- **hydromorphone** with **bupivacaine** 3 days[35]
- **fentanyl** with **ropivacaine**[26]
- **sufentanil** with **ropivacaine**[26]
- **clonidine** with **bupivacaine** 2 weeks[36]
- **clonidine** with **ropivacaine** 1 month.[26]

Compatibility data at body temperature

There are compatibility data on the following combinations at body temperature:

- **morphine sulfate** with **clonidine** ± **bupivacaine** ⩽3 months in a SynchroMed pump[37,38]
- **hydromorphone** 4 months in a SynchroMed pump[39]
- **clonidine** with **hydromorphone** 1.5 months (only stability of **clonidine** evaluated).[40]

Ideally, delivery devices with mixtures to be administered over >24h should be prepared in a sterile environment, e.g. a licensed pharmacy unit, and not on the ward/by the bedside. Drugs should be preservative-free.[5]

Undesirable effects and complications of spinal analgesia

MRI can cause implantable pumps to malfunction. Inactivation or reservoir and catheter drainage may be required: seek manufacturer's advice.

These can relate to:[41]

- the drug(s) (Table 19.3)
- medical complications, e.g. bleeding, infection (Table 19.4)
- the delivery system (Table 19.4).

All health professionals caring for patients with spinal analgesia should, as a minimum, be aware of the most serious undesirable effects and complications, and their management (Box 19.B). Respiratory failure can result from central depression of respiratory drive (opioids) or impaired motor output to the respiratory muscles at the spinal level (**bupivacaine**). Rate of onset varies: systemic redistribution of the spinally administered opioid causes respiratory depression within minutes or hours, whereas diffusion through the CSF causes a delayed onset, occurring after 6–48h. Both **bupivacaine** and **clonidine** cause hypotension, the latter also causing bradycardia.

The transient undesirable effects seen when commencing systemic opioids are also seen with spinal opioids (Box 19.C).[19,41] Clinical areas should have access to resuscitation equipment including IV fluids, **naloxone** and **ephedrine**. Before insertion of a spinal catheter, baseline blood tests will help to evaluate fitness and exclude, for example, a coagulopathy. A neurological and cardiopulmonary examination provides an essential baseline for future reference if a problem arises.

Suspected infection

In addition to the usual infective and neoplastic causes of fever in palliative care, spinal catheter-related infections can occur (often with coagulase-positive or -negative *Staphylococci*).

Exit site infection: transparent dressings allow the early identification of exit site erythema. Systemic and topical antibacterials should be started promptly; this reduces the incidence of deeper infection/meningitis.[3] However, prophylactic antibacterials should not be routinely used.

ED abscesses: present with fever, escalating pain (this is invariable; either the original pain and/or back pain at the ED site), and new neurological impairment (80%).[12] Evaluation includes blood cultures, aspiration of fluid from the spinal catheter for microscopy and culture, neurological examination, identification of other potential sources of fever and MRI (see warning about MRI above). Seek early advice from a microbiologist and spinal or neurosurgeon. The risk increases with time. Distant non-healing wounds may be a risk factor.[4]

Meningitis: presents with fever and/or meningeal irritation (neck stiffness, stretch signs). Evaluation includes blood and line microscopy and cultures, white cell count, neurological examination, and identification of other potential sources of fever. Consider also MRI, particularly if new neurological impairment is present (see warning about MRI above). Spinal catheters need

Table 19.3 Drug-related undesirable effects

Drug	*Undesirable effect*	*Frequency (%)*	*Comment*
Early onset and/or after titration			
Withdrawal of systemic opioids	Diarrhea and intestinal colic		Partly avoidable if laxatives stopped and then retitrated after change to spinal route
Opioids	Nausea and vomiting	33[3,12,42,43]	
Opioids	Pruritus	15	Less likely if already taking opioids[13,42,43]
Bupivacaine	Motor or sensory disturbance; dose-dependent	4–13	Persistent motor impairment, overall frequency in palliative care series[3,9,12]
Opioids, bupivacaine	Urinary retention	8–43[3,8,43]	
Opioids, bupivacaine	Respiratory depression	0.1–2[3,44]	
Bupivacaine, clonidine	Cardiovascular compromise	5–20	Symptomatic hypotension; clonidine also causes bradycardia[3]
Late onset (also see p.000)			
Opioids[a]	Catheter tip granulomas	0.1[23]	MRI screening revealed granulomas in 3% of patients with long-term IT infusions. Eighty percent were asymptomatic. Twenty percent had mild symptoms of unrecognized significance[45]
Opioids	Decreased libido, ±disturbed menstruation	70–95[46]	Endocrine effect seen with IT opioids if given > 1 year but may occur sooner. In patients with a long prognosis, measure testosterone and LH at baseline and annually in men, and estradiol, progesterone, LH and FSH in women[5]
Opioids	Hypocorticalism or growth hormone deficiency	15[46]	
Opioids	Edema	6–18[5,11,47]	
Opioids	Immuno-modulation	Frequency uncertain[48]	Significance uncertain. May be more pronounced with systemic opioids

a. Less commonly described with non-opioids

not be automatically removed and allow a means of obtaining CSF for culture.[3] Mild meningeal irritation can be a normal phenomenon post-procedure, and patients can be safely observed while awaiting CSF cultures if they are systemically well and the above reveal no evidence of infection.[64] A prolonged operation time when placing the catheter is a risk factor for serious catheter-related infection.[65]

New neurological impairment

It can be difficult to distinguish between new neurological signs and symptoms caused by complications of spinal analgesia vs. those caused by the disease itself (Box 19.D). Estimates of complication rates vary greatly, and often predominantly relate to peri-operative/obstetric spinal anaesthesia.[66] Disease-related neurological impairment is common: spinal cord compression occurs in ⩽6% of patients receiving spinal analgesia.[3] ED metastases are present in ⩽70% of patients with refractory cancer pain. They are associated with motor impairment, and higher **morphine** and **bupivacaine** dose requirements (although not higher pain scores). Those with spinal canal stenosis (58%) also have higher IT insertion complication rates.[67]

Catheter tip granulomas present with occlusion (worsening of the original pain) or local mass effects (vertebral pain, spinal cord or cauda equina compression). The risk increases with time.

Table 19.4 Non-drug complications of spinal analgesia

Undesirable effect	*Frequency*	*Comment*
Traumatic catheter placement		
CSF leakage headache	25% of IT[17]	Less common in recent palliative series (0–7%), perhaps because of concurrent systemic analgesia[3,49] or more modern spinal needles[50]
ED hematoma	Rare	
Neurological tissue damage	⩽0.004%[51,52]	
Infection		
Exit site infection	⩽6%	In palliative care patients cared for at home or in palliative care units[3,9,49,53]
ED abscess	⩽8%[3,4,12,53]	
Meningitis	⩽3%[3,4,9,12]	
Delivery system		
Device-related complications	8–27%	E.g. catheter-related (fracture, kinking, displacement or withdrawal); pump failure (battery failure, mechanical failure, programming or refilling error). Rates, and propensity to human error, vary between pumps[3,41,42,47,54]

Box 19.B Emergency management of life-threatening complications

Stop spinal infusion.
Administer oxygen.
Obtain IV access.
If patient arrests, follow local resuscitation procedures.

Respiratory depression (sedation often precedes bradypnea)
Sit the patient up.
If respiratory rate ⩽8 breaths/min, the patient is barely rousable, and/or cyanosed, administer 20microgram boluses of naloxone every 2min until respiratory status is satisfactory (see p.000).
Further boluses may be necessary because naloxone is shorter acting than morphine and other spinal opioids.

Hypotension[a] (systolic <80mmHg)
Lay patient flat (not head down).
Check heart rate: if <40 beats/min, treat bradycardia (below) *or*
If no evidence of fluid overload, give an IV fluid challenge, e.g. 500mL of a colloidal plasma expander over 30min.
Examine for alternative causes such as bleeding.
If no response to fluids, give ephedrine 6mg IV.

Bradycardia[a]
ECG monitoring, if available.
Administer atropine (0.6mg boluses IV, up to total 3mg).
If atropine ineffective, give ephedrine 6mg IV.

a. cardiovascular disturbance also occurs with IT baclofen withdrawal syndrome (see Box 19.A).

Box 19.C Management of common undesirable effects of spinal analgesia

Opioid discontinuation (diarrhea, colic, sweating, restlessness)
Spinal delivery results in a massive reduction in the patient's total opioid dose.
Laxatives should be discontinued and retitrated. If peripheral withdrawal symptoms occur, the pre-spinal opioid should be given p.r.n. in a dose approximately 25% of the former pain-related p.r.n. dose.

Opioid-induced pruritus
In palliative care, patients receiving spinal analgesia are generally not opioid-naïve (thus reducing the probability of pruritus) and most receive bupivacaine concurrently (this tends to restrict pruritus to the face).[55]

The concurrent use of NSAIDs may reduce the incidence of pruritus.[56,57] Treat with ondansetron (see p.000).[58] Consider switching to an alternative opioid if the pruritus persists.[59]

Opioid antagonists (naloxone, naltrexone) also abolish pruritus but will reverse analgesia.[60–63]

H_1-antihistamines are ineffective because opioid-induced pruritus is initiated centrally, and is not the result of mast cell degranulation.

Urinary retention
Drug-related urinary retention may be transient; removal of the urinary catheter after 3–4 days is successful in 3/4 of patients.[8] If persistent, may be because of the underlying disease.

Box 19.D Evaluation of new neurological impairment in patients receiving spinal analgesia

Differential diagnosis
Neurological damage caused by insertion of the catheter.

Bupivacaine-induced; dose-dependent, generally seen only when IT doses exceed 15mg/day,[5] but unmasking of incipient spinal cord compression can occur with lower doses.[5,68]

Disease process, e.g. cauda equina or spinal cord compression.

Spinal catheter complications, e.g. ED abscess or hematoma, catheter tip granuloma.

Withdrawal syndrome in patients receiving IT baclofen (see Box 19.A); neuromuscular features include spasticity, rigidity and priapism.

Initial evaluation
Neurological examination (location of problem).

Timing and rate of onset:
- immediate (spinal medication, 'unmasking' of pre-clinical impairment, neurological damage at insertion)
- days or weeks (ED abscess, disease itself)
- insidious over months (catheter tip granuloma).

Features of infection (ED abscess).
Pain at the catheter site and/or recurrence of the original pain (ED abscess or hematoma, disease itself, catheter tip granuloma; pain may precede neurological impairment)

Investigation
MRI may show both disease-related causes and spinal catheter-related space-occupying lesions (see warning about MRI above).

Pain precedes neurological features, which develop gradually over days or weeks.[69] Although more commonly a complication of ED catheters, catheter tip granulomas are also described with IT catheters, particularly where **morphine** or **hydromorphone** are used in higher concentration. The risk with **fentanyl** is thought to be lower.[6] A granuloma caused by IT **baclofen** has also been reported.[23] Masses often resolve over 2–5 months with cessation of **morphine**. In the absence of neurological impairment, consider catheter tip relocation, opioid dose reduction and/or switching opioid to **fentanyl** or a non-opioid. However, surgical excision may be required, where symptoms persist or there is neurological impairment.[23]

Exacerbation of pain

Increased pain may reflect:

- worsening of the original pain
- development of a new pain because of:
  - disease progression or co-morbidity
  - spinal catheter-related abscess, hematoma or granuloma
- reduced effect of the spinal infusion (delivery device malfunction).

Evaluation may reveal evidence of progression or new sites of disease, neurological impairment associated with spinal catheter-related mass, or infection. If external, the delivery system can be examined for disconnection, rate of delivery and contents.

A sudden increase in pain (e.g. as a result of catheter dislodgement) should be initially treated with p.r.n. opioid medication PO/SC while the cause is investigated. Alternatively, give **ketamine** 10–25mg PO/SC p.r.n. (see p.000), particularly if the pain is opioid poorly-responsive.

If the spinal infusion includes **baclofen**, and sudden failure of drug delivery is suspected, be alert to the presence of a severe life-threatening withdrawal syndrome (see Box 19.A). The sudden cessation of **clonidine** can cause severe rebound hypertension. Treat with oral **clonidine** while seeking specialist advice.[6]

Delivery device malfunction may involve:

- a problem with the pump itself (battery failure, mechanical failure)
- a problem with the catheter (kinking, fracture, displacement, occlusion)
- human error (wrong drug, dose or rate setting; overfilling or filling of the wrong port).

Plain radiographs may show a kinked, dislodged or disconnected catheter. Catheter position and patency can be confirmed by injection of a radiological contrast agent *after first aspirating the catheter dead-space to avoid delivery of the dead-space contents as a bolus*. The contrast agent must be appropriate for CSF use: *IT delivery of inappropriate radiological contrast agents can cause arachnoiditis or death*.

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