



Faculty of Pain Medicine

Australian and New Zealand College of Anaesthetists

Guidelines for longterm intrathecal infusions (Analgesics/adjuvants/antispasmodics)

1. INTRODUCTION

- 1.1 Persistent pain or spasticity with associated disability is a common problem and requires multidisciplinary approaches to assessment and management.
- 1.2 The long-term intrathecal delivery of drugs is an established, evidence based therapy for the management of refractory spasticity and cancer pain. The role of intrathecal therapy in chronic non-cancer pain is controversial and evidence of long term efficacy and safety is lacking.
- 1.3 The rationale is delivery of drugs directly to the site of action in the central nervous system for improved effect, coupled with less adverse effects, with only a small fraction of what could be the equivalent systemic dose. (1)
- 1.4 This modality of treatment is an invasive intervention, which is costly and labour intensive, with associated potential for serious risks and complications: the balance of risk and benefit needs careful consideration.
- 1.5 A range of delivery systems allows for the long-term delivery of intrathecal medication. These may be either temporary externalised systems or more permanent implanted systems.
- 1.6 Drugs may be administered as single or repeated injections, or by continuous infusion.
- 1.7 A range of drugs may be used for analgesia, e.g. opioids, clonidine and local anaesthetics,(1) whilst baclofen may be used for spasticity associated with neurological conditions of central origin.

2. PRINCIPLES OF USE

- 2.1 Intrathecal administration provides direct access into the cerebrospinal fluid for drugs acting at a spinal and/or supra spinal level.
- 2.2 There is evidence from a systematic review and randomised controlled trials of effectiveness in cancer pain (3 also note a, b) and from randomised controlled trials in spasticity (4, c, d, e). In chronic non-cancer pain systematic reviews have highlighted the lack of randomised controlled trials, inconsistent improvement in pain and function, significant dose escalation and high risk of drug adverse effects and hardware problems. (f, g) There are particular concerns about hypothalamic pituitary axis suppression (h, i), opioid induced hyperalgesia (j) and glial cell activation (k). It has been demonstrated that established intrathecal therapy for chronic non-cancer pain can be ceased in the context of a broader management approach with the potential for greater engagement with active management strategies (l) .
- 2.3 Full multidisciplinary assessment of the patient should be considered prior to use of this route of drug administration.

- 2.4 Patients must have a clear medical diagnosis for their pain or spasticity, for which more conservative methods of management (including psychological and physical therapies) have failed or are not appropriate.
- 2.5 Intrathecal drug administration can result in significant undesirable side effects, and has the possibility of serious morbidity and mortality. (5)
- 2.6 A facility for long-term monitoring, assessment and management must be in place.
- 2.7 Drugs administered into the intrathecal space need to be carefully assessed in respect of additives and preservatives, which may make them unsuitable for intrathecal use. Only a small number of medications have been deemed safe for intrathecal use. (6)
- 2.8 Care should be taken when considering off label use of drugs to ensure that additional patient education and written consent is obtained. (7)
 - 2.8.1 In Australia only baclofen is licensed for long-term intrathecal use.
 - 2.8.2 Baclofen suppliers require additional information before releasing the product.

3. PATIENT SELECTION

- 3.1 Effective management of intrathecal therapy requires appropriate patient selection. Selection should include comprehensive, multidisciplinary assessment of symptoms, disease, psychological and social factors, current and previous treatments and other treatment options.
- 3.2 Education of the patient increases their understanding of the potential benefits, risks and their responsibilities: the patient must be motivated to participate in the management plan, and consent to all aspects of the treatment.
- 3.3 The treating physician must be familiar and experienced with the therapy and device(s) to be utilised.
- 3.4 Chronic non-malignant pain
 - 3.4.1 Therapy is usually via a fully implanted pump system
 - 3.4.2 Psychological evaluation is essential:(8)
 - 3.4.2.1. To identify psychological and psychiatric disorders.
 - 3.4.2.2. To delineate psychological barriers to a successful outcome.
 - 3.4.2.3. To ensure adequate exposure to appropriate psychological therapies.
 - 3.4.2.4. To prepare a patient for psychological sequelae of intrathecal therapy, and
 - 3.4.2.5. To reinforce realistic expectations.
 - 3.4.3 Prior to the insertion of long term delivery systems, a trial of intrathecal therapy should be considered: (9)
 - 3.4.3.1. Temporary catheter system to assess efficacy drugs and doses.
 - 3.4.3.2. Trials may be bolus or infusion of drugs
 - 3.4.3.3. Noting that bolus trials are likely to give limited information
 - 3.4.3.4. Record of baseline pain levels, function and quality of life.
 - 3.4.3.5. Trial to demonstrate improvement of function and/or quality of life
- 3.5 Cancer pain:
 - 3.5.1 Normally via an external pump system, due to cost of the implanted pump.
 - 3.5.2 Importance of anticipating problems with managing the dying patient due to disease progression.

- 3.6 Spasticity:
 - 3.6.1 Therapy is usually via a fully implanted pump system
 - 3.6.2 Trial of intrathecal baclofen should be undertaken prior to implant.
 - 3.6.2.1. Via temporary catheter system to establish efficacy
 - 3.6.2.2. Appropriate assessment of the effect on function
- 3.7 Contraindications to the implantation of an intrathecal delivery system should be considered and discussed:
 - 3.7.1 Absolute contraindications
 - 3.7.1.1. Patient refusal or lack of understanding
 - 3.7.1.2. Systemic infections
 - 3.7.1.3. Failure of trial
 - 3.7.1.4. Sensitivity to components of the delivery system or proposed drugs
 - 3.7.1.5. Pathology at site of catheter placement
 - 3.7.1.6. Inadequate psychosocial support and/or coping mechanisms
 - 3.7.2 Relative contraindications
 - 3.7.2.1. Immunocompromised patients
 - 3.7.2.2. Bleeding diathesis or therapeutic anticoagulants
 - 3.7.2.3. Major affective disorders (depression, anxiety)
 - 3.7.2.4. Psychopathologies: psychosis, abnormal illness behaviours, personality disorders
 - 3.7.2.5. Evidence of current psychoactive drug abuse
 - 3.7.2.6. Poor compliance
 - 3.7.2.7. Access barriers to medical care, both routine and emergency: geographical and social isolation.

4. TYPES OF SYSTEMS

- 4.1 Percutaneous catheter
 - 4.1.1 Used with external pump
 - 4.1.2 May be tunnelled to aid patient comfort
 - 4.1.3 Requires frequent monitoring for infection and migration
 - 4.1.4 May restrict mobility unless ambulatory pump used
 - 4.1.5 Suitable for patients with limited life expectancy
- 4.2 Implanted catheter with subcutaneous injection port
 - 4.2.1 Used with external pump
 - 4.2.2 Less infection risk than percutaneous catheter
 - 4.2.3 Suitable for patients with limited life expectancy
- 4.3 Fully implanted catheter and pump
 - 4.3.1 Suitable for long term use
 - 4.3.2 Surgical skills required for implantation
 - 4.3.3 Specialised centre care required for follow up and refills
 - 4.3.4 Significant initial cost

5. PHARMACOLOGICAL THERAPIES

- 5.1 Opioids are the most frequently utilised agents for long-term intrathecal therapy. The most common opioid used is morphine sulphate. (2)
- 5.1.1 If alternate routes achieve good analgesia can be achieved with minimal side effects and risks, there is no good evidence for improved outcomes by intrathecal route.
- 5.1.2 Failure to respond to an intrathecal trial or need for a rapidly increasing dose may indicate pain poorly responsive to opioids.
- 5.1.3 Inadequate analgesia may require dose escalation of opioid over time. It is important to consider factors which may result in inadequate analgesia, including:
- tolerance
 - progression of the underlying disease
 - a new source of pain
 - opioid induced hyperalgesia
 - distress
 - social reinforcers
 - pain which is not opioid responsive
- 5.1.4 Increasing analgesic requirements may also result from failure of an infusion device, dislodgement of an intrathecal catheter, or other catheter related complications including development of a catheter tip mass.
- 5.2 A range of non-opioid intrathecal analgesic agents are utilised for long-term therapy, some of which are supported by low levels of evidence and for which safety has not been fully established. (6)
- 5.2.1 There is level I evidence that intrathecal administration of baclofen is efficacious for the management of muscle spasm of central origin (4,10)
- 5.2.2 There is level II evidence for efficacy in treating:
- neuropathic pain with intrathecal clonidine(11)
 - neuropathic pain following spinal cord injury with morphine and clonidine combined (12)
 - neuropathic pain with ziconotide (13)
- 5.2.3 Intrathecal administration of opioids and local anaesthetics and/or clonidine could be considered as an alternative in patients with poorly controlled neuropathic pain in cancer or following spinal cord injury.(14)
- 5.2.4 Ketamine(15), midazolam(16) and somatostatin(17) amongst others have had some reported benefits. However many of these combinations are “beyond licence” or “off label” and appropriate patient consent must be obtained.
- 5.3 Combinations of intrathecal analgesic agents have potential advantages. (14)
- 5.3.1 Improvement in analgesic efficacy.
- 5.3.2 Reduction in side effects if reduced doses of both agents are possible when compared with single agent therapy.
- 5.4 Combinations of agents may be unstable during long-term use from implantable reservoirs.(18)
- 5.5 Due to the large number of potential combination therapies, the evidence for the most appropriate agents in different clinical situations is limited.(14)
- 5.6 Both physician and patient should be aware of current data relating to safety and potential neurotoxicity of proposed intrathecal medications.(19) Toxicological studies to date suggest no long-term adverse effects of baclofen, morphine, bupivacaine or clonidine. (10, 18)

6. IMPLANTATION MANAGEMENT

- 6.1 Implantation requires a full aseptic environment such as an operating theatre
- 6.2 The site of exit of catheter or implanted port/pump should be agreed pre-implantation
- 6.3 Intrathecal space catheter placement should be confirmed by CSF flow, and level of catheter tip documented by intraoperative radiological screening
- 6.4 Deadspace of catheters and pumps should be noted
- 6.5 Medication for the intrathecal therapy should be clearly prescribed and checked before administration (include second person check)
- 6.6 Consider prescription being prepared by a manufacturing pharmacy
- 6.7 Care must be exercised with initial pump programming, including bolus volumes for pump and catheter deadspace
- 6.8 When using opioids, regular monitoring for postoperative somnolence and respiratory depression should be carried out, particularly in the first 24 hours
- 6.9 Adjust existing medication by other routes when intrathecal medication commenced
- 6.10 Surgical wounds should be monitored routinely

7. CONTINUING CARE

- 7.1 Continuing therapy requires regular assessment and documentation of efficacy, tailoring therapy to the individual, documenting and management of complications
- 7.2 Adequate arrangements for ongoing care should be in place to include programme changes and pump refills or medication bag changes:
 - 7.2.1 Aseptic technique
 - 7.2.2 Appropriately trained healthcare professional
 - 7.2.3 Resuscitation equipment must be available
- 7.3 Treatment requires regular assessment
 - 7.3.1 Neurological deficits can occur from the procedure and from inflammatory mass development at the catheter tip.(20) Access to neuroradiological expertise should be available
 - 7.3.2 Infections include meningitis, abscess, pump pocket or reservoir infection
 - 7.3.3 CSF leak, hygroma and post dural puncture headache
 - 7.3.4 Catheters may kink, fracture or disconnect
 - 7.3.5 Pumps may fail or be programmed incorrectly
- 7.4 Following drug changes and pump reprogramming regular assessment, documentation and management of side effects of the medication are required, for:
 - 7.4.1 Opioids
 - 7.4.1.1. Sedation and respiratory depression, especially first 24hrs
 - 7.4.1.2. Endocrine effects including hypogonadotropic hypogonadism(21)
 - 7.4.1.3. Hyperalgesia and myoclonus (22)
 - 7.4.2 Local anaesthetics
 - 7.4.2.1. Sensorimotor block (unlikely from bupivacaine < 30mg per day) (23)

- 7.4.3 Clonidine
 - 7.4.3.1. Sedation
 - 7.4.3.2. Hypotension and bradycardia
- 7.4.4 Baclofen
 - 7.4.4.1. Drowsiness, ataxia and hypotonia
 - 7.4.4.2. Life threatening withdrawal if stopped suddenly. (5)
- 7.5 Implanted pumps
 - 7.5.1 For some implanted pumps there is risk of malfunction from MRI scanners. Local advice should be sought. Programmable systems should be stopped prior to scan and recommenced once completed.
 - 7.5.2 Short wave diathermy should not be used within 30cm of the pump or catheter
 - 7.5.3 Advice should be taken from the implanting clinician before deep sea diving
 - 7.5.4 Patients should carry information about their pump and medication when travelling, particularly where security scanners are in use
- 7.6 Outcome data: practitioners should find ways to contribute to pooled data for evaluating the overall outcome, safety and complications of this therapy type.

REFERENCES

1. Wallace M, Yaksh TL. Long-term spinal analgesic delivery: a review of the preclinical and clinical literature. *Reg An & Pain Med* 2000; 25(2): 117-57.
2. Hassenbusch SJ et al. Long-term intraspinal infusions of opioids in the treatment of neuropathic pain. *J Pain Symptom Manage* 1995; 10: 527-43.
3. Ballantyne JC, Carwood C. Comparative efficacy of epidural, subarachnoid, and intracerebroventricular opioids in patients with pain due to cancer. *Cochrane Database of Systematic Reviews* 2005, Issue 1. Art. No.: CD005178.
 - a. Smith TJ, Staats PS, Deer T, Stearns LJ, Rauck RL, et al. (2002) Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity, and survival. *J Clin Oncol*; 20(19): 4040–4049.
 - b. Smith TJ, Coyne PJ, Staats PS, Deer T, Stearns LJ, et al. (2005) An implantable drug delivery system (IDDS) for refractory cancer pain provides sustained pain control, less drug-related toxicity, and possibly better survival compared with comprehensive medical management (CMM). *Ann Oncol*; 16/5: 825–833.
 - c. Middel B, Kuipers-Upmeijer H, Bouma J, Staal M, Oenema D, et al. (1997) Effect of intrathecal baclofen delivered by an implanted programmable pump on health related quality of life in patients with severe spasticity. *J Neurol*; 63(2): 204–209.
 - d. Van Schaeybroeck P, Nuttin B, Lagae L, Schrijvers E, Borgh-graef C, et al. (2000) Intrathecal baclofen for intractable cerebral spasticity: a prospective placebo-controlled, double-blind study. *Neurosurgery*; 46(3): 603–609.
 - e. Hoving MA, van Raak EP, Spincemaille GH, Palmans LJ, Becher JG, et al. (2009) Efficacy of intrathecal baclofen therapy in children with intractable spastic cerebral palsy: a randomised controlled trial. *Eur J Paed Neurol*; 13(3): 240–246.
 - f. Turner JA, Sears JM, Loeser JD (2007) Programmable intrathecal opioid delivery systems for chronic noncancer pain: a systematic review of effectiveness and complications. *Clin J Pain*; 23(2): 180–194.
 - g. Patel VB, Manchikanti L, Singh V, Schultz DM, Hayek SM, et al. (2009) Systematic review of intrathecal infusion systems for long-term management of chronic non-cancer pain. *Pain Physician*; 12(2): 345–360.
 - h. Abs R, Verhelst J, Maeyaert J, van Buyten JP, Opsomer F, et al. (2000) Endocrine consequences of long-term intrathecal administration of opioids. *Clin Endocrinol Metab*; 85(6): 2215–2222.
 - i. Roberts LJ, Finch PM, Pullan PT, Bhagat CI, Price LM (2002) Sex hormone suppression

- by intrathecal opioids: a prospective study. *Clin J Pain*; 18(3): 144–148.
- j. Angst MS, Clark JD (2006) Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology*; 104(3): 570–587.
 - k. Hutchinson MR, Bland ST, Johnson KW, Rice KC, Maier SF, et al. (2007) Opioid-induced glial activation: mechanisms of activation and implications for opioid analgesia, dependence, and reward. *Scientific World Journal*; 7: 98–111.
 - l. Hayes C, Jordan MS, Hodson FJ, Ritchard L (2012) Ceasing Intrathecal Therapy in Chronic Non-Cancer Pain: An Invitation to Shift from Biomedical Focus to Active Management. *PLoS ONE* 7(11): e49124. doi:10.1371/journal.pone.0049124
4. Penn RD. Intrathecal baclofen for spasticity of spinal origin; seven years of experience. *J Neurosurg* 1992; 77: 236-40.
 5. Coffey RJ, Ridgely PM. Abrupt intrathecal baclofen withdrawal: management of the potentially life-threatening sequelae. *Neuromodulation* 2001; 4: 142-6.
 6. Hodgson PS, Neal JM, Pollock JE, Liu SS. The neurotoxicity of intrathecal drugs given intrathecally (spinal). *Anesth Analg* 1999; 88 (4): 797-809.
 7. British Pain Society: The use of drugs beyond license in palliative care and pain management. 2005. www.britishpainsociety.org
 8. Deer T, Smith H, Cousins M, et al. Consensus guidelines for the selection and implantation of patients with non-cancer pain for intrathecal drug delivery. *Pain Physician* 2010; 13(3):E175-E213.
 9. Deer T et al. Intrathecal therapy for cancer and non-malignant pain: patient selection and patient management. *Neuromodulation* 1999; 2(2): 55-66.
 10. Penn RD, Kroin JS. Long-term intrathecal baclofen infusion for treatment of spasticity. *J Neurosurg* 1987;66:181-185.
 11. Ackerman LL, Follett KA, Rosenquist RW. Long-term outcomes during treatment of chronic pain with intrathecal clonidine or clonidine/opioid combinations. *J Pain & Symptom Manage* 2003; 26(1): 668-77.
 12. Siddall PJ, Molloy AR, Walker S, et al. Efficacy of intrathecal morphine and clonidine in the treatment of neuropathic pain following spinal cord injury. *Anesth Analg* 2000; 91:1493-1498.
 13. Rauck RL et al. A randomised, double-blind, placebo-controlled study of intrathecal ziconotide in adults with severe chronic pain. *J Pain & Symptom Manage* 2006; 31(9): 393-406.
 14. Walker SM et al. Combination spinal analgesic chemotherapy: a systematic review. *Anesth Analg* 2002; 95: 674-715.
 15. Benrath J et al. Long-term intrathecal S-Ketamine in a patient with cancer-related neuropathic pain. *BJA* 2005; 95(2): 247-9.
 16. Canavero S et al. No neurotoxicity from long-term (>5years) intrathecal infusion of midazolam in humans. *J Pain & Symptom Manage* 2006; 32(1): 1-3.
 17. Meynadier J et al. Intrathecal somatostatin in terminally ill patients. A report of two cases. *Pain* 1985; 23: 9-12.
 18. Wulf HW, Gleim M, Mignat C. The stability of mixtures of morphine hydrochloride, bupivacaine hydrochloride, and clonidine hydrochloride in portable pump reservoirs for the management of chronic pain syndromes. *J Pain Symptom Manage* 1994; 9: 308-311.
 19. Bennett G, et al. Evidence based review of the literature on intrathecal delivery of pain medication. *J Pain Symptom Manage* 2001; 20: S12-36.
 20. Allen JW et al. Opiate pharmacology of intrathecal granulomas. *Anesthesiology* 2006; 105(3): 590-8.
 21. Roberts LJ et al. Sex hormone suppression by intrathecal opioids: a prospective study. *Clin J Pain* 2002; 18: 144-8.
 22. De Conno et al. Hyperalgesia and myoclonus with intrathecal infusion of high-dose morphine. *Pain* 1991; 47: 337-9.
 23. Hassenbusch SJ et al. Polyanalgesic consensus conference 2003: an update on the management of pain by intraspinal drug delivery – report of an expert panel. *J Pain & Symptom Manage* 2004; 27(6): 540-64.

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