Transport Accident Commission & WorkSafe Victoria

Evidence Service

Implantable pain therapies: Intrathecal (IT) infusions

Plain language summary

Treatments for persistent pain can involve many therapies including; medication, physiotherapy, psychological therapy and nerve blocks. In some patients these may not work or cause unpleasant side effects. For this small group of patients, drugs can be given by intrathecal infusion. A pump is placed under the skin usually around the stomach region. Tubes from the pump trickle out the drug into the space around the spinal cord. This may give the patient pain relief.

This review looked at whether IT infusions are helpful for persistent pain that is not due to cancer. The review did not find enough evidence to confirm that IT infusions are helpful for pain. There are also possible harms such as; side effects (e.g. nausea, dizziness, sleepiness, headache, addiction) and complications such as pump malfunction, misplacement and infection.

Accompanying documents to this report	
Title	*Report number*
Implantable pain therapies: Intrathecal (IT) infusions – Evidence Summary	Research Report No. *0611-002-R7.1*
Implantable pain therapies: Intrathecal (IT) infusions – Plain Language Summary	Research Report No. *0611-002-R7.2*
Implantable pain therapies: Intrathecal (IT) infusions – Technical Report	Research Report No. *0611-002-R7.3*

Implantable pain therapies: Intrathecal (IT) infusions

Evidence summary

Overview

This evidence review is an update of a previous review requested by the Transport Accident Commission (TAC) and WorkSafe Victoria (WSV) conducted in September 2008.[1] The current report has identified further evidence for the effectiveness of IT opioids and IT ketorolac, a non-steroidal anti-inflammatory drug (NSAID). No new evidence for the effectiveness of IT baclofen and IT ziconotide was identified since the previous report.

At present, the evidence available for the effectiveness of intrathecal (IT) infusions in patients with persistent, non-cancer pain is insufficient (IT opioids, baclofen, ziconotide, and ketorolac).

Definition

For a small proportion of patients with non-cancer pain who do not experience sufficient pain relief or have intolerable side effects with conventional treatments, intrathecal (IT) infusions may be an effective treatment. A pump is implanted under the skin usually in the abdominal region. Tubes from the implanted pump are programmed to trickle out the drug at a certain rate into the space around the spinal cord (intrathecal or IT) which may provide the patient with sufficient pain relief.

The following evidence review identified a total of fifteen studies (three evidence-based guidelines, three health technology assessments, eight systematic reviews and one randomised clinical trial) of IT infusions for persistent pain that met the selection criteria.

ANALGESICS (OPIOIDS):	The most recent high quality systematic review (SR)[2] was found to be well conducted. The included studies in the SR, which were case series (low level evidence), **provided limited evidence to determine whether IT opioids are effective for chronic, persistent non-cancer pain.**
ANTI-SPASMODICS (BACLOFEN):	Only low level evidence based on a single case series study[3, 4] exists for the effectiveness of IT baclofen in the treatment of persistent pain. Therefore, there is **insufficient evidence to determine whether IT baclofen is effective for chronic, persistent non-cancer pain.**
CALCIUM CHANNEL ANTAGONISTS (ZICONOTIDE):	The most comprehensive, up-to-date high quality SR[5] identified, found that "no studies for ziconotide met the inclusion criteria for either effectiveness or complications". No further primary studies were identified according to the inclusion criteria requested in this report. Hence, there is **insufficient evidence to determine the benefits of IT ziconotide treatment for chronic, persistent non-cancer pain.**
OTHER MEDICATIONS (KETOROLAC):	A small cross-over RCT[6] did not find a statistically significant difference in treatment effect following IT ketorolac or placebo with established, simultaneous IT morphine,

	although a trend for reduced pain intensity and unpleasantness was present following IT ketorolac. Overall, this led us to conclude that **there is insufficient evidence of effectiveness of IT ketorolac on persistent pain.**

In what clinical conditions is this intervention indicated for use?

Drug infusions through implantable pumps are indicated and approved for use by the TGA for baclofen only. Morphine (opioids), ziconotide and other medications (ketorolac) are not approved and are prescribed by some physicians in an "off label" capacity. For "off label" use appropriate patient consent is required.

Findings in the following report identify the target group for use of IT infusions (opioids and ketorolac) to be adults with chronic non-cancer pain that have not experienced pain relief with conventional treatments. Insufficient evidence is available to confirm which patients IT baclofen and IT ziconotide can be used for.

What is the efficacy and effectiveness of this intervention on persistent pain in these conditions?

ANALGESICS (OPIOIDS):	There is **insufficient evidence** to answer this question.
ANTI-SPASMODICS (BACLOFEN):	There is **insufficient evidence** to answer this question.
CALCIUM CHANNEL ANTAGONISTS (ZICONOTIDE):	There is **no evidence** to answer this question.
OTHER MEDICATIONS (KETOROLAC):	There is **insufficient evidence** to answer this question.

What is the effect of this intervention on function, quality of life, return to work, medication use and use of the healthcare system?

ANALGESICS (OPIOIDS):	There is **insufficient evidence** to answer this question.
ANTI-SPASMODICS (BACLOFEN):	There is **insufficient evidence** to answer this question.
CALCIUM CHANNEL ANTAGONISTS (ZICONOTIDE):	There is **no evidence** to answer this question.
OTHER MEDICATIONS (KETOROLAC):	There is **insufficient evidence** to answer this question.

In what patient groups/conditions is use of this intervention contraindicated?

Patient groups/conditions in which use of IT infusions are contraindicated are

- When infection is present[7]
- When the pump cannot be implanted 2.5 cm or less from the surface of the skin[7]
- When body size is not sufficient to accept pump bulk and weight[7]
- Allergy or hypersensitivity to the drug being used[7, 8]
- Blood thinning medications[9]
- In patients who have another implanted device, such as a pacemaker[8]

- Drugs with preservatives[7]
- Epilepsy refractory to therapy[8]
- Previous history of psychosis[9]

The Australian and New Zealand College of Anesthetists caution the use of IT therapy in patients where psychological factors are considered to be a major pain modifying factor. [10]

What are the risks associated with use of this intervention?

Device-related adverse events were only reported for IT opioids,[2] however the same device is utilised for all other IT drugs. Adverse events include pump and catheter malfunctions and malpositioning, surgical complications and postsurgical complications.

The following drug-related adverse events were reported with IT ketorolac[6] including mild sedation (n=2, lasting < 2 hours), mild dizziness (n=1, lasting < 30 minutes, and a hot sensation in the back, headache, urinary retention, and hives (n=1, lasting< 4 hours). Following saline infusion in the RCT, mild sedation (n=2, lasting < 1 hour, mild nausea (n=2, lasting < 1 hour), and mild headache (n=1, lasting < 2 hours) were reported.

The only serious adverse event reported following IT administration of opioids was hallucinations.[2]

As no evidence was available for IT baclofen or IT ziconotide, drug-related adverse events remain unknown.

Glossary of Findings	
Insufficient	Little or no evidence exists to answer this question
Limited evidence of effectiveness	There is some evidence of effectiveness but not enough to be sure. More high quality studies are needed before conclusions can be drawn.

Transport Accident Commission & WorkSafe Victoria

Evidence Service

Implantable pain therapies: Intrathecal infusions

Evidence Review

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BACKGROUND

Implantable pain therapies (IPTs) have been used to treat patients for a variety of pain disorders. They include a range of neurostimulation procedures and intrathecal (IT) infusions of analgesic, local anaesthetic, antispasmodic and other pharmacological agents. In order to develop and update policies for the use of IPTs in patients with persistent pain, the Health Services Group of the Transport Accident Commission and WorkSafe Victoria (TAC/WSV) requested an update of the Evidence Reviews of IPTs published in September 2008[1]. In light of the complexity of the research questions and the multiple sources of information available, the previous review developed two separate reports; one for implantable IT infusions and another for neurostimulation. This approach was continued for this update.

The focus of this review is to evaluate the effectiveness and safety of implantable IT infusions on patients with persistent pain following transport-related or workplace injuries. The effect of IT infusions on pain due to systemic inflammatory conditions, vascular insufficiency, haematological disorders or cancer is outside the scope of this review.

Intrathecal (IT) infusions

For a small proportion of patients with non-cancer pain who do not experience sufficient pain relief or have intolerable side effects with conventional treatments, intrathecal (IT) infusions may be an effective treatment. This involves implanting a specialised device (pump) subcutaneously in the abdominal region. Tubes from the pump are inserted into the intrathecal space around the spine which contains cerebrospinal fluid that bathes the spinal cord, delivering medication to where it has its action, and therefore eliminating side effects of taking the drug orally or parenterally.

According to the Australian and New Zealand College of Anaesthetists' guidelines, IT delivery of drugs for long term pain management can be used for a small, carefully selected subgroup of patients. They recommend that IT infusion be used as last line therapy in those whose pain is not adequately controlled by less invasive measures (e.g. physical therapy, psychological therapy, oral and parenteral medication and neural blockade) or where other routes of medication cause side effects.[10, 11] They also caution the use of IT infusions in patients where psychological factors are considered to be a major pain modifying factor and recommend that psychological evaluation be done on all patients before starting IT treatment.

Several medications, diverse in their mechanisms of action, have been reported for use in IT pumps and can be grouped into the following categories –

- analgesics (opioids),
- anti-spasmodics (baclofen),
- calcium channel blockers (ziconotide), and
- other medications (including ketorolac and midazolam)

Within these categories medications can be administered on their own or combined with other medications or other implantable therapies, either from the same category or a different category.

In Australia only baclofen is licensed for long term IT use for spasticity. All other IT infusion medications are prescribed/administered off label under the TGA's "Access to Unapproved Therapeutic Goods" scheme.[10]

Background information relating to the different drug categories used for IT infusion is provided below.

1. Analgesics (opioids)

Opioids are medications usually used for pain relief. Common opioids are morphine, oxycodone and codeine.

The mechanism of action of opioids is through the attachment to proteins called opioid receptors, which are abundantly present in the central nervous system. Studies have found a large number of side effects associated with the use of opioids as well as complications when used in IT pumps. Some of these have severe consequences, however it is difficult to know from the information available how likely these problems are to occur.

Opioids used for IT treatment include morphine, hydromorphone, fentanyl, buprenorphine and sufentanil. These drugs have not been approved by the Australian Therapeutic Goods Administration (TGA) for IT use.

2. Anti-spasmodics (baclofen)

Baclofen is a GABA-β receptor agonist and is a medication that acts through the central nervous system to relax muscles. GABA (or gamma-aminobutyric acid) is the main inhibitory neurotransmitter used in the nervous system that regulates neuronal signalling.

The mechanism of action for baclofen is by binding to pre-synaptic GABA-β receptors, which in turn inhibits the release of neurotransmitter (GABA) onto neurons of the spinal cord that causes the sensation of pain. Post-synaptic binding of baclofen to GABA-β receptors, results in a reduction in neuronal excitability which is thought to contribute to spasticity.

Baclofen can be administered through an IT pump for the treatment of severe pain and disability, secondary to spasticity.

Baclofen is only approved by the TGA for IT use for spasticity. Lioresal® Intrathecal (baclofen injection) is indicated in patients with severe chronic spasticity of spinal origin (associated with injury, multiple sclerosis, or other spinal cord diseases) or of cerebral origin that are unresponsive to orally administered antispasmodics (including oral baclofen) and/or who experience unacceptable side effects at effective oral doses.

3. Calcium channel blockers (ziconotide)

Ziconotide is the man-made equivalent of a pain relieving chemical found in the venom of a certain type of sea snail. It is a calcium channel antagonist which is thought to inhibit neurotransmitter release from N-type calcium channels abundantly present on neurons located in the spinal cord.

In Australia ziconotide is classed as an experimental drug and is not approved for IT use by the TGA.

4. Other medications (including ketorolac and midazolam)

There are other medications which have been given intrathecally via a pump. Ketorolac is a non-steroidal anti-inflammatory drug (NSAID) which has inhibitory effects on cyclooxygenase (COX), an enzyme responsible for the production of prostanoids (prostaglandins, prostacyclin and thromboxane) which relieve pain and inflammation in the body. Ketorolac is an experimental IT drug which has only recently been tested for chronic pain in humans and animals.[6] The drug was initially administered systemically as a potent pain relief agent in postoperative pain. As severe, chronic pain may originate in the central nervous system, an attempt was made to test IT ketorolac to see if the central nervous system was also a site of action in the body. In an early open-label study, IT ketorolac did not reduce pain from applying heat stimuli to the skin, although no serious adverse events were reported.[6]

Ketorolac has not been approved by the TGA for IT use.

Other medications have been used intrathecally for the treatment of chronic, severe pain. These include clonidine, bupivacaine, sufentanil, fentanyl, midazolam and gabapentin. However, most of these drugs have only shown effectiveness in the treatment of pain in pre-clinical studies and hence are not approved by the TGA for IT use.

QUESTIONS

This Evidence Review sought to find the most up-to-date, high quality source of evidence to answer the following questions regarding IT drug infusions in persistent pain due to work-related or transport accident injuries:

- In what clinical conditions is this intervention indicated?
- What is the efficacy and effectiveness of this intervention on persistent pain in these conditions?
- What is the effect of this intervention on function (physical, psychological, social), quality of life, return to work, medication use and use of the healthcare system?
- In what patient groups/conditions is this intervention contraindicated?
- What are the risks associated with use of this intervention?

METHODS

Methods are outlined briefly below. More detailed information about the methodology used to produce this report is available in Appendices 1 and 2. All appendices are located in the Technical Report accompanying this document.

A comprehensive search of Medline, Embase and the Cochrane Library, was undertaken in March 2011 to identify relevant synthesised research (i.e. evidence-based guidelines (EBGs), systematic reviews (SRs), health technology assessments (HTAs)), and any relevant randomised controlled trials (RCTs) and controlled clinical trials (CCTs). Inclusion and exclusion criteria were established *a priori*. A comprehensive search of the internet, relevant websites and electronic health databases was also undertaken (see Appendix 2, Tables A2.2-A2.4 for search details). Reference lists of included studies were also scanned to identify relevant references.

Studies identified by the searches were screened for inclusion using specific selection criteria (see Appendix 2, Table A2.1). Synthesised evidence (EBGs, SRs and HTAs) that met the selection criteria was reviewed to identify the most up-to-date and comprehensive source. This evidence was then critically appraised to determine whether it was of high quality. This process was repeated for additional sources of evidence, until the most recent, comprehensive and high quality source of evidence was identified. Final source documents were compared to other evidence sources for consistency of findings and included studies. The available synthesised evidence was mapped (see Table 2), and the algorithm in Table 1 was followed to determine the next steps necessary to answer the clinical questions.

Table 1. Further action required to answer clinical questions

<table>
<tr><th colspan="5">Is there any synthesised research available? (e.g. EBGs, HTAs, SRs)</th></tr>
<tr><th colspan="3">Yes</th><th colspan="2">No</th></tr>
<tr><th colspan="3">Is this good quality research?</th><th colspan="2">Are RCTs available?</th></tr>
<tr><th colspan="2">Yes</th><th>No</th><th>Yes</th><th>No</th></tr>
<tr><th colspan="2">Is it current (within 2 years)?</th><td rowspan="2"></td><td rowspan="2"></td><td rowspan="2"></td></tr>
<tr><th>Yes</th><th>No</th></tr>
<tr><td>No further action</td><td>Update existing SR</td><td>Undertake new SR</td><td>Undertake new SR</td><td>Consider looking for lower levels of evidence</td></tr>
</table>

Data on characteristics of all included studies were extracted and summarised (see Appendix 4). The most recent, relevant, high quality systematic review was used to address the questions posed above.

RESULTS

An initial search of electronic databases yielded 4141 articles. After reviewing the title, abstract or full text, one EBG,[12] two HTAs,[13, 14] nine SRs[2, 5, 13-19] and three RCTs,[6, 20, 21] were found that met the selection criteria. Internet searches yielded two additional EBGs,[4, 22] one HTA[3] and one additional SR.[23] In the process of critically appraising these studies, two SRs and two RCTs were excluded.

In total 15 studies (three EBGs, three HTAs, eight SRs and one RCT) of IT infusions for persistent pain (published between 1996 and 2011) met our selection criteria (see Table 2 for number of studies and Appendix 2 Table A2.1 for selection criteria). A list and summary of included studies can be found in Appendices 3 and 4, respectively.

Table 2. Evidence map of included studies by study-type

	Synthesised Studies		Primary studies	TOTAL
Drug category	EBGs*	SRs & HTAs*		
Opioids	2 EBGs	9 SRs	-	11
Baclofen	1 EBG	2 SR/HTA	-	3
Ziconotide	-	1 SR	-	1
Other medications	1 EBG	-	1 RCT	1

**columns may not add up to totals as some systematic review (SRs) and primary studies (RCTs) identified evaluated IT infusions in more than one drug category.*

Results are reported in more detail below by drug category.

1. ANALGESICS (opioids)

Evidence identified

Searches yielded a total of 11 studies of IT opioids for the treatment of persistent pain published between 1996 and 2011. The number of studies by study design is illustrated in Table 2 above. A summary of these studies can be found in Appendix 4, Table 4.1.

The effectiveness of IT opioids on persistent pain has been assessed in numerous synthesised studies. Three SRs were recently identified as potentially relevant.[2, 15, 23] One of these SRs[15] included a study[24] that combined results for cancer and non-cancer pain patients. Our review was limited to patients with persistent pain not due to cancer and so this SR was excluded from the analysis.

Two of the most up-to-date SRs were critically appraised (see Appendix 5). It was decided that Noble, M et al[2] would be used as the primary reference as it contained a larger number of studies which were more recent and also assessed long-term functional outcomes including quality of life (QoL) and functional levels which were questions needing to be answered for the evidence review.

Table 3. Key information from most recent, comprehensive, high quality systematic review *(Noble, M et al, 2010)* - OPIOIDS

Noble M, Treadwell JR, Tregear SJ, Coates VH, Wiffen PJ, Akafomo C, et al. Long-term opioid management for chronic noncancer pain. Cochrane Database Syst Rev. [Meta-Analysis Review]. 2010(1):CD006605.	
Study design	Systematic review
Scope	**Patient/population:** n = 231 (10 case series) **Conditions indicated for use:** Adults aged at least 18 years with pain due to any cause other than cancer lasting for at least three months **Intervention:** IT morphine, IT sufentanil citrate, IT methadone, morphine clorhidrate or tramadol, IT morphine with bupivacaine and/or clonidine and/or midazolam, IT dilaudid, IT fentanyl and IT baclofen (see Appendix 4 for further details) **Outcomes assessed:** "We assessed adverse events (side effects), discontinuation from study due to adverse events, discontinuation from study due to insufficient pain relief, average change in pain score, proportion of patients with at least 50% pain relief, health-related quality of life, and function".
Efficacy and effectiveness of IT drug infusion for persistent pain	**Average change in pain scores, as assessed by visual analogue scale (VAS) (n = 220)** Before treatment commenced, the VAS scores of the included studies were combined, giving a score of 8.70 out of 10 (95% CI: 8.37 to 9.04), indicating severe pain. After treatment, this pooled VAS score was reduced to 4.45 out of 10 (95% CI: 3.44 to 5.47), indicating moderate pain. **Pts with at least 50% pain relief (n = 151)** The summarized proportion of participants (from combined included studies) who had at least a 50% reduction in pain was 44.5% (95% CI: 27.2% to 63.2%).
Effect of IT drug infusion on function, quality of life, return to work, medication use and use of the healthcare system?	**Quality of life (QoL) (n = 92)** Each study used a different instrument to assess quality of life (QoL). One of the studies had inconclusive findings,[25] one reported a small benefit,[26] and one reported a large benefit.[27] The overall effect size (or standardized mean difference, SMD) following

	statistical analysis revealed no significant improvement in quality of life after administration of IT opioids 1.02 (95% CI -0.04 to 2.09). **Function Levels (n = 98)** Each study used a different instrument to assess function. Study findings were inconsistent, with one study showing inconclusive findings,[28] another showing a moderate difference (effect size),[26] and another a large difference (effect size).[29] Following statistical analysis, all the studies showed that there was no significant improvement in functional levels after administration of IT opioid (SMD 0.56, 95% CI -0.02 to 1.13). These results however are limited by the high heterogeneity between studies.
Which patient groups/ conditions is use of IT drug infusion contraindicated?	Not reported
Risks associated with use of IT drug infusion	**Adverse Events (AEs) (n = 228, 10 studies)** Pump and catheter malfunctions and malpositioning, surgical complications, and postsurgical complications were reported. The percentage of participants whose device complications required reoperation was quite high in some studies (20-27%). Two studies reported a total of six deaths, due to chronic obstructive pulmonary disease, pericolonic abscess, and myocardial infarction (n=2), suicide, and an unknown cause (n = 1). The SR did not report if these events were due to the drug or the implantable pump itself. **Discontinuation from study due to AEs (n = 86)** Following pooled analysis of all included studies it was estimated that 8.9% of patients discontinued the study due to adverse events, however this result was not statistically significant. **Discontinuation from study due to insufficient pain relief (n = 113)** The summary rate of discontinuation due to insufficient pain relief was 7.6% (95% CI: 3.7% to 14.8%).
Conclusion/ Recommendation	"Many patients discontinue long-term opioid therapy (especially oral opioids) due to adverse events or insufficient pain relief; however, weak evidence suggests that patients who are able to continue opioids long-term experience clinically significant pain relief. Whether quality of life or functioning improves is inconclusive. Many minor adverse events (like nausea and headache) occurred, but serious adverse events, including iatrogenic opioid addiction, were rare."
Recommendation category	Insufficient evidence
Quality assessment results	This SR was well conducted and considered to have a low risk of bias (see Appendix 5 for quality appraisal)
Our comments/summary	Although this SR was well conducted it included nine observational studies that assessed IT opioids for persistent pain. The authors conclude that there is only weak evidence of therapeutic effectiveness of IT opioids for persistent pain,

	and insufficient evidence for health-related quality of life outcomes.

Findings

Due to a lack of high quality primary studies (i.e. RCTs), there is **insufficient evidence** to determine the effectiveness of IT opioids for the treatment of persistent pain.

2. ANTI-SPASMODICS (baclofen)

Evidence identified

Searches yielded one EBG, one HTA and one SR for IT baclofen for the treatment of persistent pain (published between 1996 and 2011). The HTA[4] and SR[3] were critically appraised (see Appendix 4) and it was discovered that both reviews were non-systematic literature reviews, a study type excluded in the selection criteria of this evidence review (see Appendix 5) and hence they were excluded. The number of included studies by study design is illustrated in Table 2. A summary of these studies can be found in Appendix 4, Table 4.1.

The EBG was appraised and found to be well conducted with a low risk of bias. However, it did not identify any controlled studies that met the inclusion/exclusion criteria for this report.

In summary, there is **insufficient** evidence to know whether IT baclofen is useful.

3. CALCIUM CHANNEL BLOCKERS (ziconotide)

Evidence identified

Searches yielded one SR for IT ziconotide for the treatment of persistent pain. The SR[5] was appraised and found to be well conducted with a low risk of bias. Details of the appraisal are in Appendix 5.

The authors of the SR found that *"no studies for ziconotide met the inclusion criteria for either effectiveness or the complications review"*.

4. OTHER MEDICATIONS (ketorolac)

Evidence identified

Searches yielded a total of 2 studies (1 EBG and 1 Randomised Cross Over Trial) for other IT medications for the treatment of persistent pain published between 1996 and 2011. The number of studies by study design is illustrated in Table 2. A summary of these studies can be found in Appendix 4, Table 4.1.

The EBG[22] was appraised and found to be of low quality with a potentially high risk of bias. It included a section on IT medication delivery systems, however it did not indicate the patient group (condition or age), the drug used or the outcomes reported. We chose to use the most-up-to-date, high quality evidence which was a randomised cross over trial by Eisenach[6] as the basis of this section of the report.

This cross-over trial randomised patients with chronic pain already receiving IT morphine for 6 weeks to receive preservative free ketorolac, 2mg, or placebo (saline) on their first visit, with the alternative treatment on their second visit. Patients returned after at least one week, but no more than 3 months later, for the crossover treatment. This study reported no significant difference in

pain intensity and unpleasantness between ketorolac and placebo. There was also no difference in the incidence of adverse events between groups.

These results however, are limited by small sample size and the amount and timing of ketorolac dosing. Furthermore it is unclear whether the results were subject to carryover effects between the treatment phases as a wash out period was not reported. The generalisability of the results is also unclear as the authors state "That the paper was more fundamental than practical, since there no longer exists a preservative free solution of ketorolac for spinal administration" (personal correspondence).

Table 5. Key information from most recent, comprehensive, high quality primary study *(Eisenach 2010)* – OTHER MEDICATIONS (IT ketorolac)

Eisenach, J.C., et al., Role of spinal cyclooxygenase in human postoperative and chronic pain. Anesthesiology, 2010. 112(5): p. 1225-33.	
Study design	Randomised cross-over trial
Scope	**Patient/population:** n=12 **Conditions indicated for use:** Patients with chronic pain, already receiving IT morphine for at least 6 weeks **Intervention:** IT morphine (mean 9.8mg; range 1.3 – 50mg/day) with IT ketorolac (2.0mg) **Comparator**: Saline + IT morphine (mean 9.8mg; range 1.3 – 50mg/day) **Outcomes assessed:** Pain intensity (pain score and ≥30% or 50% pain relief), unpleasantness and adverse events
Efficacy and effectiveness of IT drug infusion for persistent pain	"Both pain intensity (P = 0.01) and unpleasantness (P = 0.02) decreased with time after intrathecal injections, but there was no difference between ketorolac and saline, and there was no significant interaction between treatment and time."
Effect of IT drug infusion on function, quality of life, return to work, medication use and use of the healthcare system?	Not reported
Which patient groups/conditions is use of IT drug infusion contraindicated?	Patients allergic to ketorolac or morphine Pregnant women
Risks associated with use of IT drug infusion	No significant difference in the occurrence of adverse events was reported between ketorolac and placebo. Following IT ketorolac adverse events included mild sedation lasting < 2 hours (n = 2), mild dizziness lasting < 2 hours (n = 1), hot sensation in the back, headache, urinary retention and hives (n = 1) 4 days after injection, lasting < 4 hours. Following IT saline adverse events included mild sedation lasting < 1 hr

	(n = 2), mild nausea lasting < 1 hr (n = 2), mild headache lasting < 2 hr (n = 1). Two serious adverse events occurred. One patient experienced a numb left leg for less than 2 h after intrathecal injection of saline, and, as noted, this subject's pump contained bupivacaine. One patient committed suicide 6 months after study.
Conclusion/ Recommendation	"We failed to observe greater analgesia from intrathecal ketorolac than saline placebo in patients with primarily low back and lower extremity pain and a combination of somatic and neuropathic components". "2 mg of intrathecal ketorolac was not associated with serious side effects, failed to reduce ongoing pain in chronic pain patients more than placebo….These observations are limited by the small number of subjects studied, and patient population, and the amount and timing of ketorolac dosing." "Under the conditions of these studies, it seems that spinal cylcooxygenase activity does not contribute to chronic…pain."
Recommendation category	Insufficient evidence
Quality assessment results	The overall risk of bias was low-moderate with the authors not reporting on the allocation concealment, degree of error in group results and longer term treatment.
Our comments/summary	The authors were contacted regarding key methodological aspects which were not reported in paper. This included whether the groups were treated the same, if outcome measures were assessed independently and if the outcome assessors were blind to the intervention group. The authors stated that all of these were met. Patients were studied twice (cross-over study), hence they received placebo and ketorolac but at two alternative visits. A cross-over period of at least 1 week but no greater than 3 months was reported, suggesting some assurance of no direct placebo-ketorolac interactions which would modify the result (true effect size). However, it is unknown if the initial pain intensity and symptoms returned to test the efficacy of the second drug treatment, either saline or ketorolac. The study does not report the origin or type of pain patients enrolled in the RCT experienced, i.e. neuropathic or CRPS etc. This might have an impact on the response to pain reduction. Although the sample size for the RCT was only 12 patients, the authors of the study had justified this size well before conducting the study. Overall the study revealed no greater pain relief with IT ketorolac and IT morphine in comparison to IT morphine and saline (control).

Findings

Based on the findings of one cross-over trial there is **insufficient evidence** to determine whether IT ketorolac is effective in reducing chronic pain.

DISCUSSION & CONCLUSION

As a number of evidence syntheses assessing the effectiveness of IT infusion for chronic, persistent pain were identified, a pragmatic yet rigorous approach was taken whereby the best quality, most up-to-date source of evidence for each drug category was used to answer the review questions.

For all drug categories there is insufficient evidence to determine whether IT infusion is effective in relieving persistent pain and improving functional outcomes and quality of life in non-cancer patients. Although a number of well conducted SRs were identified, the evidence base of these was poor as the included studies were case series. Furthermore individual studies had no control groups and small sample sizes. The results of case series are difficult to interpret as influences of regression to the mean and selection bias cannot be ruled out. Furthermore the lack of a control group has the potential to obscure a relationship between treatment and outcome or suggest an association where one does not exist.

More studies are required to assess the risks associated with IT infusion. Only one systematic review reported on adverse events associated with the pump/device.[2] These included pump and catheter malfunctions and malpositioning, surgical complications, and postsurgical complications. Drug-related adverse events associated with the use of IT morphine, baclofen, ziconotide, and ketorolac alone were not reported by the primary studies. Only the randomised cross-over trial comparing morphine/ketorolac and morphine/saline combination therapy reported drug-related adverse events [6]. Although no significant difference was observed between groups, mild sedation and headache were the most commonly occurring adverse effects.

Based on the evidence, the indication for IT use is unclear. The patient groups recruited by the studies were broad, e.g. adults with non cancer pain of three months duration,[2] patients with persistent pain[3] or patients with chronic pain receiving IT morphine for at least 6 weeks.[6] Furthermore, none of the studies reported the origin or type of pain experienced by the patients.

Currently there is limited evidence to assess the efficacy of IT therapy for persistent non-cancer pain. Further studies are needed to address long term effectiveness and safety of IT agents both alone and in combination and assess in which population these are most suitable.

DISCLAIMER

The information in this report is a summary of that available and is primarily designed to give readers a starting point to consider currently available research evidence. Whilst appreciable care has been taken in the preparation of the materials included in this publication, the authors and the National Trauma Research Institute do not warrant the accuracy of this document and deny any representation, implied or expressed, concerning the efficacy, appropriateness or suitability of any treatment or product. In view of the possibility of human error or advances of medical knowledge the authors and the National Trauma Research Institute cannot and do not warrant that the information contained in these pages is in every aspect accurate or complete. Accordingly, they are not and will not be held responsible or liable for any errors or omissions that may be found in this publication. You are therefore encouraged to consult other sources in order to confirm the information contained in this publication and, in the event that medical treatment is required, to take professional expert advice from a legally qualified and appropriately experienced medical practitioner.

CONFLICT OF INTEREST

The TAC/WSV Evidence Service is provided by the National Trauma Research Institute. The NTRI does not accept funding from pharmaceutical or biotechnology companies or other commercial entities with potential vested interest in the outcomes of systematic reviews.

The TAC/WSV Health Services Group has engaged the NTRI for their objectivity and independence and recognise that any materials developed must be free of influence from parties with vested interests. The Evidence Service has full editorial control.

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