Spinal analgesics in adult patients with cancer pain: a systematic review EAPC RN Project

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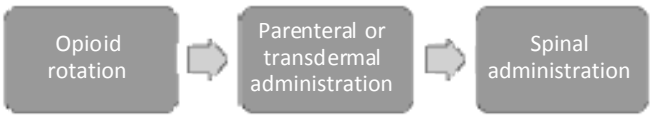
Cancer pain management

- The WHO analgesic ladder relieves 70-90%
  - About 10% may need other therapy
  - About 2% may need spinal therapy

When the analgesic ladder fails:



Hogan et al 1991, Lamer 1994, Zech et al 1995, Meuser et al 2001

Method

Aim

This systematic review aimed to analyze analgesic efficacy and side effects of analgesics opioids and non-opioids by spinal route in adult patients with cancer previously treated with systemic opioids.

Research question

"In adult patients with intractable cancer pain by systemic analgesics, what is the evidence to support the administration of analgesics given spinally considering balance between analgesia and side effects?"

Method

Inclusion criteria

- Investigation of the clinical effects of long-term spinal analgesic treatment on adult patients with cancer pain
- Previous systemic opioid treatment that failed to control cancer pain and/or intolerable side effects.
- English language

Exclusion criteria

- Postoperative, pharmacokinetic and experimental studies
- Case reports (sample < 20 patients), retrospective studies and reviews
- Studies exclusively reporting complications
- Obsolete drugs for spinal application

Search strategy

Databases: PubMed, Embase and Cochrane

Search strategy: PICO framework

Patient	cancer OR neoplasm OR tumor OR tumour OR oncol* OR carcinoma* OR malignan*
	pain
Intervention	epidural OR intrathecal OR subarachnoid OR spinal OR neuraxial
	neuraxial block OR intrathecal root OR spinal root OR neurolysis OR neuraxial infusion OR neuroaxial infusions OR epidural analgesia OR injections, epidural OR infusions, spinal OR spinal infusion OR spinal infusions OR intraspinal injections or spinal injections OR injection, spinal OR spinal injection OR injection, intraspinal OR injections, intraspinal OR intraspinal injection OR injections, intrathecal OR injection, intrathecal OR intrathecal injection OR intrathecal injections OR block* OR root* OR infusion* OR injection* OR analgesi* OR treat* OR cathe* OR needle OR pump OR device OR syringe OR cannula OR pain relief OR neurolys*
Outcome	side effects OR side effect OR adverse effect OR adverse effects OR analgesi*
NOT	procedur* pain OR postoperative pain OR perioperative pain OR non-malignan* pain OR noncancer pain OR non-cancer pain OR nonmalignan* OR peripheral nerve block OR peripheral sympathetic block OR celiac plexus OR vertebroplast* OR child* OR pediatric* OR paediatric*

Quality scoring system

Studies were graded according to a quality scoring system (GRADE):

- +4 or A= high quality (further research is very unlikely to change confidence in the estimate of effect)
- +3 or B = moderate (further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate)
- +2 or C = low (further research is very likely to have an important impact on confidence in the estimate of effect and may change the estimate)
- +1 or D = very low (any estimate of effect is very uncertain)

Atkins et al, BMJ 2004
Grade Working Group, BMJ 2010

RCTs had an initial score of +4

Points were subtracted if:

- Study limitations (blinding and allocation concealment process, losses to follow-up, failure to adhere to an intention-to-treat analysis)
- Inconsistent results/outcomes across studies
- Indirectness of the evidence (poor generalisability of the results)
- Imprecise or sparse data (wide confidence intervals, large p-value)
- High probability of bias (small number of trials, sponsored by pharmaceutical industry)

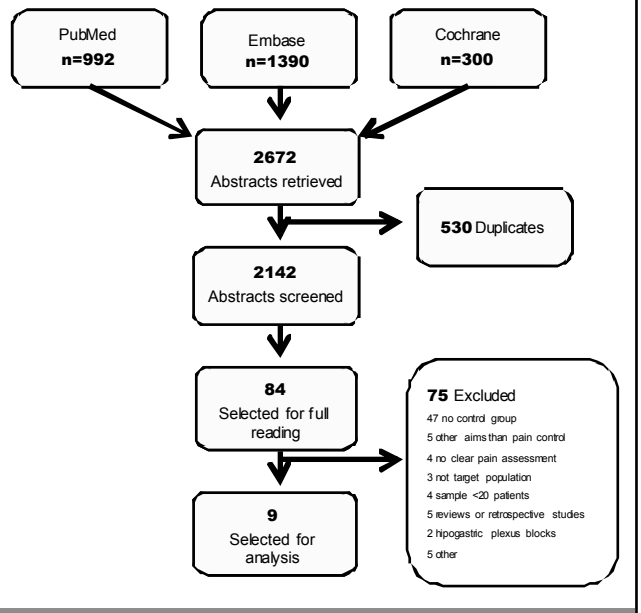
Atkins et al, BMJ 2004
Grade Working Group, BMJ 2010

Strength of recommendation

Based on the quality of evidence

1. Strong for using the intervention
2. Weak for using the intervention
3. Weak against using the intervention
4. Strong against using the intervention

Results



Results

Opioid and adjuvant analgesic vs. opioid alone (n=4)

Author, year	Design	N	Dose	Implantable system	Duration	Pain relief	Side effects
Boersma et al., 1992	RCT sb	12 epi sufentanil 10 epi sufentanil+bupivacaine	?	yes	3-4 days titration + 14 days	Yes, but treatment comparison inconclusive	-
Eisenach et al., 1995	RCT db	38 epi mor + clonidine 47 epi mor + placebo	mor: 36-67 mg/d clonidine: 30 μg/h	no	1-7 days trial + 14 days	Yes clonidine superior in neuropathic pain	Clonidine: ↑hypotension ↓nausea

morphine + / - clonidine = + clonidine
morphine + / - ketamine = + ketamine

Results

Single spinal drug in bolus vs. continuous administration (n=3)

Author, year	Design	N	Dose	Implantable system	Duration	Pain relief	Side effects n
Gourlay et al., 1991	RCT	14 epi/it morphine bolus 14 epi/it morphine continuous	24mg/d 20mg/d	yes	2 days trial + 140 d bolus + 169 d continuous	2.72 (bolus) 3.12 (continuous)	no difference
Gupta et al., 2008	RCT	37 epi aqueous phenol bolus 41 epi aqueous phenol continuous	6% (2ml)	no	1 week observation + 3 months	57% (bolus) 100% (continuous)	similar frequences

Continuous x bolus infusion = continuous

Results

Single spinal drug vs. placebo (n=1)

Author, year	Design	N	Dose	Implantable system	Duration	Pain relief	Side effects n
Staats et al., 2004	RCT db	68 it ziconotide (59 cancer) 40 it placebo (36 cancer)	max 2.4µg/h	yes	5-6 titration + 5 days	≈54 % (zicono) ≈18 % (placebo) (P=0.02)	more frequent with ziconotide, but no separate analyses for cancer

Ziconotide x placebo = ziconotide

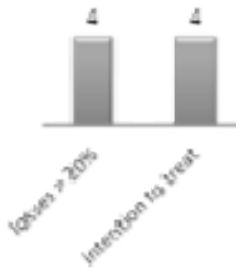
Results

Opioid +/- adjuvant analgesic vs. comprehensive medical management(n=2)

Author, year	Design	N	Dose	Implantable system	Duration	Pain relief	Side effects
Smith et al., 2002	RCT	71 it morphine/hydromorphone 72 comprehensive medical management	2 mg/d (median)	yes	1-2 days trial + 4 week	Yes, but treatments did not differ	toxicity reduction on implantable system group
Smith et al., 2005	RCT	52 it mor/hydromor /91 medical management (4 w) 57 it mor//hydromor /45 medical management (12 w) 45 it mor/hydromor /31 medical management (6 m)	250 mg/d mean oral eq.	yes	1-2 days trial + 12 weeks	Yes, but implantable system superior only at 4 weeks	toxicity reduction on implantable system group

It morphine/hydromorphone x comprehensive medical management = less toxicity, but analgesic effect not sustained for >4 weeks

Results: Quality



Results: Quality

Author, year	Drug	Limit	Consist	Direct	Imprecise or sparse data	Bias
Boersma et al., 1992 Eisenach et al., 1995 Van Dongen et al., 1999 Lauretti et al., 1999	morphine + clonidine/ketamine	-2	-	-1	-1	-1
Gourlay et al., 1991 Gupta et al., 2008	morphine bolus/continuous aqueous phenol bolus/continuous	-2	-	-1	-1	-1
Staats et al., 2004	ziconotide/placebo	-2	-	-1	-1	-1
Smith et al., 2002 Smith et al. 2005	It mor/hydromorphone (+/-adjuvant)	-2	-	-1	-	-1

Results: Quality

- Spinal opioids vs. spinal opioids + adjuvant drugs: very low quality
- Bolus vs. continuous spinal infusion: very low quality
- Spinal ziconotide vs. placebo: very low quality
- Intrathecal opioids vs. comprehensive medical management: very low quality

Conclusion

- The studies analysed provide very low quality of evidence and weak recommendation for using spinal analgesics alone or in combination with other drugs in adult cancer patients
- As spinal therapies are widely considered and used as alternatives when systemic opioids fail further research and improved methodologies are necessary.