Latest developments in invasive analgesic therapy recommendations for cancer pain according to the updated EAPC guidelines and future perspectives

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The presentation is based on three systematic reviews:

1) analgesic efficacy and side effects of opioids +/- adjuvant analgesics delivered by spinal route in patients with cancer
2) analgesic efficacy of sympathetic blocks in adult patients with cancer
3) analgesic efficacy of peripheral nerve blocks in adult patients with cancer

Methods: 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

Methods: Quality scoring system

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, small samples, 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

Methods: 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

The evidence of neuraxial administration of analgesics for cancer-related pain: a systematic review

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Cancer pain management

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

When the analgesic ladder fails:

Opioid rotation → Parenteral or transdermal administration → Spinal administration

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

Aim

Research question

'In adult patients with intractable cancer pain in spite of systemic analgesics, what is the evidence from literature to support the spinal administration of analgesics considering balance between analgesia and side effects?'

Aim

to analyze the published evidence regarding analgesic efficacy and pharmacological side effects of spinal drug delivery in patients with cancer.

Methods: 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*

Methods

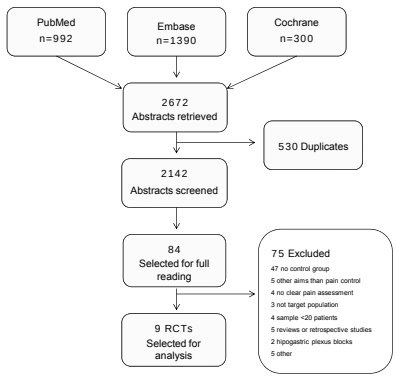
Inclusion criteria

1. RCTs, which have been conducted to investigate the effects of long-term spinal analgesic treatment.
2. Adult patients with chronic pain due to cancer.
3. Patients previously treated with systemic opioids, which failed to control cancer pain and/or induced intolerable side effects.
4. Data on the relevant outcomes (pain intensity and/or side effects).
5. Written in English language

Exclusion criteria

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

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
Van Dongen et al., 1999	RCT db	9 it morphine 11 it mor+bupivacaine	mor: 1.2-7.2 mg/d bupi: 5-21.6 mg/d	yes	10 - 40 days	Yes, but no p-values	muscular weakness mor: 1/ mor+bupi: 3
Lauretti et al., 1999	RCT db	12 epi morphine 12 epi mor+ketamine 12 epi mor+neostigmine 12 epi mor+midazolam	mor: 4mg/d ketamine: 0.2 mg/kg/d neostigmine: 100µg/d midazolam: 500µg/d	yes	no trial described 25 days	Yes ketamine is superior	no difference

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

Results

Single spinal drug in bolus vs continuous administration (n=2)

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 vs 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 vs placebo = Ziconotide

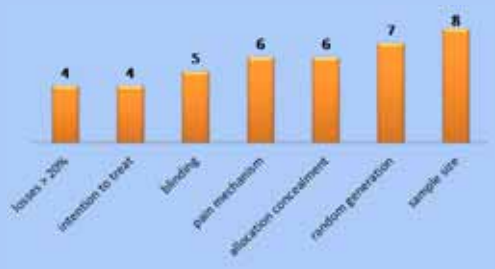
Results

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

Author, year	Design	N	Dose	Implantable system	Duration	Pain relief	Side effects
Smith et al., 2002 Smith et al., 2005	RCT	71 it mor/hydromor 72 CMM 52 it mor/hydromor 91 CMM (4 w) 57 it mor/hydromor 45 CMM (12 w) 45 it mor/hydromor 31 CMM (6 m	2 mg/d (median) 250 mg/d mean oral eq. g/d (median)	yes	1-2 days trial + 4 and + 12 weeks	not significant effect and implantable system superior only at 4 weeks	toxicity reduction on implantable system group Prolonged survival by it group

It mor/hydromor vs CMM = It
less toxicity, but analgesic effect only marginally improved at 4 weeks

Results: Quality of evidence



Conclusion

- All RCTs analysed provide very low quality of evidence and, thus, 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.
- Adjuvant drugs of interest for further studies: Bupivacaine, clonidine and ziconotide.

Sympathetic blocks for visceral cancer pain management: A systematic review

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Background

The neurolytic blocks of sympathetic pathways at different levels:

- Celiac plexus block (CPB) is targeted for cancer pain originating from upper abdominal viscera
- Superior hypogastric plexus block (SHPB) is targeted for cancer pain originating from pelvic viscera

Aim

Research question

'In adult cancer patients with abdominal pain, what is the evidence to support the performance of sympathetic blocks?`

Aim

to analyze the published evidence regarding analgesic efficacy and side effects of CPB and SHPB in patients with cancer.

Methods: 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	neuraxial coeliac plexus blockade OR superior hypogastric plexus block
	celiac plexus or plexus, celiac or coeliac plexus or plexus, coeliac or plexus coeliacus or coeliacus, plexus or solar plexus or plexus, solar or hypogastric plexus or plexus, hypogastric or pelvic plexus or plexus, pelvic block, nerve or blocks, nerve or nerve blocks or nerve blockade or blockade, nerve or blockades, nerve or Nerve blockades or chemical neurolysis or chemical neurolyses or neurolyses, chemical or neurolysis, chemical or chemodenervation or chemodenervations or deafferentation
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 vertebroplast* OR child* OR pediatric* OR paediatric*

Methods

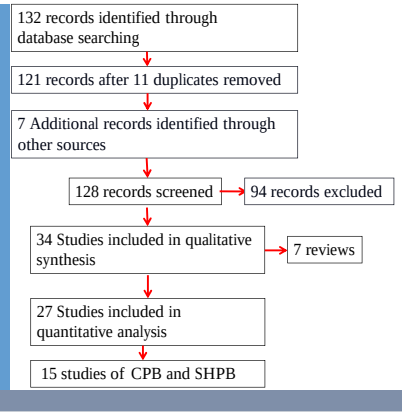
Inclusion criteria

1. Interventional techniques were compared with analgesics or placebo.
2. Adult patients with chronic pain due to cancer.
3. Data on the relevant outcomes (pain intensity and/or side effects).
4) Written in English language

Exclusion criteria

1. Other clinical indications and outcomes.
2. Studies exclusively reporting complications

Results



Results: CPB and SHPB vs analgesics or other treatments

Authors	Comparative groups	Techiques	Design	N°	Duration	Pain	Adverse effects Complications
Mercadante,1993	CPB+A A	Post	RCT	20	Till death	= pain score - opioid cons	- AE
Lillemoe, 1993 Staats, 2001	CPB+A PL+A	Intraop spl	RCT DB	137	Till death	+ pain score + survival + mood -pain interference	NA
Kawamata, 1996	CPB+A A	Post	RCT	21	Ten weeks	+pain score -opioid cons - QoL deterioration	- AE
Polati, 1998	CBP+A A	Post	RCT DB	24	Till death	= pain score -opioid cons	- AE
Shulman, 2000	CPB+A EP butambien+A	Post EP	C	24		= pain score = opioid cons	= AE
Okuyama, 2002	CPB A	Intraop	C	21	Till death	-opioid cons + survival	- AE
Jain, 2005	CBP A	Post	C	100	1 mo	+ pain score -opioid cons = QoL	- AE
Wong, 2004	CBP+A LA+A	Post	RCT DB	101	24 weeks	+ pain score = opioid cons = QoL + survival	= AE
De Oliveira, 2004	CPB/SHPB/LB Early= morphine ≤90 mg≤ CPB/SHPB/LB Late = morphine ≥90m A	CPB/SHPB/LB	RCT	44	8 weeks	At any morphine dose CPB/SHPB/LB + pain score - opioid cons + QoL	-AE

Results: CPB and SHPB vs analgesics or other treatments

Authors	Comparative groups	Techiques	Design	N°	Duration	Pain	Adverse effects Complications
Johnson,2007	CPB/TS +A A	CPB/TS	RCT	65	2 months	= pain score =opioid cons	= AE
Stefaniak. 2005	CPB/ TS A	CPB/TS	C	98	8 weeks	+pain score +QoL	NA
Zhang, 2008	CPB+A A	CPB CT post	RCT	56	3 months	+ pain score (2 weeks) - opioid cons = QoL	- AE
Wise, 2011	Early CPB+A A	EU	RCT DB	96	1 + 3 months	+ pain score = opioid cons = QoL =survival	NA
Amr, 2013	Early CPB+A Late CPB+A	Post	RCT	60	One year	-pain score + opioid cons -QoL	+AE
Mishra, 2013	SHPB +A A	EU	RCT	50	3 mo	+ pain score -opioid cons	= AE

Results: Quality of evidence

Authors	Limitation	Directeness	Imprecise or Sparse data	High probability of bias	Factors that increase quality	Quality of evidence
Mercadante,1933	-2		-1			Very low quality
Lillemoe, 1993	-1	-2		-1		Very low quality
Kawamata, 1996	-2		-1			Very low quality
Polati, 1998	-2		-1	-1		Very low quality
Shulman, 200	-2	-1	-1	-1		Very low quality
Steels, 2001	-1	-1		-1		Very low quality
Okuyama, 2002	-2	-1	-2	-1		
Jain, 2005	-2	-1	-1			
Wong, 2004					+1	High quality
De Oliveira, 2004	-2	-1	-1	-1		Very low quality
Johnson,2008	-2	-1	-1	-1		Very low quality
Stefaniak. 2005	-2	-1	- 1	-1		Very low quality
Zhang, 2008	-2	-2	-1	-1		Very low quality
Wise, 2011					+1	High quality
Amr, 2013	-1			-1		Very low quality
Mishra, 2013	-2		-1	-1		Very low quality

Discussion of CPB

- Technique: No difference were found between CPB techniques (classical, transaortic or splanchnicectomy). CT and US-guided procedures may prove to be favorable.
- Timing: Pain relief may be more pronounced, when the blocks had been performed early (WHO step 1).
- Anatomical distribution: Outcomes may be favorable if the tumor is involving the head of pancreas than body and tail. Further, spread to other structures is associated with poorer outcomes.

Conclusion

- There is strong recommendation for using CPB for cancer pain originating from pancreatic cancer.
- There is weak recommendation for using SHPB for cancer pain originating from pelvic viscera.

The evidence of peripheral nerve blocks for cancer-related pain: a systematic review

MINERVA ANESTHESIOL 2015

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Methods: 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	peripheral nerve OR nerve, peripheral OR nerves, peripheral
	block, nerve OR blocks, nerve OR nerve blocks OR nerve blockade OR blockade, nerve OR blockades, nerve OR nerve blockades OR chemical neurolysis OR chemical neurolyses OR neurolyses, chemical OR neurolysis, chemical OR chemodenervation OR chemodenervations OR deafferentation
Outcome	side effects OR side effect OR adverse effect OR adverse effects OR analgesi*
NOT	procedural pain OR postoperative pain OR perioperative pain OR non-malignan* pain OR noncancer pain OR non-cancer pain OR nonmalignan* OR vertebroplast* OR celiac plexus OR plexus, celiac OR celiac plexus OR plexus, celiac or plexus coeliacus OR coeliacus, plexus OR solar plexus OR plexus, solar OR hypogastric plexus OR plexus, hypogastric OR pelvic plexus OR plexus, pelvic OR child* OR pediatric* OR paediatric*

Methods

Inclusion criteria

1) Studies which have been conducted to investigate the effects of peripheral nerve blocks

2) Adult patients with chronic pain due to cancer

3) Data on the relevant outcomes including pain intensity

4) Written in English language

Exclusion criteria

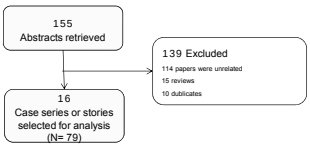
1. Post-operative pain management or other irrelevant therapies,

2) Studies with mixed populations not providing separate results for cancer patients

3) Trials without assessment of pain

4) Experimental studies

Results



The blocks applied were intercostal blocks (N=43), plexus blocks (N=13), paravertebral blocks (N=10), blocks in the head region (N=2) and others (N=11).

Local anesthetics were used in most cases; however, neurolytic blocks were used in 35 cases often preceeded by local anesthetics.

Most cases reported good pain relief and no side effects. The durations of efficacy were usually in the range of several weeks, often until death.

Conclusion

- The use of peripheral blocks for cancer pain is based upon anecdotal evidence.
- The case reports demonstrate the potential for peripheral block to give pain relief to selected cancer pain patients.

Over-all and future considerations

- The lack of “good” studies is not equal to lack of effectiveness.
- The definitive role of these techniques has to be defined.
- These techniques could lower the needed dose of conventional analgesics – especially opioids.
- Innovation in anesthetics techniques including the use of ultrasound and CT to identify nerves and other anatomical structure.
- Performance of each procedure should be based on an individual evaluation of each patient.