Kliiniline küsimus nr. 5
Kas valuravi alustamine vs mittealustamine preoperatiivses perioodis mõjutab kroonilise postoperatiivse valu tekke tõenäosust?
Tulemusnäitajad: *valu tugevus (erinevatel ajahetkedel, nt 6.,12. kuul)*

Süstemaatilised ülevaated*:*
Kokkuvõte: leitud süstemaatilistes ülevaadetes ainult ühes (Bong 2005) on hinnatud preoperatiivset valuravi alustamist vs postoperatiivne alustamine. Ülejäänutes, ka ravijuhendite soovituste aluseks olevates uuringutes on hinnatud valuravi alustamist erinevatel ajahetkedel.

ANDREAE 2012- 23 RCT, included studies comparing local anaesthetics or regional anaesthesia vs conventonal pain control, **any time window**. Operations: breast surgery, Caesarean section, hernia repair, laparotomy, amputation, thoracatomy.
Chronic pain at 6 months:
Epidural analgesia (3 RCTs, 250 pt) **reduces** the risk after open thoracotomy OR 0.34 (95% CI 0.19-0.60), p = 0.0002
Paraveretebral block (2 RCTs, 89 pt) **reduces** the risk after breast surgery OR 0.37 (95% CI 0.14-0.94) , p = 0.04

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Should thoracic epidural anaesthesia versus conventional pain control be used to prevent persistent (chronic) pain after open thoracotomy

Patient or population: open thoracotomy[1]
Settings: University Hospital
Intervention: thoracic epidural anaesthesia[2]
Comparison: conventional pain control[3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Conventional pain control	Thoracic epidural anaesthesia				
Persistent Pain Six Months after Thoracotomy telephone interview six months after surgery Follow-up: mean 6 months[4]	**Study population**[5]		**OR 0.34** (0.19 to 0.6)	250 (3 studies)	⊕⊕⊕○ **moderate**[6,7,8,9]	
	649 per 1000	**386 per 1000** (260 to 526)				
	Low[5]					
	250 per 1000	**102 per 1000** (60 to 167)				
	Moderate[5]					
	500 per 1000	**254 per 1000** (160 to 375)				
Adverse Effects of Epidural Anaesthesia - not reported	See comment	See comment	Not estimable	-	See comment	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] All studies investigated persistent (chronic) pain after open thoracotomy. The results cannot be extended to video-assisted thoracotomy or other (minimal invasive) surgeries of the chest.
[2] All included studies used thoracic epidural anaesthesia. The results cannot be extended to other interventions like paravertebral blocks.
[3] Conventional pain control with opioids and NSAID was the comparator
[4] There was insufficient data at 12 months after surgery for evidence synthesis.
[5] Event rates of persistent pain after thoracotomy are reported between 25% to 65%.
[6] While outcome observers blinding was described, study participants were not blinded; this is acceptable because participant and provider blinding is difficult in regional anaesthesia.
[7] None of the studies performed an intention to treat analysis. Considerable attrition might have lead to bias.
[8] There was no evidence of heterogeneity. The effects estimates were homogenous.
[9] Thoracic epidural anaesthesia may prevent persistent (chronic) pain after open thoracotomy in one out of four patients treated.

BONG 2005- effects of preemptive epidural analgesia on post-thoracotomy pain. 3 studies with 206 patients estimating the effect on chronic pain at 6 months.
Relative benefit in preemptive group, not statistically signifficant RR 1.32 (95% CI 0.76 – 2.3)

CHAPARRO 2013- 40 RCTs of various pharmacological interventions including intravenous ketamine (14 RCTs), oral gabapentin (10 RCTs), oral pregabalin (5 RCTs), non-steroidal anti-inflammatories (3 RCTs), intravenous steroids (3 RCTs), oral N-methyl-D-aspartate (NMDA) blockers (3 RCTs), oral mexiletine (2 RCTs), intravenous fentanyl (1 RCT), intravenous lidocaine (1 RCT), oral venlafaxine (1 RCT) and inhaled nitrous oxide (1 RCT). Drugs administred pre, intra or postoperatively, by any dose, route or frequency.
Meta-analysis suggested a modest but statistically significant reduction in the incidence of chronic pain after surgery following treatment with ketamine but not gabapentin or pregabalin. Results with ketamine should be viewed with caution since most of the included trials were small (that is < 100 participants per treatment arm), which could lead to the overestimation of treatment effect.
Available evidence does not support the efficacy of gabapentin, pregabalin, non-steroidal anti-inflammatories, intravenous steroids, oral NMDA blockers, oral mexiletine, intravenous fentanyl, intravenous lidocaine, oral venlafaxine or inhaled nitrous oxide for the prevention of chronic postoperative pain.

Results (RR, effect size)

Time	**Ketamine ↓**		**Gabapentine ↔**		**Pregabaline ↔**	
	Nr studies/ pt	Result	Nr studies/ pt	Result	Nr studies/ pt	Result
3 mo	5/384	0.82 (0.61-1.11)	5/280	0.99 (0.80-1.21)	4/439	0.70 (0.51-0.95)
6 mo	8/516	0.63 (0.47-0.83)	2/116	1.10 (0.72-1.68)	1/228	0.53 (0.30-0.93)
12 mo	2/104	0.26 (0.06-1.15)	NR	NR	1/60	0.63 (0.23-1.69)

Viited

Kokkuvõtte (abstract või kokkuvõtlikum info)	Viide kirjandusallikale
Background Regional anaesthesia may reduce the risk of persistent (chronic) pain after surgery, a frequent and debilitating condition. We compared regional anaesthesia *vs* conventional analgesia for the prevention of persistent postoperative pain (PPP). **Methods** We searched the Cochrane Central Register of Controlled Trials, PubMed, EMBASE, and CINAHL from their inception to May 2012, limiting the results to randomized, controlled, clinical trials (RCTs), supplemented by a hand search in conference proceedings. We included RCTs comparing regional *vs* conventional analgesia with a pain outcome at 6 or 12 months. The two authors independently assessed methodological quality and extracted data. We report odds ratios (ORs) with 95% confidence intervals (CIs) as our summary statistic based on random-effects models. We grouped studies according to surgical interventions. **Results** We identified 23 RCTs. We pooled data from 250 participants in three trials after thoracotomy with outcomes at 6 months. Data favoured epidural anaesthesia for the prevention of PPP with an OR of 0.33 (95% CI 0.20–0.56). We pooled two studies investigating paravertebral block for breast cancer surgery; pooled data of 89 participants with outcomes ~6 months favoured paravertebral block with an OR of 0.37 (95% CI 0.14–0.94). Adverse effects were reported sparsely. **Conclusions** Epidural anaesthesia and paravertebral block, respectively, may prevent PPP after thoracotomy and breast cancer surgery in about one out of every four to five patients treated. Small numbers, performance bias, attrition, and incomplete outcome data especially at 12 months weaken our conclusions.	**Regional anaesthesia to prevent chronic pain after surgery: a Cochrane systematic review and meta-analysis** *Cochrane Database of Systematic Reviews* 2012, Issue 10 M. H. Andreae and D. A. Andreae
Abstract **BACKGROUND:** Chronic pain can often occur after surgery, substantially impairing patients' health and quality of life. It is caused by complex mechanisms that are not yet well understood. The predictable nature of most surgical procedures has allowed for the conduct of randomized controlled trials of pharmacological interventions aimed at preventing chronic postsurgical pain. **OBJECTIVES:** The primary objective was to evaluate the efficacy of systemic drugs for the prevention of chronic pain after surgery by examining the proportion of patients reporting pain three months or more after surgery. The secondary objective was to evaluate the safety of drugs administered for the prevention of chronic pain after surgery. **SEARCH METHODS:** We identified randomized controlled trials (RCTs) of various systemically administered drugs for the prevention of chronic pain after surgery from CENTRAL, MEDLINE, EMBASE and handsearches of other reviews and trial registries. The most recent search was performed on 17 July 2013. **SELECTION CRITERIA:** Included studies were double-blind, placebo-controlled, randomized trials involving adults and evaluating one or more drugs administered systemically before, during or after surgery,	***Pharmacotherapy for the prevention of chronic pain after surgery in adults.*** *Chaparro LE*, *Smith SA*, *Moore RA*, *Wiffen PJ*, *Gilron I*. *The Cochrane Library* 2013, Issue 7

or both, which measured pain three months or more after surgery. **DATA COLLECTION AND ANALYSIS:** Data collected from each study included the study drug name, dose, route, timing and duration of dosing; surgical procedure; proportion of patients reporting any pain three months or more after surgery, reporting at least 4/10 or moderate to severe pain three months or more after surgery; and proportion of participants dropping out of the study due to treatment-emergent adverse effects. **MAIN RESULTS:** We identified 40 RCTs of various pharmacological interventions including intravenous ketamine (14 RCTs), oral gabapentin (10 RCTs), oral pregabalin (5 RCTs), non-steroidal anti-inflammatories (3 RCTs), intravenous steroids (3 RCTs), oral N-methyl-D-aspartate (NMDA) blockers (3 RCTs), oral mexiletine (2 RCTs), intravenous fentanyl (1 RCT), intravenous lidocaine (1 RCT), oral venlafaxine (1 RCT) and inhaled nitrous oxide (1 RCT). Meta-analysis suggested a modest but statistically significant reduction in the incidence of chronic pain after surgery following treatment with ketamine but not gabapentin or pregabalin. Results with ketamine should be viewed with caution since most of the included trials were small (that is < 100 participants per treatment arm), which could lead to the overestimation of treatment effect. **AUTHORS' CONCLUSIONS:** Additional evidence from better, well designed, large-scale trials is needed in order to more rigorously evaluate pharmacological interventions for the prevention of chronic pain after surgery. Furthermore, available evidence does not support the efficacy of gabapentin, pregabalin, non-steroidal anti-inflammatories, intravenous steroids, oral NMDA blockers, oral mexiletine, intravenous fentanyl, intravenous lidocaine, oral venlafaxine or inhaled nitrous oxide for the prevention of chronic postoperative pain.	
Abstract **OBJECTIVE:** The purpose of this study was to determine whether preemptive thoracic epidural analgesia (TEA) initiated before surgical incision would reduce the severity of acute post-thoracotomy pain and the incidence of chronic post-thoracotomy pain. **METHOD:** Meta-analysis of randomized controlled trials (RCTs). **SEARCH STRATEGY:** MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE were searched from 1966 to December 2004 for prospective RCTs published in all languages using the following MeSH terms: post-thoracotomy pain, epidural analgesia, chronic pain, and preemptive analgesia. **SELECTION CRITERIA:** All RCTs that compared thoracic epidural analgesia initiated before surgical incision (preemptive group) versus thoracic epidural analgesia initiated after completion of surgery (control group) in adult patients undergoing unilateral thoracotomy. **MEASUREMENTS AND MAIN RESULTS:** Three authors reviewed all citations and simultaneously extracted data on sample size, patient characteristics, surgical and analgesic interventions, methods of pain assessment, and pain scores at 24 hours, 48 hours, and 6 months postoperatively. Six studies were included with a total of 458 patients. Pooled analyses indicated that preemptive TEA was associated with a statistically significant reduction in the severity of acute pain on	**Effects of preemptive epidural analgesia on post-thoracotomy pain** *Bong CL, Samuel M, Ng JM, Ip-Yam C.* J Cardiothorac Vasc Anesth. 2005 Dec;19(6):786-93.

coughing at 24 and 48 hours (weighted mean difference -1.17 [95% confidence interval (CI) -1.50 to -0.83] and -1.08 [95% CI -1.17 to -0.99]), respectively. Acute pain was a good predictor of chronic pain. However, there was no statistically significant difference in the overall incidence of chronic pain at 6 months between the preemptive TEA group (39.6%) and the control group (48.6%). **CONCLUSION:** Preemptive TEA appeared to reduce the severity of acute pain but had no effect on the incidence of chronic pain.	
Background / purpose: Chronic postoperative pain is a well-established clinical phenomenon that is associated with adverse outcomes. The incidence of this clinical phenomenon in children, however, is not well established. The purpose of this study was to identify the incidence of chronic pain in children after surgery. **Methods:** Following a screening process, a total of 113 children and their parents were enrolled in this cross-sectional study. Data regarding persistence and characteristics of pain after surgery were obtained. **Results**: Approximately 13% of the children, most of whom underwent orthopedic procedures, reported the existence of symptoms of chronic postoperative pain. Most of the children indicated that the pain started immediately after surgery, was localized to the surgery site, and was intermittent. Children reported a median duration of pain of 4.1 months, and approximately half of the children experienced pain most days of the week. Up to 30% of the children reported interference of pain in functioning in areas such as extracurricular activities and sleep. **Discussion**: Given the large number of children at risk for experiencing chronic postoperative pain, preventative efforts are necessary. Large-scale cohort prospective studies are needed to confirm the results of this cross-sectional study.	**Acute to chronic postoperative pain in children: preliminary findings** Michelle A. Fortier, Jody Chou a, Eva L. Maurer , Zeev N. Kain *Journal of Pediatric Surgery (2011) 46, 1700–1705*

Ravijuhendid

1. Acute Pain Management: Scientific Evidence 2010 (AU-10)
2. ” Behandlung acuter perioperativer und posttraumatischer Schmertzen ” 2009” (DE-09)

AU-10

Levels of evidence	
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-controlled studies or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test and post-test
Clinical practice points	
☑	Recommended best practice based on clinical experience and expert opinion

On tõdetud, et krooniline valu on sage probleem , väga olulisteks riskifaktoriteks on ravimata pre ja postoperatiivne äge valu. Ravijuhendi soovitused ei vasta täpselt küsimusele s.t enamustes

uuringutes on hinnatud perioperatiivseid meetodeid, osades on siiski hinnatud konkreetselt valuravi preoperatiivse alustamise mõju kroonilisele postoperatiivsele valule.
Soovitused on antud operatsiooniliikide kaupa.
Tabelis uuringud, millel soovitused põhinevad.

- Some specific early anaesthetic and/or analgesic interventions reduce the incidence of chronic pain after surgery (Level II)

Author, year, level of evidence	Patients	Intervention	Control	Results
Blumenthal , 2005, II	35 pt, iliac crest bone grafting	Wound infiltration (LA infusion 48 h)	Placebo	Pain at 3 months ↓
Batoz 2009, II	52 pt, craniotomy	Wound infiltration	Placebo	Pain at 2 months ↓

Günekoloogilised operatsioonid

- Spinal anaesthesia in comparison to general anaesthesia reduces the risk of chronic postsurgical pain after hysterectomy and Ceasarean section (Level IV)

Author, year, level of evidence	Patients	Intervention	Control	Result
Nikolajsen 2004, IV	220 , Ceaserean section	Questionnaire		Incidence of chronic pain 12,3%, general anaesthesia > spinal anaesthesia
Brandsborg 2007, IV	1299, hysterectomy	Questionnaire		General anaesthesia > spinal anaesthesia (OR 0.42; CI 0.21 to 0.85)
Fassoulaki 2007, II	60, hysterectomy	Gabapentin + wound infiltration	Placebo	Incidence ↓

Fantoomvalu

- Continous regional blockade via nerve sheath catheters provides effective postoperative analgesia after amputation, but has no preventive effect on phantom limb pain (Level II)
- Perioperative epidural analgesia reduces the incidence of severe phantom limb pain (Level III-2)
- Perioperative ketamine may prevent severe phantom limb pain (expert opinion)

Author, year, level of evidence	Patients	Intervention	Control	Result
Halbert 2002, I,	12 studies, 375 pt, amputation	Treatment of acute and chronic phantom limb pain		Pre-emptive epidural , early regional blocks ↔
Gehling 2003, III-2	Systematic review 3 RCTs, amputation	Perioperative epidural analgesia	Systemic analgesia	Perioperative epidural reduces pain at 12 months (NNT 5,8 95% CI 0.32 – 28.6)

Dertwinkel 2002, III-3	28 pt, amputation	i/v ketamine preop → 72 h postop	No ketamine	Severe pain ↓, overal incidence ↔
Hayes 2004, II	45 pt, amputation	i/v ketamine	Placebo	Incidence ↔
Wilson, 2008, II	53 pt, amputation	Epidural ketamine + bupivacaine infusion	Epidural saline + bupivacaine infusion	Incidence ↔

Post-thoracotomy pain syndrome

- Perioperative epidural analgesia reduces the incidence of post-thoracotomy pain syndrome (Level II)
- Cryoanalgesia for thoracotomy relieves postoperative pain but increases the risk of post-thoracotomy pain syndrome (Level II)

Author, year, level of evidence	**Patients**	**Intervention**	**Control**	**Result**
Sentürk, 2002 ,II	69, thoracotomy	1. Pre-op epidural 2. Post- op epidural	i/v PCA	At 6 months: chronic pain ↓: pre-TEA < post-TEA < i/v PCA

Bong 2005 , I	3 RCT, 206, thoracotomy	Pre-emptive epidural		↔
Suzuki 2006, II	49 pt, thoracotomy	Epidural + i/v ketamine	Epidural + i/v placebo	At 1 and 3 months: pain scores ↓
Ju 2008, II	107, thoracotomy	Epidural	Intercostal nerve cryoanalgesia	Chronic pain ↔; allodynia and pain scores ↑ cryoanalgesia group

Mastektoomia

- Preincisional paravertebral block and perioperative use of gabapentin, mexiletine and/ or eutectic mixture of local anaesthetic reduce the incidence of postmastectomy pain (Level II)

Author, year, level of evidence	**Patients**	**Intervention**	**Control**	**Result**
Kairaluoma, 2006, II	60 pt, mastectomy	Pre-incisional paravertebral block		At 12 months: prevalence and intencity of pain ↓
Fassoulaki 2002, II	75 pt, mastectomy	Mexiletine, gabapentine 10 days	Placebo	Chronic pain ↔
Fassoulaki 2000, II	46 pt, mastectomy	EMLA pre and postoperatively	Placebo	Incidence and intencity ↓
Fassoulaki 2005, II	50 pt, mastectomy	Gabapentin + EMLA + LA wound infiltration	Placebo	Incidence ↓

DE-09

Degree of recommendation	Level of evidence	
A	**1a**	Systematic review of controlled randomized clinical trials
	1b	Controlled randomized clinical trials with a strict confidence interval

	1c	“All or nothing” therapeutic results
B	**2a**	Systematic review of cohort studies
	2b	Cohort studies (including lesser quality randomized clinical trials)
	2c	Observation of therapeutic results (outcomes research).
	3a	Systematic review of case-control studies
	3b	Case-control study
C	**4**	Case report (including cohort or case-control of poor quality)
	5	Specialists’ opinions lacking critical evaluation or based on basic matters (physiological study or study with animals)

Ravijuhendis ei ole otseselt hinnatud preoperatiivset valuravi alustamist ning soovitused on antud ainult fantoomvalude esinemissageduse vähendamiseks. Olemasolev tõendusmaterjal on vastuoluline ja kindlaid soovitusi ei anna.

- Operatsioonieelsete ja järgsete valude ning ka tugevate fantoomvalude esinemissageduse vähendamiseks võib kasutada epiduraalanalgeesiat või perifeerseid närviblokaade (C)
- Kui see ei ole võimalik, siis intravenoosne PCA kombinatsioonis mitteopioidsete analgeetikumidega. (C)
- Perioperatiivselt võib ketamiini manustada (C)- põhineb kahel uuringul mis on ära toodud AU-10 juures (Hayes 2004 ja Dertwinkel 2002.

Author, year, level of evidence	**Patients**	**Intervention**	**Control**	**Result**
Gehling 2003, LoE 1a	3 RCTs, amputation	Perioperative epidural	Systemic analgesia	Severe phantom pain ↓, incidence of phantom pain ↔
Lambert 2001, LoE 1b	n = 30, amputation	Perioperative epidural analgesia	Continuous regional blockade (intra and postop)	Incidence of phantom pain 6 and 12 months ↔
Nicolajsen 1998 . LoE 1b	n = 31, amputation	Pre- intra and postoperative epidural analgesia	Placebo and systemic analgesia	Incidence and intensity of stump and phantom pain↔
Nikolajsen 1997a, LoE 1b	n = 56, amputation	Epidural analgesia 18 hours pre and postoperatively	Placebo	Incidence and intencity of phantom and stump pain ↔
Jahangiri 1994, LoE 2b	n= 24, amputation	Epidural analgesia 24 h pre until 3 days postop	Systemic analgesia with opioids	Incidence of phantom pain at 6 and 12 months ↓
Bash 1988, Lo E 2b	n = 25 , amputation	Epidural 72 hours preop	Systemic analgesia with opioids and non- opioids	Incidence of phantom pain 6 months ↓, 12 months ↔

LAPSED

Laste kohta puuduvad küsimusele vastavad uuringud. Leidus 1 uuring mis hindas kroonilise postoperatiivse valu esinemissagedust:

> **Fortier 2011**: 113 last; ortopeedilised, üldkirurgilised ja uroloogilised operatsioonid. 13 % -l lastest esines krooniline valu operatsiooni järgselt (enamus ortopeedilised operatsioonid)

Ravijuhendites seda teemat laste osas eraldi ei käsitleta.

Otsing:

Recent queries in pubmed
Child: birth-18 years",1,15:57:33
"Search chronic[Title] AND postoperative[Title] AND pain[Title] AND chronic[Title] AND postsurgical[Title] AND pain[Title]",#7,"Search (""chronic postoperative pain"") OR ""chronic postsurgical pain"" 21,15:57:26
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Humans
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Humans
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Humans
Child: birth-18 years",116051,15:53:52

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(((prevention or preventive) and chronic postoperative pain) or chronic postsurgical pain).mp. [mp=title, short title, abstract, full text, keywords, caption text]