## Kliiniline küsimus nr 13

Kas postoperatiivses etapis on ägeda valu ravis tulemuslikum kombineeritud farmakoloogilise valuravi kasutamine vs monoteraapia kasutamine?

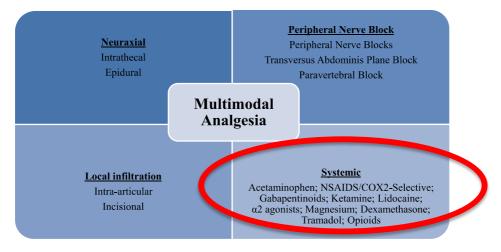
**Tulemusnäitajad**: valu tugevus, valu vähenemine, lisavaluvaigisti vajadus (sh opiaadi vajadus), aeg esimese lisavaluvaigisti vajaduseni, ärevuse vähenemine, postoperatiivsete tüsistuste esinemissagedus, valuvaigistitest tingitud kõrvaltoimed, rehospitaliseerimine valu tõttu, patsiendi (eestkostja) rahulolu valuraviga, meetodi ohutus, haiglaravi kestus

### Background

The concept of multimodal "opioid-sparing" analgesic techniques (balanced analgesia) aims to improve analgesia by combining analgesics with additive or synergistic effects. Theoretically, the use of a combination of analgesics from different pharmacologic drug classes for managing perioperative pain should improve the safety and efficacy of pain therapy due to the differing mechanisms of action and side-effect profiles of the individual drugs.

There are a several analgesic combinations for which such an effect has been shown in meta-analyses such as combinations of paracetamol with NSAIDs and paracetamol with opioids. Other proven combinations include non-selective NSAIDs and COX-2 inhibitors with opioids and alpha-2- delta modulators (gabapentinoids i.e., gabapentin and pregabalin) with opioids. The N-Methyl-D-Aspartate (NMDA) antagonists ketamine and magnesium as well as the alpha-2 agonists clonidine and dexmedetomidine in combination with opioids are also supported by meta-analyses. Perioperative use of intravenous lidocaine infusion and corticosteroids, namely dexamethasone, have also been shown to be useful adjuncts to opioid analgesia. (Joshi *et al.* 2014)

Adjuvants can also reduce opioid related side effects, however, they may cause other side effects limiting their use. They have variable effects on pain scores and opioid consumption. The optimal regimens for systemic administration of these agents have yet to be determined as has the clinical significance of this reduction in pain intensity and reduced opioid consumption. Their routine use as a part of miultimodal analgesia is not yet widely established and their role in the perioperative outcome remains unclear. (Loveridge and Patel 2013)



**Fig. 1.** Basic components of multimodal analgesic regimens.

Figure 1. Gritsenko et al. 2014

## Ravijuhendid

## Kokkuvõte

Kõik kolm ravijuhendit soovitavad kasutada multimodaalse analgeesia kontseptsiooni.

Ravijuhendid **DE-07** ja **AU-10** viitavad multimodaalse analgeesia asjus samadele süstemaatilistele ülevaadetele ja meta-analüüsidele, mis on avaldatud hiljemalt aastal 2005 (vaata tabelit 1). Mõlemad juhendid annavad samad soovitused:

1. Tugeva ja mõõduka valu puhul kombineerida opioide ja mitte-opioide.

2. PCA opioidile lisatud paratsetamool ja koksiibid vähendavad vajaminevaid opioidide koguseid, kuid ei ole tõestatud, et nad võiksid vähendada opioidide kõrvaltoimete esinemist.

3. NSAIDid lisatuna PCA opioididele vähendavad vajaminevaid opioidide koguseid ning ka iivelduse, oksendamise ja uimasuse esinemist, kuid selle kliiniline tähendus ei ole selge.

Juhend AU-10 annab soovitused ka adjuvantide kasutamise kohta:

1. Perioperatiivne ketamiini manustamine vähendab PCA opioidi vajaminevaid koguseid ja iivelduse ning oksendamise esinemist. Siiski ei ole nii opioidide kõrvaltoimete vähenemine kui ka valu tugevuse vähenemine kliiniliselt olulised.

2. Deksametasooni lisamine vähendab platseboga võrreldes postoperatiivse valu, iivelduse, oksendamise ning peapöörituse vähenemist

Ravijuhend **URO-13** ei viita multimodaalse analgeesia kohta käivatele meta-analüüsidele. Soovitused on esitatud patsiendirühmade kaupa:

1. Ambulatoorsetele patsientidele soovitatakse postoperatiivse valu raviks vältida opioide ja kasutada NSAIDide, paratsetamooli ja lokaalanesteetikumide kombinatsiooni.

2. Geriaatrilistele patsientidele soovitatakse multimodaalse analgeesia kasutamist.

3. Rasvunud patsientidel soovitatakse vältida opioide ja eelistada epiduraalanalgeesiat kombinatsioonis NSAIDi või paratsetamooliga.

4. Kriitilises seisundis või kognitiivse funktsiooni halvenemisega patsientidele soovitatakse postoperatiivse valu vähendamiseks kasutada paratsetamooli, kuna see vähendab vajaminevaid opioidide koguseid.

**PROSPECT recommendations (**ESRA Procedure-specific systematic review summary <u>http://postoppain.org/frameset.htm</u>

PROSPECT soovitab kõigi seni hinnatud kirurgiliste protseduuride puhul kasutada "multimodaalset" analgeesiat.

**Tabel 1.** Kokkuvõte ravijuhendites DE-07 ja AU-10 olevate multimodaalse analgeesia teemaliste meta-analüüside kohta

\*PARA - paracetamol \*ADR – adverse drug reaction

Author; year	Aim	No of trials, patients	Results concerning multimodal analgesia
Remy <i>et al.</i> 2005	To determine the morphine-sparing effect of PARA* + PCA morphine; to evaluate its effects on opioid-related ADRs*	7 RCTs (265 pt PCA morphine + PARA; 226 patients PCA morphine alone)	PARA + PCA morphine: morphine-sparing effect 20% (mean 9 mg (CI 15 -3; p=0.003) over the first postop 24 h Opioid consumption ↓
Elia <i>et al.</i> , 2005	To quantify and compare the morphine-sparing capacity of PARA, NSAIDs, and coxibs after major surgery; to test the evidence that their use in conjunction with PCA morphine provides a clinically relevant benefit	52 RCTs PARA: (10 trials, 379 pt) as multiple- dose regimens. NSAID: (33 trials, 1509 pt) as single- dose, multiple- dose or continuous infusions. COX-2: (14 trials, 1019 pt) as single-dose or multiple- dose regimens.	<ul> <li>Average 24-h morphine consumption ↓ significantly with all regimens (by 15–55%)</li> <li>PARA: 8.3 mg</li> <li>NSAID: 10.3mg (single dose), 18.3mg (continuous infusion), 19.7mg (multiple- dose)</li> <li>Coxibs: 10mg (multiple low-dose), 13.3mg (multiple high-dose)</li> <li>Pain intensity at 24 h ↓</li> <li>NSAIDs (1cm on the 0-10cm VAS scale, effect was not statistically significant with single-dose regimens, average ↓ 0.75 cm).</li> <li>PARA: 0.29 cm (no significant effect)</li> <li>PONV and sedation ↓</li> <li>NSAID: significantly reduced incidence of PONV 28.8% to 22.0% (NNT15) and of sedation from 15.4% to 12.7% (NNT 37), increased risk of severe bleeding from 0% to 1.7% (NNH 59).</li> <li>Coxibs: increased risk of renal failure in cardiac patients (from 0 to 1.4%, NNH 73)</li> </ul>
Romsing et al., 2005	To review opioid- related ADRs in studies of opioid- sparing postop pain treatment with rofecoxib, celecoxib, parecoxib, valdecoxib.	19 RCTs including 26 comparisons	Opioid consumption ↓ Significant opioid-sparing effect about 35% Reduction of opioid-related ADRs: significantly reduced risk for only dizziness (minor clinical relevance, NNT 33).
Marret et al., 2005	To evaluate the risk of morphine ADRs in pt treated with NSAIDs	22 RCTs	PONV and sedation ↓ Significantly decreased PONV by 30% (nausea alone by 12%, vomiting alone by 32%) Decreased sedation by 29%. Pruritus, urinary retention, and respiratory depression were not significantly decreased
Hyllested <i>et al.</i> 2002	To compare the analgesic and ADRs of PARA with those of other NSAIDs in postop pain, to compare the effects of PARA ±NSAID combination with those of either drug alone	PARA vs NSAID (36 studies, 3362 patients); PARA + NSAID vs PARA alone (7 studies, 613 patients)	Opioid consumption ↓ only with NSAID Of 33 studies, 2 showed that NSAIDs reduced opioid requirement or remedication only compared with paracetamol. 16 studies showed no differences between paracetamol and NSAIDs in pain scores, and 10 of these studies also showed no differences in opioid requirement or remedication.
Romsig <i>et al.</i> 2002	To review the analgesic efficacy of rectally or parenterally administered PARA for postop pain, to test the evidence for a possible	24 RCTs; 9 RCTs compared PARA (15-20 mg/kg or 0.5- 1.5g single- or multidose) with a combination	4 studies: significantly lower pain scores with PARA+NSAID combination vs. PARA alone (VAS reduction 12±34 mm at 4h). Time to first analgesic request (2 studies) increased significantly (by 180min) in the combination group in 1 study). Supplementary analgesic consumption was significantly reduced (2 studies), by 34±73%

additive analgesic	of	over periods of 8, 24 and 48h in the PARA +
effect of the	PARA+NSAID	NSAID group. In the 5 other trials, no
combination of	(diclofenac,	difference between study groups was
PARA+NSAID	ketoprofen,	observed.
compared with	ketorolac,	No ADRs attributed to the concomitant
either drug alone in	suprofen,	administration of PARA and NSAIDs were
postop pain	tenoxicam)	reported

# 1."Behandlung acuter perioperativer und postraumatischer Schmertzen" 2009 (DE-07)

#### The grading system of the guideline

Degree of recommendation	Level of evidence	
A		
	1b	Controlled randomized clinical trials with a strict confidence interval
	1c	"All or nothing" therapeutic results
В	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)

For strong and moderate pain opioids should be combined with non-opioids. (GoR: A) For the balanced analgesia regimen (Dahl *et al.* 1990) should non-opioid always given as basic analgesia for the opioid-spearing effect.

It is not certainly be proved that the combination of paracetamol or coxib and opioid reduces opioid-induced side effects despite of the opioid sparing effect (LoE: 1a) (Elia et al., 2005; Remy et al., 2005; Romsing et al., 2005), which is partly the fault of documentation of side effects in the studies (Romsing et al., 2005).

Aditional administration of NSAID reduces the occurence of PONV and sedation compared to the iv PCA monotherapy with morphine, altought the clinical relevance of this effect is controversial (LoE: 1a) (Elia et al., 2005; Marret et al., 2005).

Two or more NSAIDS or NSAID + coxib cannot be used at the same time.

Table 2. Me	Fable 2. Metaanalyses of opioid + non-opioid combination vs opioid monotherpy				
Autor, Year, Level of evidence	Study	Therapy	Control	Result	
· ·	7 RCTs; different surgeries	i.v. PCA Morphine + Paracetamol (i.v. or oral)		Opioidconsuption ↓ PONV ↔ Sedation ↔	
Elia et al., 2005; LoE: 1a	52 RCTs different surgeries	i.v. PCA (Morphine) + Paracetamol, NSAID or coxib	i.v. PCA + Placebo	All non-opioids: Opioidconsuption $\downarrow$ <b>Paracetamol:</b> postop. pain $\leftrightarrow$ side effects $\leftrightarrow$ <b>NSAID:</b> postop. pain $\downarrow$ (only continous giving or multiople doses) PONV $\downarrow$ (NNT: 15) Sedation $\downarrow$ (NNT: 37) other side-effects $\leftrightarrow$ bleeding risk $\uparrow$ (1,7% vs 0%) <b>Coxibs:</b> side effects $\leftrightarrow$ renal function $\downarrow$ (1,4%vs 0%)	
,	22 RCTs different	i.v. PCA + NSAID (18 RCTs) or coxib	-	PONV ↓ Sedation ↓	

#### Translated tables from the guideline:

1a	surgeries	(4 RCTs)	placebo)	other side effects $\leftrightarrow$
al., 2005;	ditterent	Coxid + additional	additional	Opioid consumption ↓ Dizziness ↓ Other side-effects ↔

Table 3.	Abdominal surgery	. RCTs. non-or	bioid + iv PCA v	with opioid vs.	iv PCA alone
		,			

Author, Year, Level of evidence	Patients	Therapy	Control	Result
Kraft et al., 2006; LoE 1b (RCT)	resection	i.v. PCA + 1. Paracetamol 2. Parecoxib or Valdecoxib	alleinige i.v. PCA	Opioidconsumption ↓
I  empel et al., 1996;	n= 103 abdominal und urological surgery	i.v. PCA + Analgin	i v PCA + Placebo	Opioidconsumption ↓ postop pain ↔ ADRs ↔
12003a. 1 oF 1p	n= 191 abdominal surgery		continous i.v. analgesia	Opioidconsumption ↓ postop. pain ↔

## 2. Acute Pain Management: Scientific Evidence 2010 (AU10)

Levels	s of evidence
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
П	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
Clinica	al practice points
$\checkmark$	Recommended best practice based on clinical experience and expert opinion

The combination of paracetamol and NSAID was clearly more effective than paracetamol alone, but evidence for superiority relative to the NSAID alone was more limited and of uncertain clinical significance (Hyllested et al. 2002, Level I, Romsig et al. 2002, Level I).

Non-selective NSAIDs are integral components of **multimodal analgesia** (Kehlet 1997; Brodner *et al.* 2001; Barrat *et al.* 2002). However, while useful analgesic adjuncts, they are inadequte as the sole analgesic agent in the treatment of severe postoperative pain. When giving in combination with opioids after surgery, non-selective NSAIDs resulted in better analgesia, reduced opioid consumption and lower incidence of PONV and sedation (Elia *et al.* 2005 Level I; Marret *et al.* 2005 Level I). There was no effect on pruritus, urinary

retention, and resipratory depression (Marret *et al.* 2005 Level I). Pain scores  $\downarrow$ , opioid consumption  $\downarrow$ , PONV  $\downarrow$ , sedation  $\downarrow$ 

pruritus, urinary retention, and resipratory depression  $\leftrightarrow$ 

In patients <70y undergoing cardiothoracic surgery, the use of NSAIDs reduced pain scores and opioid requirement (Bainbridge et al. 2006, Level I) although the use of these drugs in patients following coronary artery bybass surgery is controversial. Pain scores  $\downarrow$ , opioid consumption  $\downarrow$ 

#### **Guideline recommendations:**

- Paracetamol given in addition to PCA opioids reduces opioid consumption but does not result in a decrease in opioid-related side effects (N) (Level I).
- Non-selective NSAIDs given in addition to PCA opioids reduce opioid consumption and the incidence of nausea, vomiting an sedation (N) (Level I)
- Coxibs given in addition to PCA opioids reduce opioid consumption but do not result in a decrease in opioid-related side effects (N) (Level I).
- Perioperative low-dose ketamine used in conjunction with PCA morphine is opioid sparing and reduces the incidence of nausea and vomiting (N) (Leve I, Cochrane review).
- In general, a perioperative low-dose ketamine infusion is opioid-spring, but does not produce a clinically significant reduction in pain scores or opioid-related adverse effects (S) (Level I).
- Dexamethasone, compared with placebo, reduces postoperative pain, nausea and vomiting, and fatigue (Level II).

## 3. Guidelines on Pain Management 2010 (URO-13)

LE	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

#### GR Nature of recommendations

A Based on clinical studies of good quality and consistency addressing the specific recommendations

- A and including at least one randomised trial
- B Based on well-conducted clinical studies, but without randomised clinical trials
- C Made despite the absence of directly applicable clinical studies of good quality

The concept of multimodal (balanced) analgesia is that combining different doses and routes of administration of analgesics improves the effectiveness of pain relief after surgery and reduces the maximal dosage and adverse effects (Kehlet et al. 2002) (LE: 2b).

It seems to be more effective when different drugs are administered via different routes than when different drugs are administered via a single route (American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting 2004) (LE: 2b).

Recommendation	LE GR
Multimodal pain management should be used whenever possible because it helps to	2bB
increase efficacy while minimising adverse effects.	200

#### **Special populations**

#### **Ambulatory surgical patients**

A multimodal analgesic plan uses a combination of NSAIDs or paracetamol plus local anaesthetics used as peripheral nerve blocks, tissue infiltration, or wound instillation so as to avoid the use of opioids, which can prolong hospital stay (Beauregard et al. 1998; Rawal et al.1997, LE: 2a; Crews 2002 LE: 2b).

Recommendations	LE	G	R
For postoperative pain control in outpatients, <b>multimodal analgesia</b> with a combination of	2b		
NSAIDs or paracetamol plus local anaesthetics should be used.	20	D	
lf possible, avoid opioids.	3	В	

#### **Geriatric patients**

Pain perception appears to be reduced in geriatric patients, and requirement for analgesia generally decreases with increasing age (Gibson et al. 2001; Gloth 2000).

Postoperative delirium in elderly patients is a common complication and is often multifactorial. It may be associated with administration of pethidine (Marcantonio et al. 1994).

Multimodal postoperative analgesia may be the pain management technique of choice in elderly patients, as the drug doses required are lower. However, it is important to be vigilant for adverse reactions, because they tend to increase in number in the geriatric population (Gloth 2000) (LE: 2b).

Recommendation	LE	GR
Multimodal and epidural analgesia are preferable for postoperative pain management in	2b	D
elderly patients because these techniques are associated with fewer complications.	20	В

#### **Obese patients**

Obese patients appear to be at higher risk for certain postoperative complications, including respiratory, cardiovascular and thromboembolic episodes, and wound infections. Administration of opioids to obese patients is associated with sudden respiratory arrest, therefore, a combination of NSAIDs or paracetamol with an epidural local anaesthetic might be the safest analgesic solution (Choi et al. 2000; Cullen 2001, LE: 2b).

If absolutely necessary, opioids should be used with caution under careful titration to avoid depression of the respiratory drive (Cullen 2001).

Recommendations	LE	G	R
Postoperative use of opioids should be avoided in obese patients unless absolutely necessary.	2b	в	
An epidural local anaesthetic in combination with NSAIDs or paracetamol is preferable.	2b	в	

**Critically ill or cognitively impaired patients** - regional or multimodal analgesia might be more effective because drug doses are reduced and behavioural interventions and patient-controlled methods are unsuitable (LE: 3).

Recommendations	LE	GR
The use of paracetamol is recommended for postoperative pain management because it	1b	D
reduces consumption of opioids.		D

#### Süstemaatilised ülevaated

Süstemaatilised ülevaated hindavad erinevate ravimirühmade tõhusust ja ohutust multimodaalses valuravis.

#### Paratsetamool, NSAID ja koksiibid

2 hilisemat metaanalüüsi kui ravijuhistes avaldatud, on tehtud samade autorite poolt ja sisult samad (Maund et al. 2011 ja McDaid et al. 2010).

Leiti, et kõik 3 vähendavad statistliselt oluliselt 24h kumulatiivset PCA morfiini kogust.

NSAIDid vähendavad oluliselt PONVi, ükski kolmest ei vähenda oluliselt sedatsiooni.

Siiski võttes arvesse olemasolevat tõendust, vähest morfiini koguse vähenemist ja laia usaldusvahemikku kõrvaltoimete esinemise osas ei saa and tugevat soovitust nende kolme ravimirühma rutiinseks lisamiseks iv PCA morfiinile esimese 24 postoperatiivse tunni jooksul.

## Alfa-2 adrenoretseptori agonistide (klonidiin ja deksmedetomidiin)

kohta leidus 1 meta-analüüs (Blaudszun *et al.* 2012). Mõlemad ravimid vähendasid 24h opioidi kogust, valu tugevust ja PONVi, kuid suurenes intraoperatiivse ja postoperatiivse hüpotensiooni oht. Nende ravimite roll multimodaalses analgeesias ei ole hetkel selge.

#### Gabapentinoidid

Gabapentiini kohta leidus 4 meta-analüüsi, mis kõik olid avaldatud 2006-2007 aastal. Kõigis metaanalüüsides leiti valu tugevuse ja opioidide koguste vähenemine ja kõrvaltoimetest sedatsiooni suurenemine, kui gabapentinoid oli lisatud raviskeemi.

Pregabaliini kohta käivad 3 meta-analüüsi on avaldatud 2010-2011 aastal ja nende põhjal ei saa anda kindlat soovitust pregabaliini kasutamise kohta mutlimodaalse analgesia skeemides vahetus postop perioodis. Yao et al. 2014 aastal avaldatud meta-analüüs näitas, et peale günekoloogilisi operatsioone on pregabaliinil postoperatiivselt opioidide kogust vähendav ja täiendav valuvaigistav toime ilma kõrvaltoimete esinemissageduse suurenemiseta.

#### NMDA retseptiori antagonisti ketamiini

kohta leidus 5 meta-analüüsi aastatest 2004-2011. Viimastel aastatel avaldatud metaanalüüsid leidsid, et anesteetilistest annustes madalamas annuses kasutatud ketamiini vähendab postoperatiivselt 24h jooksul opioidi vajadust ja PONVi. Hallutsinatsioonide esinemine sagenes ketamiini kasutamisel.

#### Magneesium

Kui 2007.a avaldatud meta-analüüs ei leidnud magneesiumil olevat olulist rolli multmimodaalse valuravi skeemides, siis 2013 a avaldatud meta-analüüs (Albrech et al. 2013) leidis, et perioperatiivne magneesiumi manustamine vähendas oluliselt 24h opioidide vajadust ja vähemal määral ka postoperatiivse valu tugevust ilma kõrvaltoimete riski suurendamata.

#### Lidokaiin

Perioperatiivse lidokaiini rolli multimodaalses valuravis vaatleb 4 metaanalüüsi (avaldatud 2008-2012), mis leidsid, et iv lidokaiin vähendas nii opioidide koguseid, valu tugevust kui PONVi.

#### Deksametasoon

2 meta-analüüsi leidsid, et deksametasoon vähendab valu tugevust ja opioidide koguseid.

## Paracetamol, NSAID and coxibs

- Maund, E., et al. "Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs for the reduction in morphine-related side-effects after major surgery: a systematic review." *British journal of anaesthesia* 106.3 (2011): 292-297.
- **McDaid** C, Maund E, Rice S, Wright K, Jenkins B, Woolacott N. "Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs) for the reduction of morphine-related side effects after major surgery: a systematic review. *Health Technol Assess* **2010**;14(17).

	Maund et al. 2011; McDaid et al. 2010
Aim	To determine which class, if any, of non-opioid analgesic (PARA, NSAIDs, or COX-2 inhibitor) is most effective at reducing morphine consumption and morphine-related adverse effects when used as part of multimodal analgesia after major surgery. Review provides a substantial update on this topic (inclusion of 20 new trials, excluding drugs that are no longer licensed (valdecoxib and rofecoxib) and studies published by S.S. Reuben which have been retracted due to data falsification).
Trials included	60 trials (12 PARA, 16 coxibs, 38 NSAIDs), 54 trials were placebo-controlled. There were no trials that directly compared all 3 classes of drug. All participants received PCA morphine for at least 24 h after major surgery. Types of surgeries: thoracic (2), orthopaedic (23), gynaecological (17), obstetric (5), general (13 studies). Number of participants ranged from 20 to 514, >40% of trials had ≤20 participants in each trial arm. The assessed quality was variable.

	Results
Opioid	<b>Opioid consumption</b> $\downarrow$ (56 trials)
consumption	Compared with placebo, there was a statistically significant reduction in mean
•	cumulative 24h morphine consumption with PARA (mean reduction 6.34mg; 95%CI
	9.02-3.65), NSAIDs (10.18mg; 95%CI 11.65-8.72) and COX-2 inhibitors (10.92mg;
	95%CI 12.77-9.08).
	Any benefits that NSAIDs and COX-2 inhibitors had over paracetamol were marginal
	and no longer statistically significant, when the model was adjusted for baseline
	morphine consumption.
Opioid	PONV (43 trials)
adverse	Significant reduction in nausea and PONV with NSAIDs compared to placebo (OR
effects	0.70; 95% CrI 0.53 to 0.88) but not for PARA or coxibs, nor for NSAIDs compared to
cheets	PARA or coxibs.
	Sedation (19 trials)
	There was no statistically significant difference between any intervention and
	comparator. Compared to placebo, there was a trend towards increased sedation with PARA (OR 1.62; 95%CI 0.32-5.02) and decreased sedation with NSAIDs (OR 0.53;
	(OR 0.52, 30.001 0.32, 30.001 0.32, 30.001 0.32, 30.001 0.001 0.001
	95%CI 0.20-1.01) and coxibs (OR 0.63; 95%CI 0.18-1.49), with wide CI indicating
	considerable uncertainty. There was no statistically significant difference between intervention and placebo for
	secondary morphine-related outcomes, with the exception of pruritus, where PARA
	and NSAIDs were statistically significantly more effective at reducing pruritus
	compared with placebo.
Non-opioid	Surgical bleeding was not reported in any PARA studies and in a single coxib study.
ADRs	Based on 6 trials (n = 695), 2.4% of participants receiving an NSAID experienced
	surgery-related bleeding compared to 0.4% with placebo.
Conclusion	There was a decrease in 24h morphine consumption, compared to placebo, ranging
	from 6.3 mg to 10.9 mg, when PARA, NSAID or COX-2 inhibitors were added to PCA
	morphine following surgery. When the three drug classes were compared to each
	other the differences in morphine consumption were small and unlikely to be of clinical
	significance. In addition, the benefits in terms of reduction of morphine-related adverse
	effects do not strongly favour one of the three non- opioid analgesics.
Implications	All three non-opioid analgesics were effective at reducing PCA morphine consumption
for the	in the first 24 hours following major surgery.
health-care	The difference between NSAIDs and COX-2 inhibitors was marginal and not
	statistically significant. The adjusted results suggest a mean difference of <2mg of
	morphine over 24h when any of the drug classes was compared to the others.
	In terms of morphine-related ADRs, which is the more clinically relevant outcome, the
	results do not strongly favour one class of non-opioid analgesic: NSAIDs were ranked
	highest for reducing the primary morphine-related adverse effects but they were only
	marginally better than COX-2 inhibitors and paracetamol. Any morphine-sparing
	effects of these non-opioid analgesics need to be balanced against any ADRs related
	to the analgesics themselves.
	There were a small number of surgical bleeding events, GI bleeding and oliguria for
	participants treated with an NSAID.
	Taking the evidence as a whole, the uncertainty suggested by the size of the
	probabilities of being most effective, the small reduction in morphine consumption and
	the wide confidence intervals for adverse effects outcomes, there does not appear to
	be a strong case for recommending routine addition of any of the three non-opioids to
	PCA morphine in the 24h immediately after surgery. In addition, there does not appear
	to be a strong case for favouring one drug class above the others.

# Alpha-2 adrenoreceptor agonists (Clonidine and dexmedetomidine)

• Blaudszun G, Lysakowski C, Elia N, Tramèr MR. "Effect of perioperative systemic a2 agonists on postoperative morphine consumption and pain intensity: systematic review and metaanalysis of randomized controlled trials". Anesthesiology **2012**;116(6):1312-22.

Aim	To find out: what extent periop systemic□alpha-2 agonists ↓ postop opioid consumption and pain intensity; whether there are additional beneficial effects, such as a ↓ in the incidence of opioid-related ADRs, including hyperalgesia; whether there is a clinically relevant difference in the analgesic properties between clonidine and dexmedetomidine.
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Trials	30 studies (1,792 patients, 933 received clonidine or dexmedetomidine)
	Results
Opioid consumption	Opioid consumption ↓ (26 trials) There was evidence of postop morphine-sparing at 24h; WMD□4.1mg (95%CI□6.0- 2.2) with clonidine and 14.5mg (22.1- 6.8) with dexmedetomidine. Clonidine reduced morphine consumption 12-24h postoperatively Dexmedetomidine reduce morphine consumption in the postop period between 2 and 24h (earlier onset of benefit than seen with clonidine)
Pain intensity at 24h ↓         Perin intensity at 24h ↓         Weighted mean difference was □ 0.7 cm (1.2-0.1) on a 10-cm VAS scale wand 0.6 cm (0.9-0.2) with dexmedetomidine.         Clonidine:       Pain scores improved during the first 24h. At 48 h postor analgesic benefit was seen.         Dexmedetomidine:       Decreased VAS scores seen up to 24h postoperativel	
Opioid adverse effects	PONV ↓ The incidence of early nausea was decreased with both. Sedation: Clonidine: No in sedation or delay in recovery from anaesthesia was seen
Non-opioid- related adverse effects	Clonidine: increased the risk of intraop and postop hypotension (NNH, 20) Dexmedetomidine: Lower rates (NNT 2.3 vs 13 in clonidine) of intraoperative hypertension were seen. Increased the risk of postoperative bradycardia (NNH, 3). Recovery times were not prolonged.
Effect on chronic postop pain	Clonidine: None of the trials reported an effect
Conclusion	Periop systemic alpha-2 agonists ↓ postop opioid consumption, pain intensity, and nausea. Recovery times are not prolonged. Common ADRs are bradycardia and arterial hypotension. The impact of alpha 2 agonists on chronic pain or hyperalgesia remains unclear because valid data are lacking.

## **Gabapentinoid anticonvulsants**

### Gabapentin

- Seib RK, Paul JE. Preoperative gabapentin for postoperative analgesia: a meta- analysis. Can J Anaesth 2006;53(5):461-9.
- **Ho** KY, Gan TJ, Habib AS. "Gabapentin and postoperative pain e a systematic review of randomized controlled trials." Pain 2006;126(1e3):91-101.
- **Hurley** RW, Cohen SP, Williams KA, Rowlingson AJ, Wu CL. The analgesic effects of perioperative gabapentin on postoperative pain: a meta-analysis. Reg Anesth Pain Med 2006;31(3):237-47
- **Mathiesen**, Ole, Steen Møiniche, and Jørgen B. Dahl. "Gabapentin and postoperative pain: a qualitative and quantitative systematic review, with focus on procedure." *BMC anesthesiology* 7.1 (2007): 6.

	Seib et al. 2006	Ho et al. 2006	Hurley et al. 2006	Mathiesen, et al. 2007
Aim	whether GABA* ↓ pain scores, analgesic consumption, and/or analgesia-related ADRs in the first 24h postop	To evaluate the efficacy and tolerability of periop GABA administration for the control of acute postoperative pain.	To investigated the impact of periop administration of GABA on postop outcome	To analyse the 24h postop effect of GABA on acute pain in adults
Trials	8 studies, 663 pt* (333 received GABA) Surgeries: different	16 RCTs, 1151 pt (614 received GABA)	12 RCTs, 896 pt	23 trials,1529 pt (810 GABA) Surgeries:different
Study medicine dosing	Multiple dosing (62 pt) Single dose preop (271 pt) Controls (330 pt)	GABA 300-1200mg Single preop dose (11 trials); 2 separate preop doses (1 trial); >2 preop doses (4 trials)		Single dose (300- 1200mg, 16 trials); Repeat dosing (7 studies)
Opioid Opioid consumption ↓ lower opioid consumption (p<0.03		Opioid consumption ↓ 1200mg single dose preop: WMD 27.9mg (95%CI 31.52-24.29) -	Opioid consumption ↓ (OR =	In 12 of the 16 studies opioid consumption significantly ↓

	in the GABA treatment arm (WMD 13.7; 95% CI 8.9– 18.5)	in favor of GABA <1200mg single dose preop: ↓ postop morphine consumption compared with control (WMD,15.98mg; 95%CI□23.45-8.50) Multiple doses periop: 24% ↓ in total PCA morphine use compared with control	-17.84; CI, -23.50 to -12.18).	compared with placebo. Opioid sparing with GABA was of variable clinical importance (2- 59mg)
Pain reduction	Pain intensity ↓ (WMD 15.9; 95% CI 7.1–24.7),	Pain intensity ↓ only with single preop dose 1200mg single dose: significant ↓ in pain intensity at rest compared with control in the early (6h, WMD, 16.55mm; 95%CI 25.66-7.44) and late (24h, WMD 10.87mm; 95%CI 20.90-0.84) postop period <1200mg single dose preop: statistically significant ↓ in pain intensity at rest compared with control at 6h (WMD, 22.43 mm; 95% CI 27.66-17.19). Lower pain scores at rest at 24h (WMD13.18mm; 95%CI 19.68-6.68) Multiple doses periop: no difference between GABA and control at 6 and 24h after surgery	Pain intensity ↓ The pooled VAS scores at 4h and 24h were ↓ (WMD -1.57; 95%CI -2.14 to -0.99 and WMD = -0.74; CI, -1.03 to -0.45, respectively).	Pain at rest Early postop 12 of 23 trials, significantly lower pain scores (reduction 10 - 29mm VAS). Late postop(24h) 10 of 23 studies - significantly lower pain score, (reduction 5 - 23mm VAS) Pain scores during activity Early postop 5 of 11 trials - significant↓ (8- 22mm VAS). Late postop 4 of 9 trials - significantly lower pain score (6- 21mm on the VAS score).
Time to first request for rescue analgesic	-	1200 mg single dose preop: statistically significant delay in time to first request for analgesia (WMD 7.42min; 95%CI 0.49– 14.34)		-
Opioid adverse effects	No significant differences between the gabapentin and control groups I ncidence of GABA- related side effects (dizziness, light headedness, visual disturbance and headache) similar in the GABA and control groups	1200mg single dose: vomiting ↓ (Peto OR 0.42; 95%CI 0.24–0.76, NNT 8). Urinary retention ↓ (NNT 7). <1200mg single dose: Sedation risk ↑ <1200mg GABA compared to control (Peto OR 6.95;95%CI 3.96–12.20, NNH 4) Multiple doses periop: statistically significant ↓ incidence of nausea (Peto OR 0.54; 95% CI 0.31–0.95, NNT 9), ↓ incidence of pruritus (Peto OR 0.21; 95% CI 0.05–0.87, NNT 13)	Sedation and anxiolysis ↑ (OR = 3.28; Cl, 1.21-8.87) PONV, dizziness ↔	No difference
Conclusion	Although GABA given preop ↓ pain scores	The periop administration of GABA	Periop oral GABA is a	Periop use of GABA has a

and analgesic consumption in the first 24h after surgery, the clinical significance of this finding has yet to be determined. Significant reduction in the incidence of ADRs could not be demonstrated	is effective in reducing pain scores, opioid requirements and opioid-related ADRs in the first 24h after surgery. Sedation was associated with its use but no serious ADRs were observed.	useful adjunct for the management of postop pain	significant 24h opioid sparing effect and improves pain score for both abdominal hysterectomy and spinal surgery.
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GABA\* - gabapentin

pt\* - patients WMD- weighted mean difference

### Pregabalin

- **Moore** RA, Straube S, Wiffen PJ, Derry S, McQuay HJ. Pregabalin for acute and chronic pain in adults. Cochrane Database Syst Rev 2009;(3):CD007076.
- Zhang J, Ho KY, Wang Y. Efficacy of pregabalin in acute postoperative pain: a meta-analysis. •
- Br J Anaesth 2011;106(4):454e62. **Engelman** E, Cateloy F. "Efficacy and safety of perioperative pregabalin for post-operative pain: a meta-analysis of randomized-controlled trials". Acta Anaesthesiol Scand • 2011;55(8):927-43.

	Moore et al. 2010	Zhang et al. 2011	Engelman et al. 2011
Aim	To assess analgesic efficacy and associated ADRs of pregabalin in acute and chronic pain.	To evaluate the available literature on the efficacy of periop pregabalin in the management of acute postop pain	-
Trials included	6 studies (649 patients) Surgeries: various	11 RCTs, 899 (521 received pregabaline) Surgeries: various	18 studies, 1547 pt; (850 pregabalin, 697 controls) Surgeries: various
Study medicine dosing	50-300mg	50-600 mg single preop dose (7) single postop dose(1) 2 separate preop and postop doses (3)	50-750 mg
Postoperative analgesia / comparator	Placebo, ibuprofen po, diazepam po, dexamethasone po	iv fentanyl, iv PCA fentanyl, iv PCA oxycodone, iv PCA morphine, iv ketorolac, iv morphine; po ibuprofen	Ketorolac i.v, ibuprofen po, epidural Fentanyl +bupivacaine, Celecoxib po, Morphine i.v., codeine po, paracetamol po, Piritramide i.v, Fentanyl i.v., hydrocodone iv, oxycodone PCA etc
Postop analgesic consumption		↓ postop opioid consumption (WMD, 213.40 mg; 95%Cl 222.78-24.02). Significant heterogeneity among studies	↓ amount of postop analgesics (30.8% of non-overlapping values – OR 0.43). 150, and 300 or 600 mg/day provided identical results
Pain reduction	Studies did not present a sufficiently	Pain intensity ↔ at rest / on movement at 2h or 24h	Pain intensity ↓
Adverse effects	homogeneous group of trials to allow a pooled analysis.	↓ risk of vomiting (RR 0.73; 95%CI 0.56–0.95, NNT 18), ↑risk of visual disturbance (RR 3.29; 95%CI 1.95–5.57, NNH 6) No differences for other ADRs	↑ risk of dizziness, light- headedness and visual disturbances ↓ occurrence of PONV in patients who did not receive anti-PONV prophylaxis.
Conclusion	There was no clear	Pregabalin offered no	Pregabalin during a short

evidence of beneficial effects of pregabalin in established acute postoperative pain	improvement in pain scores, but it did ↓ cumulative 24h postop opioid consumption. Doses >300mg had greater reducing effect than < 300mg	perioperative period provides additional analgesia in the short term, but at the cost of additional ADRs. The lowest effective dose was 225–300 mg/day.
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• Yao, Zhiwen, Chong Shen, and Ying Zhong. "Perioperative Pregabalin for Acute Pain After Gynecological Surgery: A Meta-analysis." *Clinical therapeutics* (2014).

**Aim**: to evaluate pregabalins ability to control acute postop pain after gynecologic surgery **Trials**: 6 valid RCTs, 452 patients

**Results**: The pregabalin-treated patients consumed fewer opioids during the first 24h postop (WMD -8.5mg; 95%CI -11.29 to -5.71 mg; P<0.00001).

Pain intensity at rest and on movement or coughing revealed a statistically significant pain relief effect of pregabalin during 24h postop (at rest: WMD -6.20 mm; 95% CI -11.83 to -0.58 mm; P =0.03; on movement or coughing: WMD, -5.32 mm; 95% CI -9.73 to -0.91 mm; P= 0.02). No differences were found between the pregabalin and control groups for the adverse effects.

**Conclusions**: Pregabalin has an analgesic and opioid-sparing effect and does not increase the frequency of adverse effects in acute postoperative pain management after gynecologic surgery.

• **Tiippana**, Elina M., et al. "Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety." *Anesthesia & Analgesia* 104.6 (**2007**): 1545-1556.

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**Aim**: to evaluate the available literature examining the analgesic efficacy, adverse effects, and clinical utility of gabapentinoids in postop pain management

**Trials**: 22 RCTs, perioperative administration of gabapentin or pregabalin (1 trial) for postoperative pain relief, 786 patients received gabapentin, 99 pregabalin

Gabapentin doses 300-1200 mg, pregabalin 50 or 300 mg.

**Results:** Pain relief was better in the gabapentin groups compared with the control groups. The opioid-sparing effect during the first 24h after a single dose of gabapentin 300–1200 mg, administered 1–2 h preoperatively, ranged from 20% to 62%. The combined effect of a single dose of gabapentin was a reduction of opioid consumption equivalent to 30 +/-4 mg of morphine during the first 24h after surgery. Gabapentin- induced reduction in the 24h opioid consumption was not significantly dependent on the gabapentin dose. Gabapentin reduced opioid-related ADRs, such as nausea, vomiting, and urinary retention (NNT 25, 6, and 7, respectively). The most common adverse effects of the gabapentinoids were sedation and dizziness (NNH 35 and 12, respectively).

**Conclusion**: Gabapentinoids effectively reduce postop pain, opioid consumption, and opioidrelated ADRs after surgery. Conclusions about the optimal dose and duration of the treatment cannot be made because of the heterogeneity of the trials.

#### NMDA receptor antagonists

#### Ketamine

- Bell, Rae F., et al. "Perioperative ketamine for acute postoperative pain." *Cochrane Database Syst Rev* 1 (2010).
- Laskowski K, Stirling A, McKay WP, Lim HJ. A systematic review of intravenous ketamine for postoperative analgesia. Can J Anaesth 2011;58(10):911-23.
- **Carstensen**, Mads, and A. M. Møller. "Adding ketamine to morphine for intravenous patientcontrolled analgesia for acute postoperative pain: a qualitative review of randomized trials." *British journal of anaesthesia* (2010): aeq041.
- Elia, Nadia, Christopher Lysakowski, and Martin R. Tramer. "Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials." *Anesthesiology* 103.6 (2005): 1296-1304.

• **Subramaniam**, Kathirvel, Balachundhar Subramaniam, and Richard A. Steinbrook. "Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review." *Anesthesia & Analgesia* 99.2 (**2004**): 482-495.

	Bell et al. 2010	Laskowski et al 2011	Carstensen and Møller 2010	Elia et al. 2005	Subramania m et al. 2004
Aim	To evaluate the effectiveness and tolerability of ketamine administered perioperatively in the treatment of acute postop pain in adults.	To assess wether periop iv ketamine is a useful addition in pain management regimens.	To compare the effectiveness and safety of postop administered ketamine in addition to opioid for i.v. PCA compared with i.v. PCA with opioid alone	To better understand the Bbenefits and risks of ketamine for the control of postoperative pain	To assess the value ketamine added to opioid analgesia to opioid tolerance
Trials included	37 trials (2240 pt)	70 studies, 4701 pt (2652 ketamine)	11 studies, 887 pt (448 ketamine)	53 trials (2839 pt)	37 trials (2385 pt)
Study medicin e dosing	Iv, im bolus, PCA, epidural PCA, epidural bolus	<0.5 mg/kg 0.501–1 mg/kg >1 mg/kg Pre-incision Post-incision	5 dosage regimens 1:1morphine:keta mine ratio 1:5,11 0.4:1,25 1:0.75 1:2	prophylactic iv ketamine (median dose 0.4 mg/kg, range (0.1– 1.6)) (16 trials in 850 adults	lv, im bolus, PCA,
Postope rative analgesi a / compar ator	26 trials had placebo control, 11 trials ketamine in addition to a basic regimen with morphine vs morphine alone	Bolus +/- PCA Infusion +/- PCA PCA alone Bolus alone	-	-	-
Postop analgesi c consum ption	↓ 24h PCA morphine consumption	↓ postop analgesics consumption	Postop analgesics consumption ↔ 6 studies - statistically significant ↓ in morphine consumption Morphine-sparing effect 45% - 60%.	Cumulative morphine consumption at 24 h was significantly ↓ (WMD 15.7mg)	-
Pain reductio n	Pain intensity ↓		6 studies showed a statistically significant ↓ in pain intensity with ketamine compared with morphine alone, 1 reported a statistically significant ↓ in pain during cough only. 4 studies found no improvement in pain control when adding ketamine to morphine	Pain intensity ↓ WMD for postop pain intensity (0–10 cm visual analogue scale) was -0.89 cm at 6 h, -0.42 at 12 h, -0.35 at 24 h and -0.27 at 48 h.	Pain intensity ↔ Overall WMD of □5.4 mm (95% CI, □1.26, 0.18) for VAS at rest was statistically not significant between the groups
Time to first analgesi c	-	↑ in the time to first analgesic	-	-	-

Adverse effects	↓ PONV	<sup>↑</sup> Hallucinatio ns and nightmares ↔ sedation When ketamine was efficacious for pain, ↓ PONV in the ketamine group.	1 study found significantly ↓ heart rate in the ketamine group (P,0.0065). 1 study found a significant ↑ incidence of desaturation in the morphine group during the first and second postop night (P,0.008). In 7 studies opioid-related ADRs were statistically significantly ↑ in the morphine group psychotomimetic ADRs: 9 studies found no significant ↑ but 2 did	The highest risk of hallucinations was in awake or sedated patients receiving ketamine without benzodiazepin e; compared with controls, the odds ratio (OR) was 2.32 (95%CI, 1.09– 4.92, NNH 21)	No reduc- tion in opioid- related side effects such as PONV, pruritus, and respiratory depression ^psychomime tic effects
Conclus ion	Ketamine in subanaesthetic dose is effective in reducing morphine requirements in the first 24h after surgery. Ketamine also reduces PONV. Adverse effects are mild or absent.	Iv ketamine is an effective adjunct for postop analgesia. Particular benefit observed in painful procedures, incl. upper abdominal, thoracic, and major orthopedic surgeries.	The benefit of adding ketamine to morphine in i.v. PCA for orthopaedic or abdominal surgery remains unclear.	The role of ketamine, as a component of periop analgesia, remains unclear. No significant difference was seen when ketamine was administered in similar doses before or after surgery	As compared to morphine alone, IV PCA with ket- amine and morphine did not improve analgesia.

#### Magnesium

 Albrecht, E., et al. "Peri-operative intravenous administration of magnesium sulphate and postoperative pain: a meta-analysis." *Anaesthesia* 68.1 (2013): 79-90.

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**Aim**: to define quantitatively the effect of periop iv magnesium on acute postop pain. **Trials**: 25, 1461 patients, abdominal surgery (48%), hysterectomy (24%) and orthopaedic surgery (24%). Magnesium administered as a single bolus (6 trials 24%), as a bolus followed by infusion (15 trials, 60%), as an infusion (2 trials 8%), and combined with tramadol PCA in 2 trials (8%). Bolus dose ranging between 30-50 mg/kg. Infusion 500 mg/h or 8-15 mg/kg/h The total periop dose: 1.03g-23.5g.

**Results**: Independent of the mode of administration periop magnesium reduced cumulative iv morphine consumption by 24.4% (mean difference: 7.6mg, 95%CI -9.5 to -5.8mg;p<0.00001) at 24h postop. Numeric pain scores at rest and on movement at 24h postop were reduced by 4.2 (95%CI -6.3 to -2.1; p < 0.0001) and 9.2 (95%CI -16.1 to -2.3;p = 0.009) out of 100, respectively.

**Conclusion**: Periop iv magnesium reduces opioid consumption, and to a lesser extent, pain scores, in the first 24h postop, without any reported serious ADRs. Most studies did not report pain relief beyond 24 h. Therefore, the role of magnesium in the prevention of chronic pain is not known.

 Lysakowski, Christopher, et al. "Magnesium as an adjuvant to postoperative analgesia: a systematic review of randomized trials." *Anesthesia & Analgesia* 104.6 (2007): 1532-1539.

**Aim**: to assess whether magnesium has a clinically relevant effect on postop pain and analgesia requirements, and what the optimal regimen is .

Trials: 14 RCTs, 778 patients (404 received magnesium)

Median cumulative dose of magnesium sulfate was 8.5 g (range, 2.6–16.3)

**Results**: postoperative pain intensity was significantly decreased in 4 (29%) trials, was no different from placebo in 7 (50%), and was increased in 1 (7%); 2 trials (14%) did not report on pain intensity. Postoperative analgesic requirements were significantly reduced in 8 (57%) trials, were no different from placebo in 5 (36%), and were increased in 1 (7%). Magnesium-treated patients had less postoperative shivering (relative risk 0.38, 95% CI 0.17–0.88, NNT 14). 7 trials reported on magnesium serum levels. In all, serum levels were increased in patients who received magnesium; in six, serum levels were decreased in those who received placebo.

**Conclusion**: These trials do not provide convincing evidence that periop magnesium may have favorable effects on postop pain intensity and analgesic requirements.

## Lidocaine

- **McCarthy** GC, Megalla SA, Habib AS. Impact of intravenous lidocaine infusion on postoperative analgesia and recovery from surgery: a systematic review of randomized controlled trials. Drugs **2010**;70(9):1149-63.
- Marret, E, et al. "Effects of nonsteroidal antiinflammatory drugs on patient-controlled analgesia morphine side effects: meta-analysis of randomized controlled trials." *Anesthesiology* 102.6 (2005): 1249-1260
- Sun Y, Li T, Wang N, Yun Y, Gan TJ. Perioperative systemic lidocaine for post- operative analgesia and recovery after abdominal surgery: a meta-analysis of randomized controlled trials. Dis Colon Rectum 2012;55(11):1183e94. Erratum in: Dis Colon Rectum 2013;56(2):271.
- Vigneault L, Turgeon AF, Côté D, Lauzier F, Zarychanski R, Moore L, et al. Perioperative intravenous lidocaine infusion for postoperative pain control: a meta-analysis of randomized controlled trials. Can J Anaesth 2011;58(1):22e-54

Perioperative administration of iv lidocaine seems to have particular benefits in abdominal surgery. This may be because IV lidocaine confers specific benefit to visceral pain.

**McCarthy** *et al.* 2010; Marret *et al.* 2008; Sun *et al.* 2012 and Vigneault *et al.* 2011 have all conducted meta-analyses that have suggested benefit. There was variation between dosing (common regimen 1.5-2 mg/kg bolus before surgery followed by an infusion of 1.5-3 mg/kg/h continued postoperatively for up to 24h).

Intraop anaesthetic and postop opioid analgesic requirements were  $\downarrow$  for up to 48h. Postop pain scores were  $\downarrow$  for up to 24h.

The period of ileus was shorter and GI functional recovery was faster. This resulted in PONV and length of hospital stay. Side effects were minimal (dry mouth, light-headedness). **Sun et al.** reported early and late pain score  $\downarrow$  both at rest and with activity.

#### Dexamethasone

- Waldron NH, Jones CA, Gan TJ, Allen TK, Habib AS. Impact of perioperative dexamethasone on postoperative analgesia and side-effects: systematic review and meta-analysis. Br J Anaesthesia 2013;110(2):191-200
- **De Oliveira** Jr GS, Almeida MD, Benzon HT, McCarthy RJ. Perioperative single dose systemic dexamethasone for postoperative pain: a meta-analysis of ran- domized controlled trials. Anesthesiology **2011**;115(3):575e88

**Waldron et al. 2013** evaluated the effect of a single dose dexamethasone on postop pain. Most of the studies analysed were investigating dexamethasone's role as an antiemetic and so pain scores were often a secondary outcome. The study concluded that those patients receiving single or multiple doses of dexamethasone (1.25-20mg) had lower pain scores 2h after surgery. Dexamethasone-treated patients used less opioids at 2h and 24h, required less rescue analgesia, had longer time to first dose of analgesic, and shorter stays in recovery. There was no dose response with regard to the opioid-sparing effect. Higher blood glucose levels were seen at 24h postoperatively in the dexamethasone group.

**De Olivera et al. 2011** investigated the use of single dose dexamethasone on postop pain and opioid use compared to placebo. Dexamethasone was more effective than placebo in reducing pain at rest and at movement for up to 24h. A dose dependent effect was seen in cumulative 24h opioid consumption with an equally effective reduction seen in moderate (0.11 mg/kg-0.2mg/kg) and high dose (>0.2 mg/kg) groups. No effect was seen with low dose (<0.1mg/kg) dexamethasone. The preop administration seemed to result in more effective analgesia when compared to intraop administration.

Neither study found any evidence of dexamethasone decreasing wound healing or causing an increase in wound infections.

**Lisa kliinilisele küsimusele 13**: regionaalanalgeesia üksi vs regionaalanalgeesia kombineerituna mittesteroidsete põletikuvastaste ainetega.

Kokkuvõte: ei leidnud süstemaatilist ülevaadet mis vastaks teemale. Tabelis on leitud üksikuuringud kuid ainult epiduraalanalgeesiaga.

Saksa juhend (DE-09) soovitab kasutada epiduraalanalgeesiat koos mitte-opiaatsete valuvaigistitega (soovituse tase B). Soovitus põhineb üksikuuringutel, mis on järgenavs tabelis ära toodud.

Autor, aasta, tõestuse tase	Patsiendid	Uuringugrupp	Kontroll	Tulemused
Lim 2001 LoE:1b	n=48, keisrilõige	PCEA+ diklofenak rektaalselt	PCEA + platseebo	Valuvaigisti vajadus ↓( 33%) Valu tugevus ↔
Feng 2004	n= 30, põlveliigese endoproteesimine	PCEA+ rofekoksiib 25 mg	PCEA+platseebo	Valu ↓; opiaadi vajadus ↓; verekaotus ↔
Buvanendran 2003	n= 66, põlveliigese endoproteesimine	Rofekoksiib 50 mg pre ja postoperatiivselt 2 nädalat + PCEA	PCEA + platseebo	Epiduraali doos↓; opiaadi vajadus ↓; valu ↓ ; PONV ↓; rahulolu ↑
Hirabayashi 1995 LoE: 1b	n= 80, Iaparatoomiad	Epiduraali püsiinfusioon + diklofenak rektaalselt	Epiduraali püsiinfusioon	Valu↓

Hirabayashi 1994 ∟oE:1b	ülemine püsiinfusioon+ püsiinfusioon valuva				aigisti
Scott 1994 LoE:1b	n= 26 abdominaalne hüsterektoomia	Epiduraali püsiinfusioon + pre ja postop diklofenak im	Epiduraali Valu püsiinfusioon + platseebo		, 
Mogensen 1992 LOE: 1b	n= 44 ülemine Iaparotoomia	Epiduraali püsiinfusioon + pre ja postop piroksikaam	Epiduraali püsiinfusioon + platseebo	Valuva vajadi valu <del>(</del>	us ↔ ;
Bigler 1992 LoE:1b	n= 28 torakotoomia	Epiduraalanalgeesia +diklofenak im	Epiduraalanalgeesia + platseebo	Valu √ kõrva ↔	; Itoimeid
Kokkuvõtte					Viide kirjandu
cyclooxygena replacement METHODS: Thirty patien mg (group Rl received epic epidural anal + 0.02 mg/m pain intensity and analgesia and serum cy Tumor necros h, 12 h, 24 h blood loss an RESULTS: The pain scor joints moven analgesia sat 1.5) mg in th Leucocyte an h post-opera group RE tha h, IL8 at 24h the amount of CONCLUSION Preoperative increases and	ase-2 nonsteroidal antii (TKR). ts underwent elective k E, n = 15) or placebo ( lural combined isoflural gesia after surgery for 1 droperidol). Modified y. The outcomes include a satisfaction. Daily mo ytokine concentrations sis factor-alpha) were of and 48 h after surgery d postoperative drainal res were significantly let nent on the first and se isfaction (P < 0.05). The e E group and (6.8 +/- d neutrophil counts we tively (P < 0.05). Serue n group E at the end of after surgery (P < 0.0 f intraoperative and po l: cyclooxygenase-2-spect	group E, n = 15) 1 hour ne anesthesia during surg 72 hrs (0.1 mg/ml morpl verbal rate scale was use ed pain scores during res priphine consumption was (including interleukin 6, i determined before surger / in two groups using RIA ge from the knees were r ess in the group RE than i cond postoperative day, ne mean dose of morphin - 0.7) mg in the RE group re much higher in group m TNF-alpha concentration f surgery, 6 h, 12 h posto 5). There were no signific ostoperative blood loss be cific nonsteroidal anti-infl	andomly given oral rofeco prior to surgery. All patie gery and patient-controlle hine + 1.2 mg/ml bupivate ed to evaluate postoperate it and movement of knee recorded. Circulation leue interleukin 8, interleukin ry, at the end of surgery, the amount of intraope measured. in group E during rest and with an improvement in the for first 24 h was (8.1	nts ed caine tive joints cocyte 10, 2 h, 6 erative d knee cotal +/- h, 24 in 6 at 48 ct to 0.05).	21. Postoperative a anti-inflammato rofecoxib after f replacement. Feng Y, Ju H, An HY, Zhou
adverse effect OBJECTIVE: To assess the selective inhi arthroplasty DESIGN, SET	e effect of combined probing outco e effect of combined probitor of cyclooxygenase (TKA). TING, AND PATIENTS:		int challenge.		Effects of perior administration of cyclooxygenase on pain manage recovery of func knee replaceme randomized con Buvanendran A Tuman KJ, Lu

	2002, enrolling 70 patients aged 40 to 77 years and undergoing TKA at a university hospital in the United States. INTERVENTIONS: Patients were randomly assigned to receive 50 mg of oral rofecoxib at 24 hours and at 1 to 2 hours before TKA, 50 mg daily for 5 days postoperatively, and 25 mg daily for another 8 days, or matching placebo at the same times. MAIN OUTCOME MEASURES: Postoperative outcomes including postsurgical analgesic consumption and pain scores achieved, nausea and vomiting, joint range of motion, sleep disturbance, patient satisfaction with analgesia, and hematologic and coagulation parameters. RESULTS: Total epidural analgesic consumption and in-hospital opioid consumption were less in the group receiving rofecoxib compared with the group receiving placebo (P<.05). Median pain score (visual analog scale [VAS], 0-10) achieved for the knee was lower in the rofecoxib group compared with the placebo group during hospital stay (2.2 [interquartile range [IQR], 1.4-3.2] vs 3.5 [IQR, 2.7-4.3], P<.001) and 1 week after discharge (2.6 [IQR, 1.4-3.5] vs 3.7 [IQR, 2.9-4.7], P =.03). There was less postoperative vomiting in the rofecoxib group (6%) compared with the placebo group (26%) (P =.047), as well as a decrease in sleep disturbance compared with the placebo group at discharge (active flexion: mean [SD], 84.2 degrees [11.1 degrees ] vs 73.2 degrees [13.4 degrees ], P = .05) and at 1 month postoperatively (109.3 degrees [8.5 degrees ] vs 100.8 degrees [1.1.8 degrees ], P =.01), with shorter time in physical therapy to achieve effective joint range of motion. The rofecoxib group was more satisfied with analgesia and anesthesia at discharge compared with the placebo group (median satisfaction score, 4.3 [IQR, 3.0-4.7] vs 3.3 [IQR, 2.3-4.3], respectively; P = .03), and the differences persisted at 2-week and at 1-month follow-up. There was no intergroup difference in surgical blood loss (P>.05 for both intraoperative and postoperative blood loss). CONCLUSION: Perloperative use of an inhibitor of cyclooxyge	Elmofty D, Mo Rosenberg AG.
	but without differences in pain scores or need for supplementary analgesics between the two groups. Pulmonary function decreased similarly in the two groups. Thus we were unable to show enhanced analgesia by supplementing an otherwise effective low-dose epidural bupivacaine and morphine treatment with piroxicam after thoracic surgery with chest drains	thoracotomy. Bigler D, Mølle Jensen M, Berti Hjortsø NC, Ke
-	ABSTRACT In a randomized, double-blind, placebo-controlled trial, we assessed the value of adding rectal piroxicam to a low-dose epidural regimen for postoperative pain relief. Forty-four patients scheduled for major upper abdominal surgery during combined thoracic epidural (bupivacaine + morphine) and general anesthesia were studied. Postoperative analgesia was achieved by using epidural bupivacaine (10 mg/h) plus morphine (0.2 mg/h) for 72 h. In addition, the patients randomly received a placebo or rectal piroxicam (40 mg 12 h before surgery, 20 mg with premedication, and 20 mg every 24 h for 72 h). Pain was evaluated every 4 h at rest, during coughing on demand, and during mobilization. The sensory level of analgesia was evaluated by pinprick. We found no significant difference between piroxicam and placebo with regard to postoperative pain scores or need for supplementary analgesics. Thus, we were unable to demonstrate enhanced analgesia by	Anesth Analg. 10 Mar; 74(3): 366- Systemic piroxic adjunct to comb epidural bupivac morphine for por pain reliefa do study. Mogensen T, V Jonsson T, Mat Lund C, Kehlet

Systematic review (with homogeneity) of randomised, controlled trials	1a					
Study criteria	Level of evide					
Cesarean epidural local anesthetic/opioid requirements by 33% for the first 24 hr post- operatively						
between the groups. CONCLUSION: A single administration of 100 mg diclofenac suppository is effective in reducing post-						
suppository used 52.8 +/- 17.8 ml of local anesthetic mixture while those who did not, used $74$ +/- 25 ml (P <0.005). Pain scores and satisfaction scores did not differ significantly						
RESULTS: The two groups of patients were similar demographically. Patients who received a diclofenac						
operatively for pain scores on movement, dermatomal level of sensory blockade, degree of notor blockade and volume of local anesthetic used. At conclusion of the study, patients' satisfaction scores were recorded.						
vas no baseline infusion. The study commenced upon the patient's first demand for analgesia post-operatively and the patients were assessed at one, six, 12 and 24 hr post-						
egional anesthesia were enrolled into this randomised double-blind study. The patient- controlled epidural analgesia device was programmed to deliver a bolus of 4 ml of local inesthetic mixture with a lockout period of ten minutes and an hourly limit of 12 ml. There	JL, Pan AX					
//ETHODS: Forty-eight ASA physical status I or II term parturients scheduled for elective LSCS under	Lim NL, Lo					
of diclofenac (100 mg suppository) to women who had undergone lower segment Cesarean section (LSCS) under combined spinal-epidural anesthesia, and received post-operative patient-controlled epidural analgesia (PCEA) with ropivacaine 0.2% and fentanyl 2 microg x ml(-1).						
PURPOSE: To assess the analgesic efficacy of administering, immediately after surgery, a single dose	Apr; 48(4): 38 Single dose d					
Abstract	Can J Anaest					
abdominal surgery, such effects of rectal diclofenac obtained after upper abdominal surgery vere not demonstrable						
epidural infusion of buprenorphine and bupivacaine produced enhanced analgesia and educed pain scores measured by VAS after upper abdominal surgery. However, after lower	Hirabayashi					
study group received rectal diclofenac 50 mg immediately after surgery in addition to the same epidural injection method described above. Adding rectal diclofenac to continuous	relief after up abdominal su					
Subsequently infusion was started with the solution of epidural buprenorphine 15 nicrograms in 1 ml of 0.23% bupivacaine at a rate of 1 ml.h-1 for 48 h. Forty patients in	with continuc infusion with and bupivaca					
This investigation was conducted to determine the analgesic efficacy of rectal diclofenac coupled with continuous epidural infusion with buprenorphine and bupivacaine for pain relief after upper and lower abdominal surgery. Forty patients in control group received epidural	May; 44(5): 6					
ABSTRACT	Masui. 1995					
	Horiguchi Y Saitoh K, Fu					
postoperative pain relief by epidural buprenorphine and bupivacaine plus rectal ndomethacin was more effective than that by epidural buprenorphine and bupivacain	Hirabayashi H, Shimizu					
immediately after surgery and subsequently infused 15 micrograms buprenorphine in 1 ml of 0.25% bupivacaine at a rate of 1 ml.h-1 for 48 h. The remaining 20 patients were rectally given 50 mg of indomethacin in addition to the same epidural method described above. The patients who did not need additional narcotics in the control and indomethacin groups were 45% and 80%, respectively ( $P < 0.05$ ). In upper abdominal surgery,						
						We examined the analgesic effects of indomethacin as an adjunct to postoperative epidural analgesia in 40 patients who underwent upper abdominal surgery. Twenty patients in control group were epidurally given 0.1 mg of buprenorphine in 8 ml of 0.25% bupivacaine
ABSTRACT	Oct; 43(10): 1					

All or none, i.e. prior to availability of new therapy, all died, now with therapy some survive; or, prior to therapy some died, now with therapy none die	1c
Systematic review (with homogeneity) of cohort studies	2a
Individual cohort study (including low quality randomised controlled trial, e.g. <80% follow up)	2b
Outcomes research	2c
Systematic review (with homogeneity) of case-controlled studies	3a
Individual case-controlled study	3b
Case-series, and poor quality cohort and case-controlled studies	4
Expert opinion without explicit critical appraisal, or based on physiology, bench research or first principles	5

# Protseduuri-põhine soovituste tabel multimodaalse analgesia ja adjuvantide kasutamise kohta

	Pre-op		Intra-op		Post-op	
	Recommend ed	Not recommende d	Recomm ended	Not recommende d	Recomm ended	Not recommende d
Abdomina I hysterect omy		Systemic analgesics (e.g. IV COX- 2 inhibitors, conventional NSAIDs, strong opioids), except to secure sufficient analgesia when the patient wakes up (e.g. oral COX-2 inhibitors) (grade A) Clonidine, NMDA- receptor antagonists (grade A)		NMDA- receptor antagonists (grade A)	COX-2 inhibitors or NSAIDs, in combinati on with strong opioids for high- intensity pain (VAS>5) or with weak opioids for moderate - (VAS<5> 3) or low- intensity pain (VAS<3) (grade A) Paraceta mol for moderate - (VAS>3< 5) or low- intensity pain (VAS>3 5) or low- intensity pain (VAS>3 5) or low- intensity (VAS>3 5) or low- intensity (VAS) 5) or low- intensi	Concomitant administration of COX-2 inhibitors or NSAIDs with epidural analgesia (grade B) Paracetamol for high- intensity pain (VAS>5) (grade B) NMDA- receptor antagonists (grade A) Clonidine (grade A)

					NSAIDs	
Colonic	COX-2-	IV clonidine	COX-2-	IV clonidine	(grade A) COX-2-	Gabapentin/p
Resection	inhibitors	(Grade D)	inhibitors	(Grade D)	inhibitors	regabalin
	(Grade B)	because it is	(Grade B)	because it	(Grade B)	(Grade D)
	(only for	associated	(only for	associated	(only for	due to a lack
	patients who	with an	patients	with an	patients	of procedure-
	do not receive	increased risk of	who do not	increased risk of	who do not	specific evidence
	epidural	hypotension	receive	hypotension,	receive	evidence
	analgesia)	and	epidural	sedation and	epidural	NMDA
	analgesia)	bradycardia	anaesthe	bradycardia	analgesia	receptor
	Continuous		sia)		or with	antagonists
	administratio	NSAIDs	,	Calcium	the	(Grade D)
	n of pre-	(Grade B)		channel	cessation	because of
	/intra-op IV	because pre-		antagonists	of	limited
	lidocaine if	op		(Grade B),	epidural	procedure-
	continued	administration of these		based on limited	analgesia	specific
	during the immediate	agents can		procedure-	)	evidence of analgesic
	postop period	increase the		specific	Conventi	efficacy
	(Grade B),	risk of intra-		evidence	onal	Sinceoy
	when	and postop		showing a	NSAIDs	
	epidural	bleeding		lack of postop	(Grade A)	
	analgesia is			analgesic	only for	
	not feasible	Corticosteroid		effect	patients	
	or contra-	s for			who do	
	indicated	analgesia		Gabapentin/p	not .	
		(Grade A) because of		regabalin	receive	
		procedure-		(Grade D) due to a lack	epidural analgesia	
		specific		of procedure-	or with	
		evidence		specific	cessation	
		showing no		evidence	of	
		significant			epidural	
		benefit in		Continuous	analgesia	
		reducing pain		administration	)	
		scores and		of IV	B.7	
		concerns that they could		lidocaine limited to the	IV lidocaine	
		affect		pre-/intra-op	(Grade B)	
		anastomotic		period (Grade	(when	
		and wound		D) because of	· ·	
		integrity (but		inconsistent	is not	
		they may be		and	feasible	
		used for		insufficient	or contra-	
		reduction of		procedure-	indicated)	
		PONV)		specific evidence	Paraceta	
		Gabapentin/p		CAIGELICE	mol	
		regabalin		NMDA	(Grade B)	
		(Grade D)		receptor	for	
		due to a lack		antagonists	moderate	
		of procedure-		(Grade D)	- or low-	
		specific		because of	intensity	
		evidence		limited	pain (only	
		Continueur		procedure-	for	
		Continuous administration		specific evidence of	patients that do	
		of IV		analgesic	not	
		lidocaine		efficacy	receive	
		limited to the		Sinceoy	epidural	
		pre-/intra-op			analgesia	
		period (Grade			, or after	
		D) because of			cessation	
		inconsistent			of	
		and			epidural	

		insufficient procedure- specific evidence NMDA receptor antagonists (Grade D) because of limited procedure- specifc evidence		analgesia )	
Haemorrho id Surgery	Conventional NSAIDs (Grade B), COX-2 inhibitors (Grade B), and paracetamol (Grade B), administered in time to provide sufficient analgesia in the early recovery period	Gabapentino ids (Grade D) because there is no procedure- specifi c evidence and becaus e the benefit:risk ratio is not sufficiently favour able for this ambula tory proced ure Ketamine (Grade D) because there is no procedure- specifi c evidence and becaus e the benefit:risk ratio is not sufficiently favour able for this ambula tory proced ure	Conventi onal NSAIDs (Grade B), COX- 2- inhibitors (Grade B), and paraceta mol (Grade B), administe red in time to provide sufficient analgesia in the early recovery period	Conventi ona I NSAIDs (Gr ade B), COX-2 inhi bito rs (Grade B) Paraceta mol (Grade B), for low- moderate pain	Gabapentino ids (Grade D) because there is no procedure- specifi c evidence and becaus e the benefit: risk ratio is not sufficie ntly favourable for this ambula tory procedure Ketamine (Grade D) because there is no procedure- specifi c evidence and becaus e there is no procedure- specifi c evidence and becaus there is no procedure- specifi c

herniorrap hy	Conventional NSAIDs (Grade A) or COX-2 inhibitors (Grade A)	Clonidine (Grade D) Corticosteroid (Grade D) Gabapentin/p regabalin (Grade D) Ketamine (Grade D)		Clonidine (Grade D) Gabapentin/p regabalin (Grade D) Ketamine (Grade D)	NSAIDs (grade A) or COX-2 inhibitors (grade A) Paraceta mol , for routine pai n the rap y in co mbi nati on wit h conventio nal NSAIDs/ CO X-2 inhibitors (Gr ade B)	Gabapentin/p regabalin (Grade D) Ketamine (Grade D)
laparosco pic cholecyst ectomy	Corticosteroi ds - dexamethaso ne (Grade B for analgesic effects) COX-2 inhibitors (Grade B) Gabapentinoi ds gabapentin (Grade B)	Alpha-2- adrenergic receptor agonists- clonidin e (Grade D) Conventional NSAID (Grade B) NMDA antagonists - dextromethor phan (Grade D) ketamine (Grade D) magnesium (Grade B) Paracetamol (Grade B)	Conventi onal NSAIDs - at end of surgery (Grade D) COX-2 inhibitors (Grade D)	NMDA antagonist - dextromethor phan (Grade D) ketamine infusion (Grade D) magnesium infusion (Grade B)	Conventi onal NSAIDs ( Grade A) COX-2- inhibitors (Grade A) Paraceta mol (Grade A)	NMDA antagonist ketamine (Grade D) magnesium (Grade B)
Non- cosmetic breast Surgery	Major breast surgery Gabapentinoi ds (Grade A) COX-2- inhibitors (GradeD)/par acetamol (Grade B) in short breast	Major breast surgery NSAIDs (Grade B) because of inconsis tent procedure- specific and	-	Corticosteroid s for analgesia (Grade D) due to insufficient procedure- specific evidence	Major breast surgery Conventi onal NSAID (Gr ade A) or COX- 2-	Major breast surgery Mexiletine (Grade D) because of limited and conflicting

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provide analgesia in the early recovery period     e for sendinist analgesia and     r (Grade B) and     r (Grade B) and     r (Grade B) and     r (Grade B) and     Paracetamol alone       Minor breast surgery COX-2- inhibitors     corticosteroid analgesia     orticosteroid analgesia     orticosteroid analgesia     opioid analgesia       0/(Grade B) and (Grade B) in short breast surgery procedures to period     corticosteroid analgesia     opioid analgesia     de to insufficient analgesia       0/(Grade B) analgesia     corticosteroid analgesia     gast analgesia     de to insufficient analgesia     de to insufficient analgesia       0/(Grade B) analgesia     corticosteroid analgesia     gast analgesia     de to insufficient analgesia       0/(Grade B) analgesia     corticosteroid analgesia     gast analgesia     de to insufficient analgesia       0/(Grade B) analgesia     porcedu analgesia     gast analgesia     de to insufficient analgesia       0/(Grade B) analgesia     porcedu analgesia     gast analgesia     mod analgesia       0/(Grade B) analgesia     porcedu analgesia     gast analgesia       0/(Grade B) analgesia     s broce     procedu analgesia       0/(Grade B) analgesia     porcedu analgesia     porcedu analgesia       0/(Grade B) analgesia     procedu and     gast analgesia       0/(Grade B) analgesia     procedu and       0     procedu and     ga	pro	cedures to	evidenc		bito	re
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		transferable				
		evidence to				
		show whether				
		pre-op				
		administration				
		has any				
		analgesic				
		benefit				
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		with postop				
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Radical	COX-2-	Ketamine -	-	_	COX-2-	
prostatect	inhibitors	Not	_	-	selective	
	should be	recommende			inhibitors	
omy	administered	d for routine			are	
	at the	use (GoR D)			recomme	
	appropriate	because of			nded	
	time (pre- or	conflicting			(GoR B)	
	intra-	procedure-			based on	
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	to provide	evidence			ble	
	sufficient	(LoE 4),			evidence	
	analgesia in	despite			from	
	the early	favourable			multiple	
	recovery	transferable			procedur	
	period (GoR	evidence			es	
	B), based on	from more			showing	
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	evidence	surgical			efficacy	
	from diverse	procedures			(LoE 1),	
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	Pre-op				Lidocaine	
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L	analycaic		I			

	efficacy (LoE 1), despite lack of procedure- specific evidence				due to strong transfera ble evidence from multiple procedur es showing analgesic efficacy (LoE 1) despite lack of procedur e-specific evidence Paraceta mol should be administe red at the appropria te time (pre- or intraoper atively) to provide sufficient analgesia in the early recovery period (GoR D)	
Thoracoto my		alpha-2- adrenergic receptor agonists: clonidine (Grade A) dexmedetomi dine (Grade D) Corticosteroid (Grade D) Conventional NSAIDs (Grade A) COX-2 inhibitors (Grade D) Ketamine (Grade D) Gabapentin/p regabalin (Grade D)	-	Conventional NSAIDs (Grade D) COX-2- inhibitors (Grade D) Ketamine (Grade D) Gabapentin/p regabalin (Grade D)	Conventi onal NSAIDs, if regional analgesia is inadequat e (Grade A) COX-2- inhibitors, if regional analgesia is inadequat e (Grade B) Paraceta mol, if regional analgesia is inadequat e, as part of a multianal gesic regimen (Grade D)	alpha-2- adrenergic receptor antagonists dexmedetomi dine (Grade D) Ketamine (Grade D) Gabapentin/p regabalin (Grade D) Paracetamol alone for high intensity pain (VAS>50 mm) (Grade B)

total hip arthroplas ty	COX-2 inhibitors in time to provide sufficient analgesia when the patient wakes (grade D)	Conventional NSAIDs (grade A) Alpha-2- delta-receptor modulators (grade A) Ketamine (grade D) Corticosteroid s (grade D)			COX-2 inhibitors or conventio nal NSAIDs (grade A) in combinati on with paraceta mol and/or strong opioids for high- intensity pain (grade A) or with paraceta mol and/or weak opioids for moderate - or low- intensity pain (grade D) Paraceta mol (grade D) Paraceta mol (grade A) in combinati on with conventio nal NSAIDs or COX- 2- selective inhibitors, with or without rescue opioids (grade B)	Ketamine (grade D) Corticosteroid (grade D)
Total Knee Arthropla sty	-	gabapentinoi ds (Grade D), due to a lack of procedure- specific evidence Conventional NSAIDs (Grade B) because of limited procedure- specific evidence and increased risk	-	NMDA antagonists Dextromethor phan (Grade D) because of inconsistent analgesia Ketamine (Grade D) due to limited procedure- specific evidence	Conventi onal NSAID/C OX-2- (Grade A) + strong opioids (Grade A), titrated to effect (for high intensity pain) + paraceta mol	Gabapentinoi ds) (Grade D) due to lack of procedure- specific evidence Clonidine (Grade D) because of limited procedure- specific evidence IV ketamine infusion (Grade D)

specific evidence (may be used for reasons other than postoperative analgesia)selective inhibitors (Grade A) +/- weak opioids (Grade D) due to insufficient analgesic effect (for moderate D han (Grade D) due to inconsistent evidence of analgesic effectsParacetamol alone for high intensity pain (Grade D) due to insufficient analgesic efficacyNMDA antagonists D) due to inconsistent evidence of analgesic effectsNMDA effect or low intensity pain) + paraceta mol (Grade B)Paracetamol alone for high intensity pain (Grade D) due to inconsistent evidence of analgesic effectsKetamine (Grade D) because of limited procedure- procedure- procedure-Ketamine (Grade D) because of limited procedure- procedure-	C s di of	f bleeding corticosteroid (Grade D) ue to a lack f procedure-	(Grade B) Conventi onal NSAID/C OX-2-	because of limited procedure- specific evidence
for reasons other than postoperative analgesia)+/- weak opioids (Grade B), titrated to effect (for moderate or low intensity pain) + paraceta mol (Grade B)(Grade D) due to insufficient analgesic efficacyNMDA antagonists Dextromethor phan (Grade D) due to inconsistent evidence of analgesic effects(Grade D) due to insufficient analgesic efficacyKetamine (Grade D) because of limited procedure-(Grade D) effect(Grade B)				
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NMDA       effect (for         antagonists       Dextromethor         Dextromethor       or low         phan (Grade       pain) +         D) due to       pain) +         inconsistent       evidence of         evidence of       mol         analgesic       (Grade B)         effects       Ketamine         (Grade D)       because of         because of       limited         procedure-       limited	ai	naigesia)	<i>, , , , , , , , , ,</i>	
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Ketamine (Grade D) because of limited procedure-			(Grade B)	
(Grade D) because of limited procedure-	et	lfects		
(Grade D) because of limited procedure-	ĸ	etamine		
because of limited procedure-				
limited procedure-				
specific	p.	rocedure-		
specific		pecific		
evidence	ev	vidence		

Epiduraalanalgeesia + paratsetamool vs epiduraalanalgeesia ilma paratsetamoolita

- Kliinilistes uuringutes on epiduraalanalgeesia enamasti lisatud "baasanalgeesiale" (paratsetamool + NSAID, nt. Choi et al. "The addition of epidural local anesthetic to systemic multimodal analgesia following lumbar spinal fusion: RCT." *Canadian J Anesth* 61.4 (2014): 330-339).
- Ülevaateuuringutest on näha, et paratsetamooli kasutatakse sageli adjuvandina epiduraalanalgeesiaga paraleelselt (nt. Soinikoski et al. "A national survey into perioperative anesthetic management of patients with a fractured neck of femur." *BMC anesthesiology*12.1 (2012): 14)
  - "paracetamol and NSAIDs were commonly used as first-line analgesics and as adjuvants of neuraxial techniques "
- Ei leidunud ühtegi meta-analüüsi ega süsteemset ülevaadet, kus oleks otseselt võrreldud postoperatiivset epiduraalanalgeesiat koos paratsetamooli või ilma paratsetamoolita.
- Juhendites soovitatakse epiduraalanalgeesiale lisaks kasutada NSAIDide asemel paratsetamooli, kui patsiendil on neerupuudulikkus.

## Pubmed otsingusõnad:

1. (("analgesia"[All Fields] AND "epidural"[All Fields]) AND "paracetamol"[All Fields]) OR "acetaminophen"[All Fields] AND (Randomized Controlled Trial[ptyp] AND "2009/11/05"[PDat] : "2014/11/03"[PDat] AND "humans"[MeSH Terms])

#### 2. "Acetaminophen" OR "Paracetamol" AND "Analgesia, Epidural" [MeSH])

3. Paracetamol OR Acetaminophen AND Adjuvant AND Neuraxial analgesia

Leitud 1 abstrakt, mis vastab täpselt uuringuküsimusele. Selle abstrakti täisteksti (või artiklit) ei paista olemas olevat.

Zackova, M., et al. "Analgesic effectiveness of intravenous paracetamol during continuous epidural infusion for postoperative analgesia in thoracic surgery: 36." *Regional Anesthesia and Pain Medicine* 31.5 (2006): 23.

36. Analgesic effectiveness of intravenous paracetamol during continuous epidural infusion for postoperative analgesia in thoracic surgery

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Background and Aims: Epidural opioids infusion provide good analgesia after thoracotomy. This study aims to assess the best postoperative analgesia for thoracotomy by using intravenous paracetamol in association of epidural analgesia.

Methods: Through a randomized blind study, involving 46 patients undergoing thoracotomy, we performed a clinical evaluation of two different analgesic techniques. Thoracic (T7-T8 or T8-T9) epidural infusion of morphine 0,07mg/ml with levobupivacaine 1.25 mg/ml was given to both groups. Epidural catheter was connected to elastomeric pump 275 ml for 48 hrs (5ml/h). The II group received also intravenous paracetamol 1g at the time of skin closure and repeated after 8 hrs, 16hrs and 24 hrs from the end of thoracotomy. The SQV, Ramsey sedation score, vital parameters and side effects were recorded every 3 hours. Petidine 50mg was used in case of unsatisfactory analgesia. The patient's satisfaction was check 72 hrs after the surgery. Data was analysed using Anova and  $\chi^2$ test.

**Results:** Mean SQV value at 3 hours significantly lower in II group (2.45 vs 1.90). Mean SQV at 12 hours value was still lower in II group (2.30 vs 1.85) and at 24 hrs was main VQS almost similar in both groups. Only 7 patients in I group and 3 patients in II group required supplementary analgesia. Analgesic efficacy of the treatment was considered to be excellent in 53,2% in I group and in 61.3% in II group.

**Conclusions:** The results obtained show that both techniques ensure an excellent analgesia with only moderate adverse effects due to opioids. The combination of epidural analgesia with administration of paracetamol can be considered another way of multimodal approach of postoperative analgesia guaranteeing easy management and some more advantage for patient. 1. Baron CM, Kowalskj SE, Greengrass R. Continuous thoracic epidural fentanyl infusion. Anaest. Analg. 1996; 82(4): 760-768.

## Ravijuhendid

**DE-07** 

Paraleelselt PCEA-ga manustada mitteopioide (koksiibid, nsNSAIDid või paratsetamool)- paraku on sellele faktile viitavates uuringutes kasutatud vaid NSAIDe.

## **URO-13**

An epidural local anaesthetic in combination with NSAIDs or paracetamol is preferable (2b evidence - Evidence obtained from at least one other type of well-designed quasi-experimental study, samas ei ole juhendis sellel kohal mitte ühelegi uuringule viidatud.

## "Prospect" pain soovitused:

- **Colonic resection:** Paracetamol is recommended for pain of moderate- (>30 VAS <50) or low- (VAS =30) intensity, in combination with coxibs or nsNSAIDs only for patients who do not receive epidural analgesia or with cessation of epidural analgesia (Grade D, LoE 4)
- **Thoracotomy**: Paracetamol is recommended if analgesia is inadequate with regional techniques (Grade B)

# Ülevaateartiklid

**1.** Fischer, H. B. J., and C. J. P. Simanski. "A procedure-specific systematic review and consensus recommendations for analgesia after total hip replacement (THR)." *Anaesthesia* 60.12 (2005): 1189-1202.

**Abstrakt:** THR is a major surgical procedure usually associated with significant pain in the early postop period. Several anaesthetic and analgesic techniques are in common clinical use for this procedure but, to date, clinical studies of pain after THR have not been systematically assessed. Using the Cochrane protocol, we have conducted a systematic review of analgesic, anaesthetic and surgical interventions affecting postop pain after THR. In addition to the review, transferable evidence from other relevant procedures and clinical practice observations collated by the Delphi method were used to develop evidence-based recommendations for the treatment of postoperative pain. For primary THR, PROSPECT recommends either general anaesthesia combined with a peripheral nerve block that is continued after surgery or an intrathecal (spinal) injection of local anaesthetic and opioid. The primary analgesic technique should be combined with a step-down approach using paracetamol plus nsNSAIDs, with strong or weak opioids as required. Soovitused artiklis:

- Postoperative high-intensity pain<sup>:</sup> Establish epidural infusion as the nerve block regresses, ±PCEA, + Coxibs or nsNSAIDs ± rescue strong opioids i.v.
- Low- and moderate- intensity pain (VAS score < 50): Coxibs or nsNSAIDs + paracetamol, ± weak opioids

# RCTd

1. Mac, Thien Bich, et al. "Acetaminophen decreases early post-thoracotomy ipsilateral shoulder pain in patients with thoracic epidural analgesia: a double-blind placebo-controlled study." J Cardiothor Vascular Anesth 19.4 (2005): 475-478.

effective epidural analgesia, **Objective**: Despite up to 85% of postthoracotomy patients complain of moderate-to-severe ipsilateral shoulder pain. This study assessed the efficacy of acetaminophen in decreasing postoperative shoulder pain after a thoracotomy.

**Design:** Double-blind randomized and placebo-controlled study, University medical center, 65 patients.

**Intervention:** Patients were randomized into 2 groups; 31 patients received acetaminophen (group A), and 34 patients received a placebo (group P). After induction of anesthesia, patients received either a loading dose of acetaminophen, 1000 mg intrarectally, or a placebo suppository. Thereafter, acetaminophen, 650 mg, or a placebo, was administered intrarectally every 4 hours for 48 hours postoperatively.

**Results**: Postoperative pain at the surgical site and shoulder pain were assessed separately every 4 hours for 48 hours using a numerical rating scale (NRS). Rescue analgesia for severe shoulder pain (NRS > 7) consisted of subcutaneous hydromorphone. Sixty-three patients experienced shoulder pain (97% prevalence). Demographic and intraoperative data were similar between the 2 groups. Average NRS for shoulder pain was higher in group P compared with group A at 8, 12, and 16 hours postoperatively (3.1 +/- 2.9, 2.6 +/- 2.6, 2.3 +/- 2.4 vs 1.8 +/- 2.6, 1.2 +/- 1.5, 1.3 +/- 1.8; P < 0.05). The total dose of hydromorphone did not differ between the 2 groups at 16, 24, and 48 hours.

## **Conclusion**:

#### Acetaminophen decreases post-

thoracotomy ipsilateral shoulder pain when given preemptively and regularly during the first 48 hours postoperatively in patients who received thoracic epidural analgesia.

2. Paech, M. J., et al. "RCT of parecoxib, celecoxib and paracetamol as adjuncts to patient-controlled epidural analgesia after caesarean delivery." *Anaesthesia and intensive care* 42.1 (2014): 15-22.

**Background:** The benefit of combining non-opioid analgesics with neuraxial opioids for analgesia after caesarean delivery has not been clearly established. Larger doses of paracetamol or cyclooxygenase-2 inhibitors have not been evaluated.

**Method**: A randomised, double blind, double-dummy, parallel group placebocontrolled clinical trial was conducted among women having elective caesarean delivery under spinal anaesthesia, followed by pethidine patient-controlled epidural analgesia. Patients received placebos (group C); intravenous parecoxib 40 mg then oral celecoxib 400 mg at 12 hours (group PC); intravenous paracetamol 2 g then oral 1 g six-hourly (group PA); or these regimens combined (group PCPA).

**Results**: The primary outcome was 24-hour postoperative patient-controlled epidural pethidine use and the main secondary outcome was postoperative pain. One hundred and thirty-eight women were recruited but 27 subsequently met exclusion criteria, leaving 111 who were randomised, allocated and analysed by intention-to-treat (n=23, 30, 32 and 26 in groups C, PC, PA and PCPA respectively). There were no

differences between groups for pethidine consumption, based on either intention-totreat (median 365, 365, 405 and 360 mg in groups C, PC, PA and PCPA respectively, P=0.84) or per protocol analysis (17 major violations). Dynamic pain scores did not differ between groups but requirement for, and dose of, supplementary oral tramadol was least in group PCPA (incidence 23% versus 48%, 70% and 58% in groups C, PC and PA respectively, P=0.004).

**Result:** The addition of regular paracetamol, cyclooxygenase-2 inhibitors or both to pethidine patient-controlled epidural post-caesarean analgesia did not provide a pethidine dose-sparing effect during the first 24 hours.