

Kliiniline küsimus nr 13

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

Tulemusnäitajad: valu tugevus, valu vähenemine, lisavaluvaigisti vajadus (sh opiaadi vajadus), aeg esimese lisavaluvaigisti vajaduseni, ärevuse vähenemine, postoperatiivsete tüsistuste esinemissagedus, valuvaigistitest tingitud kõrvaltoimed, rehospitalseerimine 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 multimodal analgesia is not yet widely established and their role in the perioperative outcome remains unclear. (Loveridge and Patel 2013)

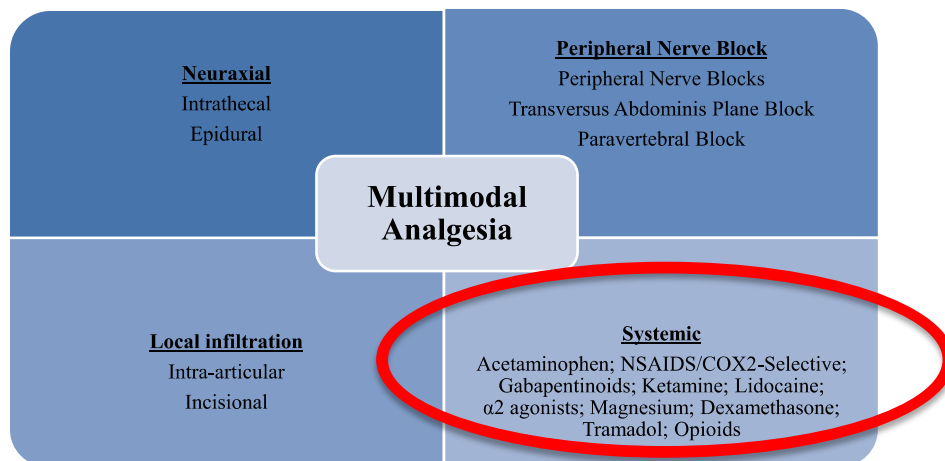


Fig. 1. Basic components of multimodal analgesic regimens.

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 opiidile lisatud **paratsetamool** ja **koksiibid** vähendavad vajaminevaid opiidide koguseid, kuid ei ole tõestatud, et nad võiksid vähendada opiidide kõrvaltoimete esinemist.
3. **NSAIDid** lisatuna PCA opiididele vähendavad vajaminevaid opiidide 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 opiidide 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. **Ambulatoorsele** 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 opiidide koguseid.

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

PROSPECT soovib 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 et al. 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 et al., 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.	Average 24-h morphine consumption ↓ significantly with all regimens (by 15–55%) <ul style="list-style-type: none"> PARA: 8.3 mg NSAID: 10.3mg (single dose), 18.3mg (continuous infusion), 19.7mg (multiple-dose) Coxibs: 10mg (multiple low-dose), 13.3mg (multiple high-dose) Pain intensity at 24 h ↓ <ul style="list-style-type: none"> NSAIDs (1cm on the 0-10cm VAS scale, effect was not statistically significant with single-dose regimens, average ↓ 0.75 cm). PARA: 0.29 cm (no significant effect) PONV and sedation ↓ <ul style="list-style-type: none"> 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). Coxibs: increased risk of renal failure in cardiac patients (from 0 to 1.4%, NNH 73)
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 et al. 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 et al. 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 effect of the combination of PARA+NSAID compared with either drug alone in postop pain	of PARA+NSAID (diclofenac, ketoprofen, ketorolac, suprofen, tenoxicam)	over periods of 8, 24 and 48h in the PARA + NSAID group. In the 5 other trials, no difference between study groups was observed. No ADRs attributed to the concomitant administration of PARA and NSAIDs were reported
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1. "Behandlung acuter perioperativer und postraumatischer Schmerzen" 2009 (DE-07)

The grading system of the guideline

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)

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-sparing 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).

Additional administration of NSAID reduces the occurrence of PONV and sedation compared to the iv PCA monotherapy with morphine, although 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.

Translated tables from the guideline:

Table 2. Metaanalyses of opioid + non-opioid combination vs opioid monotherapy

Autor, Year, Level of evidence	Study	Therapy	Control	Result
Remy <i>et al.</i> , 2005; LoE: 1a	7 RCTs; different surgeries	i.v. PCA Morphine + Paracetamol (i.v. or oral)	i.v. PCA (alone or + placebo)	Opioidconsumption ↓ PONV ↔ Sedation ↔
Elia <i>et al.</i> , 2005; LoE: 1a	52 RCTs different surgeries	i.v. PCA (Morphine) + Paracetamol, NSAID or coxib	i.v. PCA + Placebo	All non-opioids: Opioidconsumption ↓ Paracetamol: postop. pain ↔ side effects ↔ NSAID: postop. pain ↓ (only continuous giving or multiple doses) PONV ↓ (NNT: 15) Sedation ↓ (NNT: 37) other side-effects ↔ bleeding risk ↑ (1,7% vs 0%) Coxibs: side effects ↔ renal function ↓ (1,4% vs 0%)
Marret <i>et al.</i> , 2005b; LoE:	22 RCTs different	i.v. PCA + NSAID (18 RCTs) or coxib	i.v. PCA (alone or +	PONV ↓ Sedation ↓

1a	surgeries	(4 RCTs)	placebo)	other side effects ↔
Romsing et al., 2005; LoE: 1a	19 RCTs different surgeries	Coxib + additional opioids	Placebo + additional opioids	Opioid consumption ↓ Dizziness ↓ Other side-effects ↔

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

Author, Year, Level of evidence	Patients	Therapy	Control	Result
Kraft et al., 2006; LoE 1b (RCT)	n= 170 Colon resection	i.v. PCA + 1. Paracetamol 2. Parecoxib or Valdecoxib	alleinige i.v. PCA	Opioidconsumption ↓
Tempel et al., 1996; LoE 1b (RCT)	n= 103 abdominal und urological surgery	i.v. PCA + Analgin	i.v. PCA + Placebo	Opioidconsumption ↓ postop pain ↔ ADRs ↔
Stamer et al., 2003a; LoE 1b (RCT)	n= 191 abdominal surgery	i.v. PCA Tramadol + Analgin	continous i.v. analgesia (Tramadol + analgin)	Opioidconsumption ↓ postop. pain ↔

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

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	
<input checked="" type="checkbox"/>	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 inadequate 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 respiratory depression (Marret *et al.* 2005 Level I).

Pain scores ↓, opioid consumption ↓, PONV ↓, sedation ↓
pruritus, urinary retention, and respiratory depression ↔

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 bypass surgery is controversial. Pain scores ↓, opioid consumption ↓

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 and 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) (Level I, Cochrane review).
- In general, a perioperative low-dose **ketamine infusion** is opioid-sparing, 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
3	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 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 increase efficacy while minimising adverse effects.	2b	B

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	GR
For postoperative pain control in outpatients, multimodal analgesia with a combination of NSAIDs or paracetamol plus local anaesthetics should be used .	2b	B
If possible, avoid opioids.	3	B

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 elderly patients because these techniques are associated with fewer complications.	2b	B

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	GR
Postoperative use of opioids should be avoided in obese patients unless absolutely necessary.	2b	B
An epidural local anaesthetic in combination with NSAIDs or paracetamol is preferable.	2b	B

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 reduces consumption of opioids.	1b	B

Süsteematilised ülevaated

Süsteematilised ülevaated hindavad erinevate ravimirühmade tõhusust ja ohutust multimodaalses valuravis.

Paratsetamool, NSAID ja koksiihid

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 statistiliselt 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 anda tugevat soovitus nende kolme ravimirühma rutiinseks lisamiseks iv PCA morfiinile esimese 24 postoperatiivse tunni jooksul.

Alfa-2 adrenoretseptori agonistide (klonidiin ja deksmedetomidin)

kohta leidis 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 leidis 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 soovitusi pregabaliini kasutamise kohta multimodaalse 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 retseptori antagonisti ketamiini

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

Magneesium

Kui 2007.a avaldatud meta-analüüs ei leidnud magneesiumil olevat olulist rolli multimodaalse valuravi skeemides, siis 2013 a avaldatud meta-analüüs (Albrecht 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 consumption	<p>Opioid consumption ↓ (56 trials)</p> <p>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).</p> <p>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.</p>
Opioid adverse effects	<p>PONV (43 trials)</p> <p>Significant reduction in nausea and PONV with NSAIDs compared to placebo (OR 0.70; 95% CrI 0.53 to 0.88) but not for PARA or coxibs, nor for NSAIDs compared to PARA or coxibs.</p> <p>Sedation (19 trials)</p> <p>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; 95%CI 0.20-1.01) and coxibs (OR 0.63; 95%CI 0.18-1.49), with wide CI indicating considerable uncertainty.</p> <p>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.</p>
Non-opioid ADRs	<p>Surgical bleeding was not reported in any PARA studies and in a single coxib study. Based on 6 trials (n = 695), 2.4% of participants receiving an NSAID experienced surgery-related bleeding compared to 0.4% with placebo.</p>
Conclusion	<p>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.</p>
Implications for the health-care	<p>All three non-opioid analgesics were effective at reducing PCA morphine consumption in the first 24 hours following major surgery.</p> <p>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.</p> <p>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.</p> <p>There were a small number of surgical bleeding events, GI bleeding and oliguria for participants treated with an NSAID.</p> <p>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.</p>

Alpha-2 adrenoreceptor agonists (Clonidine and dexmedetomidine)

- **Blaudszun G, Lysakowski C, Elia N, Tramèr MR.** "Effect of perioperative systemic α_2 agonists on postoperative morphine consumption and pain intensity: systematic review and meta-analysis of randomized controlled trials". *Anesthesiology* **2012**;116(6):1312-22.

Aim	To find out: what extent periop systemic α -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 reduction	Pain intensity at 24h ↓ Weighted mean difference was □ 0.7 cm (1.2-0.1) on a 10-cm VAS scale with clonidine and 0.6 cm (0.9-0.2) with dexmedetomidine. Clonidine: Pain scores improved during the first 24h. At 48 h postoperatively no analgesic benefit was seen. Dexmedetomidine: decreased VAS scores seen up to 24h postoperatively
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 investigate 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 consumption	Opioid consumption ↓ lower opioid consumption (p<0.05)	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 Incidence 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; CI, 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 pregabalin) 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	Studies did not present a sufficiently homogeneous group of trials to allow a pooled analysis.	↓ postop opioid consumption (WMD, 213.40 mg; 95%CI 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		Pain intensity ↔ at rest / on movement at 2h or 24h	Pain intensity ↓
Adverse effects		↓ 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.

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 opioid-related 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 patient-controlled 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	Subramaniam 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 whether 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 medicine 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 1:1 morphine: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	Iv, im bolus, PCA,
Postoperative analgesia / comparator	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 analgesic consumption	↓ 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 reduction	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 analgesic	-	↑ in the time to first analgesic	-	-	-

Adverse effects	↓ PONV	↑ Hallucinations 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 benzodiazepine; compared with controls, the odds ratio (OR) was 2.32 (95%CI, 1.09–4.92, NNH 21)	No reduction in opioid-related side effects such as PONV, pruritus, and respiratory depression ↑ psychomimetic effects
Conclusion	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 ketamine 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 ↓ for up to 48h.](#)

[Postop pain scores were ↓ 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 ↓ 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 randomized 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 (soovitus 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, laparotoomiad	Epiduraali püsiinfusioon + diklofenak rektaalselt	Epiduraali püsiinfusioon	Valu↓

Hirabayashi 1994 LoE: 1b	n= 40, ülemine laparatoomia	Epiduraali püsiinfusioon+ indometatsiin rektaalselt	Epiduraali püsiinfusioon	Valu ↓; valuvaigisti vajadus ↓
Scott 1994 LoE: 1b	n= 26 abdominaalne hüsterektoomia	Epiduraali püsiinfusioon + pre ja postop diklofenak im	Epiduraali püsiinfusioon + platseebo	Valu ↓
Mogensen 1992 LOE: 1b	n= 44 ülemine laparotoomia	Epiduraali püsiinfusioon + pre ja postop piroksikaam	Epiduraali püsiinfusioon + platseebo	Valuvaigisti vajadus ↔ ; valu ↔
Bigler 1992 LoE: 1b	n= 28 torakotoomia	Epiduraalanalgeesia +diklofenak im	Epiduraalanalgeesia + platseebo	Valu ↓; kõrvaltoimeid ↔

Kokkuvõtte	Viide kirjandus
<p>OBJECTIVE: To evaluate the analgesic efficacy and systemic anti-inflammation of preoperative cyclooxygenase-2 nonsteroidal antiinflammatory drug, rofecoxib, after total knee replacement (TKR).</p> <p>METHODS: Thirty patients underwent elective knee replacement were randomly given oral rofecoxib 25 mg (group RE, n = 15) or placebo (group E, n = 15) 1 hour prior to surgery. All patients received epidural combined isoflurane anesthesia during surgery and patient-controlled epidural analgesia after surgery for 72 hrs (0.1 mg/ml morphine + 1.2 mg/ml bupivacaine + 0.02 mg/ml droperidol). Modified verbal rate scale was used to evaluate postoperative pain intensity. The outcomes included pain scores during rest and movement of knee joints and analgesia satisfaction. Daily morphine consumption was recorded. Circulation leucocyte and serum cytokine concentrations (including interleukin 6, interleukin 8, interleukin 10, Tumor necrosis factor-alpha) were determined before surgery, at the end of surgery, 2 h, 6 h, 12 h, 24 h and 48 h after surgery in two groups using RIA. The amount of intraoperative blood loss and postoperative drainage from the knees were measured.</p> <p>RESULTS: The pain scores were significantly less in the group RE than in group E during rest and knee joints movement on the first and second postoperative day, with an improvement in total analgesia satisfaction ($P < 0.05$). The mean dose of morphine for first 24 h was (8.1 +/- 1.5) mg in the E group and (6.8 +/- 0.7) mg in the RE group ($t = -2.71$, $P < 0.01$). Leucocyte and neutrophil counts were much higher in group E than in group RE at 12 h, 24 h post-operatively ($P < 0.05$). Serum TNF-alpha concentration was significantly lower in group RE than group E at the end of surgery, 6 h, 12 h postoperatively, as well as IL6 at 48 h, IL8 at 24h after surgery ($P < 0.05$). There were no significant differences in respect to the amount of intraoperative and postoperative blood loss between two groups ($P > 0.05$).</p> <p>CONCLUSION: Preoperative cyclooxygenase-2-specific nonsteroidal anti-inflammatory drug rofecoxib increases analgesia satisfaction, reduces opioid requirement and demonstrates a systemic anti-inflammatory effect after TKR</p>	<p>Zhonghua Wai Ke 2004 May 22; 42(10): 21.</p> <p>Postoperative analgesia and anti-inflammatory effect of rofecoxib after total knee replacement.</p> <p>Feng Y, Ju H, Yang Y, An HY, Zhou Y</p>
<p>CONTEXT: Controlling postoperative pain after knee replacement while reducing opioid-induced adverse effects and improving outcomes remains an important challenge.</p> <p>OBJECTIVE: To assess the effect of combined preoperative and postoperative administration of a selective inhibitor of cyclooxygenase 2 on opioid consumption and outcomes after total knee arthroplasty (TKA).</p> <p>DESIGN, SETTING, AND PATIENTS: Randomized, placebo-controlled, double-blind trial conducted June 2001 through September</p>	<p>Effects of perioperative administration of a selective cyclooxygenase 2 inhibitor on pain management and recovery of function after total knee replacement: a randomized controlled trial</p> <p>Buvanendran A, Tuman KJ, Lub</p>

<p>2002, enrolling 70 patients aged 40 to 77 years and undergoing TKA at a university hospital in the United States.</p> <p>INTERVENTIONS:</p> <p>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.</p> <p>MAIN OUTCOME MEASURES:</p> <p>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.</p> <p>RESULTS:</p> <p>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 on the night of surgery ($P = .006$) and on the first ($P = .047$) and second ($P < .001$) days postoperatively. Knee flexion was increased in the rofecoxib group compared with the placebo group at discharge (active flexion: mean [SD], 84.2 degrees [11.1 degrees] vs 73.2 degrees [13.6 degrees], $P = .03$; passive flexion: 90.5 degrees [6.8 degrees] vs 81.8 degrees [13.4 degrees], $P = .05$) and at 1 month postoperatively (109.3 degrees [8.5 degrees] vs 100.8 degrees [11.8 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).</p> <p>CONCLUSION:</p> <p>Perioperative use of an inhibitor of cyclooxygenase 2 is an effective component of multimodal analgesia that reduces opioid consumption, pain, vomiting, and sleep disturbance, with improved knee range of motion after TKA</p>	<p>Elmofly D, Mo Rosenberg AG.</p>
<p>ABSTRACT</p> <p>Twenty-eight patients scheduled for lung resection with lateral thoracotomy and postoperative chest drains during combined thoracic epidural bupivacaine plus morphine and general anaesthesia were studied. Postoperative pain treatment was continuous epidural infusion of bupivacaine 0.25% 5 ml h⁻¹ plus morphine 0.2 mg h⁻¹ for 48 h and, in addition, the patients received rectal piroxicam 40 mg randomly and double-blind 12 h and 1 h before surgery and 20 mg 24 h⁻¹ postoperatively or placebo. Pain was evaluated at rest, during cough and mobilisation, together with pulmonary function (FEV₁, FVC, PEF_R) and sensory level of analgesia repeatedly for 48 h. The results showed efficient pain relief, 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</p>	<p>Acta Anaesthesiol Scand 1992 Oct; 36(7):</p> <p>Effect of piroxicam in addition to continuous thoracic epidural bupivacaine and morphine on postoperative lung function after thoracotomy.</p> <p>Bigler D, Mølle Jensen M, Bertil Hjørtso NC, Ke</p>
<p>ABSTRACT</p> <p>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</p>	<p>Anesth Analg. 1995 Mar; 74(3): 366-7.</p> <p>Systemic piroxicam adjunct to combined epidural bupivacaine and morphine for postoperative pain relief--a double-blind study.</p> <p>Mogensen T, V Jonsson T, Mat Lund C, Kehlet</p>

adding piroxicam to an otherwise very effective low-dose epidural bupivacaine and morphine treatment after upper abdominal surgery	
<p>ABSTRACT</p> <p>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 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, postoperative pain relief by epidural buprenorphine and bupivacaine plus rectal indomethacin was more effective than that by epidural buprenorphine and bupivacaine</p>	<p>Masui. 1994 Oct; 43(10): 1598-1601 Effect of indomethacin as an adjunct to postoperative pain relief by continuous epidural infusion of bupivacaine and buprenorphine</p> <p>Hirabayashi Y, H, Shimizu R, Saitoh K, Fukuda T</p>
<p>ABSTRACT</p> <p>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 buprenorphine 0.1 mg in 8 ml of 0.25% bupivacaine immediately after surgery and subsequently infusion was started with the solution of epidural buprenorphine 15 micrograms in 1 ml of 0.23% bupivacaine at a rate of 1 ml.h⁻¹ for 48 h. Forty patients in 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 epidural infusion of buprenorphine and bupivacaine produced enhanced analgesia and reduced pain scores measured by VAS after upper abdominal surgery. However, after lower abdominal surgery, such effects of rectal diclofenac obtained after upper abdominal surgery were not demonstrable</p>	<p>Masui. 1995 May; 44(5): 650-653 Rectal diclofenac coupled with continuous epidural infusion with buprenorphine and bupivacaine for pain relief after upper and lower abdominal surgery</p> <p>Hirabayashi Y, H, Shimizu R, Saitoh K, Fukuda T</p>
<p>Abstract</p> <p>PURPOSE:</p> <p>To assess the analgesic efficacy of administering, immediately after surgery, a single dose 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).</p> <p>METHODS:</p> <p>Forty-eight ASA physical status I or II term parturients scheduled for elective LSCS under regional 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 anesthetic mixture with a lockout period of ten minutes and an hourly limit of 12 ml. There was 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-operatively for pain scores on movement, dermatomal level of sensory blockade, degree of motor blockade and volume of local anesthetic used. At conclusion of the study, patients' satisfaction scores were recorded.</p> <p>RESULTS:</p> <p>The two groups of patients were similar demographically. Patients who received a diclofenac 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 between the groups.</p> <p>CONCLUSION:</p> <p>A single administration of 100 mg diclofenac suppository is effective in reducing post-Cesarean epidural local anesthetic/opioid requirements by 33% for the first 24 hr post-operatively</p>	<p>Can J Anaesth. 2000 Apr; 48(4): 383-6 Single dose diclofenac suppository reduces post-Cesarean PCEA requirements.</p> <p>Lim NL, Lo WJ, Lim JL, Pan AX</p>
Study criteria	Level of evidence
Systematic review (with homogeneity) of randomised, controlled trials	1a
Individual, randomised, controlled trials with statistically significant results	1b

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 soovitude tabel multimodaalse analgesia ja adjuvantide kasutamise kohta

	Pre-op		Intra-op	Post-op		
	Recommend ed	Not recommende d		Not recommende d	Recomm ended	Not recommende d
Abdominal hysterectomy	-	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 combination 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) Paracetamol for moderate - (VAS>3<5) or low-intensity (VAS<3) pain, in combination with COX-2 inhibitors or	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 (grade A)	
Colonic Resection	<p>COX-2-inhibitors (Grade B) (only for patients who do not receive epidural analgesia)</p> <p>Continuous administration of pre-/intra-op IV lidocaine if continued during the immediate postop period (Grade B), when epidural analgesia is not feasible or contra-indicated</p>	<p>IV clonidine (Grade D) because it is associated with an increased risk of hypotension and bradycardia</p> <p>NSAIDs (Grade B) because pre-op administration of these agents can increase the risk of intra- and postop bleeding</p> <p>Corticosteroids for analgesia (Grade A) because of procedure-specific evidence showing no significant benefit in reducing pain scores and concerns that they could affect anastomotic and wound integrity (but they may be used for reduction of PONV)</p> <p>Gabapentin/pregabalin (Grade D) due to a lack of procedure-specific evidence</p> <p>Continuous administration of IV lidocaine limited to the pre-/intra-op period (Grade D) because of inconsistent and</p>	<p>COX-2-inhibitors (Grade B) (only for patients who do not receive epidural anaesthesia)</p>	<p>IV clonidine (Grade D) because it is associated with an increased risk of hypotension, sedation and bradycardia</p> <p>Calcium channel antagonists (Grade B), based on limited procedure-specific evidence showing a lack of postop analgesic effect</p> <p>Gabapentin/pregabalin (Grade D) due to a lack of procedure-specific evidence</p> <p>Continuous administration of IV lidocaine limited to the pre-/intra-op period (Grade D) because of inconsistent and insufficient procedure-specific evidence</p> <p>NMDA receptor antagonists (Grade D) because of limited procedure-specific evidence of analgesic efficacy</p>	<p>COX-2-inhibitors (Grade B) (only for patients who do not receive epidural analgesia or with the cessation of epidural analgesia)</p> <p>Conventional NSAIDs (Grade A) (only for patients who do not receive epidural analgesia or with cessation of epidural analgesia)</p> <p>IV lidocaine (Grade B) (when epidural is not feasible or contra-indicated)</p> <p>Paracetamol (Grade B) for moderate - or low-intensity pain (only for patients that do not receive epidural analgesia, or after cessation of epidural</p>	<p>Gabapentin/pregabalin (Grade D) due to a lack of procedure-specific evidence</p> <p>NMDA receptor antagonists (Grade D) because of limited procedure-specific evidence of analgesic efficacy</p>

		insufficient procedure-specific evidence NMDA receptor antagonists (Grade D) because of limited procedure-specific evidence			analgesia)	
Haemorrhoid 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	Gabapentinoids (Grade D) because there is no procedure-specific evidence and because the benefit:risk ratio is not sufficiently favourable for this ambulatory procedure Ketamine (Grade D) because there is no procedure-specific evidence and because the benefit:risk ratio is not sufficiently favourable for this ambulatory procedure	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		Conventional NSAIDs (Grade B), COX-2 inhibitors (Grade B) Paracetamol (Grade B), for low-moderate pain	Gabapentinoids (Grade D) because there is no procedure-specific evidence and because the benefit:risk ratio is not sufficiently favourable for this ambulatory procedure Ketamine (Grade D) because there is no procedure-specific evidence and because the benefit:risk ratio is not sufficiently favourable for this ambulatory procedure

herniorrhaphy	Conventional NSAIDs (Grade A) or COX-2 inhibitors (Grade A)	Clonidine (Grade D) Corticosteroid (Grade D) Gabapentin/pregabalin (Grade D) Ketamine (Grade D)		Clonidine (Grade D) Gabapentin/pregabalin (Grade D) Ketamine (Grade D)	NSAIDs (grade A) or COX-2 inhibitors (grade A) Paracetamol for routine pain therapy in combination with conventional NSAIDs/COX-2 inhibitors (Grade B)	Gabapentin/pregabalin (Grade D) Ketamine (Grade D)
laparoscopic cholecystectomy	Corticosteroids - dexamethasone (Grade B for analgesic effects) COX-2 inhibitors (Grade B) Gabapentinoids gabapentin (Grade B)	Alpha-2-adrenergic receptor agonists - clonidine (Grade D) Conventional NSAID (Grade B) NMDA antagonists - dextromethorphan (Grade D) ketamine (Grade D) magnesium (Grade B) Paracetamol (Grade B)	Conventional NSAIDs - at end of surgery (Grade D) COX-2 inhibitors (Grade D)	NMDA antagonist - dextromethorphan (Grade D) ketamine infusion (Grade D) magnesium infusion (Grade B)	Conventional NSAIDs (Grade A) COX-2 inhibitors (Grade A) Paracetamol (Grade A)	NMDA antagonist ketamine (Grade D) magnesium (Grade B)
Non-cosmetic breast Surgery	Major breast surgery Gabapentinoids (Grade A) COX-2-inhibitors (Grade D)/paracetamol (Grade B) in short breast	Major breast surgery NSAIDs (Grade B) because of inconsistent procedure-specific and	-	Corticosteroids for analgesia (Grade D) due to insufficient procedure-specific evidence	Major breast surgery Conventional NSAID (Grade A) or COX-2-	Major breast surgery Mexiletine (Grade D) because of limited and conflicting

	<p>surgery procedures to provide sufficient analgesia in the early recovery period</p> <p>Minor breast surgery COX-2-inhibitors (Grade D)/paracetamol (Grade B) in short breast surgery procedures to provide sufficient analgesia in the early recovery period</p>	<p>transferable evidence for benefit of pre- vs. postop administration, and increased risk of bleeding</p> <p>Corticosteroids for analgesia (Grade D) due to insufficient procedure specific evidence</p> <p>COX-2 inhibitors (except in short breast surgery procedures) (Grade D) as transferable evidence shows inconsistent benefit of pre- vs. postop administration, and there is no procedure-specific evidence</p> <p>NMDA antagonists</p> <p>Dextromethorphan (Grade B) due to limited procedure-specific evidence</p> <p>Magnesium for analgesia (Grade B) due to transferable</p>			<p>inhibitor (Grade B) Paracetamol alone or in combination with other non opioid analgesics (Grade B) for low moderate intensity pain</p> <p>Paracetamol in combination with opioid analgesics (Grade D) for high intensity pain</p> <p>Minor breast surgery Conventional NSAID (Grade A) or COX-2 selective inhibitor (Grade B) Paracetamol alone or in combination with other non opioid analgesics</p>	<p>procedure specific evidence</p> <p>Paracetamol alone for high intensity pain (Grade B) due to insufficient analgesic efficacy</p> <p>Minor breast surgery Gabapentins (Grade B) because pain intensity is commonly not severe enough to justify an adjunct to the usual analgesic agents</p> <p>Mexiletine (Grade D) because of limited and conflicting procedure specific evidence</p> <p>Paracetamol alone for high intensity pain (Grade B) due to insufficient analgesic efficacy</p>
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		<p>evidence showing a lack of analgesic effects</p> <p>Paracetamol (except in short breast surgery procedures) (Grade D) as there is no procedure-specific or transferable evidence to show whether pre-op administration has any analgesic benefit compared with postop administration</p> <p>Minor breast surgery</p> <p>Gabapentins (Grade D) because pain intensity is commonly not severe enough to justify an adjuvant to the usual analgesic agents</p> <p>Conventional NSAIDs (Grade D) because of inconsistent procedure specific and transferable evidence for benefit of pre- vs. postop administration</p> <p>Corticosteroids for analgesia</p>			<p>(Grade B) for low moderate intensity pain</p> <p>Paracetamol in combination with opioid analgesics (Grade D) for high intensity pain</p>	
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		<p>(Grade D) due to insufficient procedure specific evidence</p> <p>COX-2-inhibitors (except in short breast surgery procedures) (Grade D) as transferable evidence shows inconsistent benefit of pre- vs. postop administration, and there is no procedure-specific evidence</p> <p><i>NMDA antagonists</i></p> <p>Dextromethorphan (Grade B) due to limited procedure-specific evidence</p> <p>Magnesium for analgesia (Grade B) due to transferable evidence showing a lack of analgesic effects</p> <p>Paracetamol (except in short breast surgery procedures) (Grade D) as there is no procedure-</p>				
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		specific or transferable evidence to show whether pre-op administration has any analgesic benefit compared with postop administration				
Radical prostatectomy	<p>COX-2-inhibitors should be administered at the appropriate time (pre- or intra-operatively) to provide sufficient analgesia in the early recovery period (GoR B), based on transferable evidence from diverse procedures showing analgesic efficacy (LoE 1)</p> <p>Pre-op dexamethasone is recommended both for its analgesic and anti-emetic effects (GoR B), based on transferable evidence from multiple procedures (LoE 1), despite lack of procedure-specific evidence</p> <p>Pre-operative gabapentins are recommended (GoR B) based on transferable evidence from multiple procedures showing analgesic</p>	<p>Ketamine - Not recommended for routine use (GoR D) because of conflicting procedure-specific evidence (LoE 4), despite favourable transferable evidence from more painful surgical procedures (LoE 1)</p>	-	-	<p>COX-2-selective inhibitors are recommended (GoR B) based on transferable evidence from multiple procedures showing analgesic efficacy (LoE 1), despite a lack of procedure-specific evidence</p> <p>Lidocaine infusion is recommended for radical prostatectomy (GoR B), due to transferable evidence from multiple procedures showing analgesic efficacy (LoE 1) despite limited procedure-specific evidence</p> <p>Paracetamol is recommended (GoR B)</p>	

	efficacy (LoE 1), despite lack of procedure-specific evidence				due to strong transferable evidence from multiple procedures showing analgesic efficacy (LoE 1) despite lack of procedure-specific evidence Paracetamol should be administered at the appropriate time (pre- or intraoperatively) to provide sufficient analgesia in the early recovery period (GoR D)	
Thoracotomy	-	alpha-2-adrenergic receptor agonists: clonidine (Grade A) dexmedetomidine (Grade D) Corticosteroid (Grade D) Conventional NSAIDs (Grade A) COX-2 inhibitors (Grade D) Ketamine (Grade D) Gabapentin/pregabalin (Grade D)	-	Conventional NSAIDs (Grade D) COX-2 inhibitors (Grade D) Ketamine (Grade D) Gabapentin/pregabalin (Grade D)	Conventional NSAIDs, if regional analgesia is inadequate (Grade A) COX-2 inhibitors, if regional analgesia is inadequate (Grade B) Paracetamol, if regional analgesia is inadequate, as part of a multianalgesic regimen (Grade D)	alpha-2-adrenergic receptor antagonists dexmedetomidine (Grade D) Ketamine (Grade D) Gabapentin/pregabalin (Grade D) Paracetamol alone for high intensity pain (VAS>50 mm) (Grade B)

total hip arthroplasty	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) Corticosteroids (grade D)	-	-	COX-2 inhibitors or conventional NSAIDs (grade A) in combination with paracetamol and/or strong opioids for high-intensity pain (grade A) or with paracetamol and/or weak opioids for moderate- or low-intensity pain (grade D) Paracetamol (grade A) in combination with conventional NSAIDs or COX-2-selective inhibitors, with or without rescue opioids (grade B)	Ketamine (grade D) Corticosteroid (grade D)
Total Knee Arthroplasty	-	gabapentinoids (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 Dextromethorphan (Grade D) because of inconsistent analgesia Ketamine (Grade D) due to limited procedure-specific evidence	Conventional NSAID/COX-2- (Grade A) + strong opioids (Grade A), titrated to effect (for high intensity pain) + paracetamol	Gabapentinoids (Grade D) due to lack of procedure-specific evidence Clonidine (Grade D) because of limited procedure-specific evidence IV ketamine infusion (Grade D)

		<p>of bleeding</p> <p>Corticosteroids (Grade D) due to a lack of procedure-specific evidence (may be used for reasons other than postoperative analgesia)</p> <p>NMDA antagonists Dextromethorphan (Grade D) due to inconsistent evidence of analgesic effects</p> <p>Ketamine (Grade D) because of limited procedure-specific evidence</p>			<p>(Grade B)</p> <p>Conventional NSAID/COX-2-selective inhibitors (Grade A) +/- weak opioids (Grade B), titrated to effect (for moderate or low intensity pain) + paracetamol (Grade B)</p>	<p>because of limited procedure-specific evidence</p> <p>Paracetamol alone for high intensity pain (Grade D) due to insufficient analgesic efficacy</p>
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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 checked 72 hrs after the surgery. Data was analysed using Anova and χ^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. I. 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**: 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.

Objective: Despite effective epidural analgesia, up to 85% of post-thoracotomy 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 placebo-controlled 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-to-treat (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.