Kliiniline küsimus nr 4.

Is postoperative pain intensity affected by preemptive (preventive) administration of analgesics versus no administration of analgesics?

Critical outcome indicators: pain intensity, need for supplemental analgesics, time to first dose of analgesic, side-effects (adverse effect) of analgesics, frequency of postoperative complications, time of presence in recovery (post-anaesthesia care-unit)

Kliiniline küsimus nr 7.

Is the outcome of pain management affected by commencment the pain management intraoperative vs postoperative period?

Critical outcome indicators: pain intensity, reduction of pain, need for supplemental analgesics (including opioid), frequency of postoperative complications, rehospitalization due to pain, patient (legal guardian) satisfaction with pain treatment time of presence in recovery (post-anaesthesia care-unit)

Kokkuvõte:

Me ei leidnud uuringuid, mis võrdleksid valuravi alustamist intraoperatiivses versus postoperatiivses perioodis. Seega ei saa hinnata, kuidas see mõjutab valuravi tulemust. Enamikes uuringutes on keskendutud erinevate analgeesia tehnikate võrdlemisele enne ja peale nahalõiget ja nende mõjule ägedale postoperatiivsele valule.

Postoperatiivses valuravis on peamine eesmärk saavutada parim analgeetiline tulemus võimalikult väikeste ravimite annustega vältimaks nendest põhjustatud kõrvaltoimeid. See on saavutatav multimodaalse ja ennetava (preemptive) analgeesiaga. Efektiivsed ennetavad analgeesia tehnikad kasutavad väga erinevaid farmakoloogilisi vahendeid vähendamaks või blokeerimaks valuretseptorite aktiveerumisest johtuvat perifeerset ja tsentraalset sensitisatsiooni aga ka valu neurotransmitterite aktiivsust või produktsiooni.

Ravim / meetod	Operatsioon	Ravijuhendi soovitus	Tulemusnäitaja	Viide
Torakaal epiduraalanalgeesia	Torakotoomia	DE-09 -jah	Äge valu ↓ 24 h ja 48 h, kroonilist valu ei mõjuta	Bong: 6 studies ,458 pt
Lokaalanesteetikumid intraperitoneaalselt	Laparoskoopilised operatsioonid		Postop valu ↓ 4, 8, 24 h (VAS)	Coughlin SM, 26 RCTs
Infiltratsioon lokaalanesteetikumidega	Opi liiki pole mainitud		Postop valu ↓ 4 ja 24 h (VAS). Preop vs postop lõike infiltratsioonil vahet ei olnud.	Coughlin SM, 26 RCTs
Deksametasoon	Opi liiki pole mainitud		↓ valu skoori 2 ja 24 h peale op-i. ↓ opiaadi vajadus 2 ja 24 h peale op-i. ↓ lisavaluvaigisti vajadus. ↓ PACU-s viibimise aeg. ↑ veresuhkru taset veres 24 h peale op-i.	Waldron NH; 45 RCTs, 5796 pt
Ketorolac	Opi liiki pole mainitud	DE-09 NSAID-de ei soovitata TEP ja HIP puhul	60 mg ↓ opiaadi tarbimist ja PONV-i	De Oliveira GS ; 13 RCTs, 782 pt
Koksiibid	Opi liiki ei ole mainitud	Sama	Preop koksiibid ↓ postop valu ja analgeetikumide tarbimist. PONV- ↔ Intraop verekadu ja anesteesiast ärkamine ↔	Straube S; 22 RCTs, 2246 pt

Ravim / meetod	Operatsioon	Ravijuhendi soovitus	Tulemusnäitaja	Viide
NMDA retseptorite antagonistid (ketamiin, dekstrometorfaan)	Ülakõht, rindkere ja suured ortopeedilised operatsioonid	AU-10 jah	↓ postop valu ja analgeetikumide tarbimist.	Laskowski K; 40 RCTs McCartney CJ; 70 RCTs, 4701 pt
Tramadool	Hüsterektoomia, hemikolektoomia, appendektoomia		100 mg tramadooli preop↓ postop valu ja analgeetikumide tarbimist.	Castro F, De La Paz-Estrada C, Wordliczek J
Gabapentiin	Opi liiki ei ole mainitud	DE-09 jah, URO-13 jah	↓ postop valu ja opiaatide tarbimist, kõrvaltoimed ↔	Seib RK; 8 RCTs

Systematic reviews

There is good quality evidence available from 6 meta-analysis of RCT-s and 4 systematic reviews about preemptive administration of analgesics versus no administration of analgesics.

Preemptive analgesia

In a meta-analysis (66 studies, N=3261) the primary outcome measures analyzed were the pain intensity scores, supplemental analgesic consumption, and time to first analgesic consumption. When the data from all three outcome measures were combined, the ES (effect size index) was most pronounced for preemptive administration of epidural analgesia (ES, 0.38; 95% confidence interval [CI], 0.28-0.47), local anesthetic wound infiltration (ES, 0.29; 95% CI, 0.17-0.40), and NSAID administration (ES, 0.39; 95% CI, 0.27-0.48). Whereas preemptive epidural analgesia resulted in consistent improvements in all three outcome variables, preemptive local anesthetic wound infiltration and NSAID administration improved analgesic consumption and time to first rescue analgesic request, but not postoperative pain scores. The least proof of efficacy was found in the case of systemic NMDA antagonist (ES, 0.09; 95% CI, -0.03 to 0.22) and opioid (ES, -0.10; 95% CI, -0.26 to 0.07) administration, and the results remain equivocal.

Preemptive epidural analgesia

A **meta-analysis of 6 studies including 458 patients**: Pooled analyses indicated that preemptive thoracic epidural analgesia (TEA) was associated with a statistically significant **reduction in the severity of acute pain on coughing at 24 and 48 hours** (weighted mean difference -1.17 [95% confidence interval (CI) -1.50 to -0.83] and -1.08 [95% CI -1.17 to -0.99]), respectively. Acute pain was a good predictor of chronic pain. However, there was no statistically significant difference in the overall incidence of chronic pain at 6 months between the preemptive TEA group (39.6%) and the control group (48.6%). Preemptive TEA appeared to reduce the severity of acute pain but had no effect on the incidence of chronic pain.

Local analgesia – timing

26 studies were included in the analysis. **Preemptive incisional local anesthetic was superior to placebo in terms of visual analog pain scores (VAS) at 4 h** (weighted mean difference [WMD], -9.49 mm; 95% confidence interval [CI], -15.50 to -3.48) and **24 h** (WMD, -4.75 mm; 95%CI, -8.90 to 0.60). However, no difference was found between these measures and those for postoperative incision-site infiltration. **Preemptive intraperitoneal local anesthetic was superior to placebo in terms of VAS at 4 h** (WMD, 5.76 mm; 95%CI, -11.27 to -0.25), **8 h** (WMD, -9.64 mm; 95%CI, -13.68 to -5.60), 12 h (WMD, -4.68 mm; 95%CI, -5.86 to -3.49), **and 24 h** (WMD, -5.57 mm; 95%CI, -8.35 to -2.79), **and superior to postoperative anesthesia administration at 8 h** (WMD, -7.42; 95%CI, -13.40 to -1.45), **12 h** (WMD, -7.27 mm; 95%CI, -10.26 to -4.28), **and 24 h** (WMD, -7.95 mm; 95%CI, -12.33 to -3.56). Preemptive administration of local anesthetic at the incision site reduces postoperative pain compared with placebo but achieves an analgesic effect similar to that of postincisional anesthetic infiltration. Preemptive local anesthetic administered intraperitoneally decreases postoperative pain compared with both placebo and postoperative infiltration. Surgeons should use local analgesia in laparoscopic surgery to decrease postoperative pain, but the timing of administration is significant only for intraperitoneal infiltration.

Peripheral nerve blocks and intravenous local anaesthetics

In this review (included 89 studies) they examined several types of peripheral nerve blocks, covering a variety of surgical procedures and examined the effects of intentionally administered

IV local anesthetic (lidocaine) for suppression of postoperative pain. Importantly, the very large number of studies using neuraxial blockade techniques (epidural, spinal) has not been included in this review. The overall results showed a strongly positive effect of local anesthetics, by either route, for suppressing postoperative pain scores and analgesic (opiate) consumption. In only a few situations were the effects equivocal. Enhanced effectiveness with the addition of adjuvants was not uniformly apparent. The differential benefits between drug delivery before, during, or immediately after a surgical procedure are not obvious, and a general conclusion is that the significant antihyperalgesic effects occur when the local anesthetic is present during the acute postoperative period, and its presence during surgery is not essential for this action.

Dexamethazone

In this meta-analysis 45 studies and 5796 patients were included. Patients receiving dexamethasone had **lower pain scores at 2 h** {mean difference (MD) -0.49 [95% confidence interval (CI): -0.83, -0.15]} **and 24 h** [MD -0.48 (95% CI: -0.62, -0.35)] **after surgery**. Dexamethasone-treated patients **used less opioids at 2 h** [MD -0.87 mg morphine equivalents (95% CI: -1.40 to -0.33)] **and 24 h** [MD -2.33 mg morphine equivalents (95% CI: -4.39, -0.26)], **required less rescue analgesia for intolerable pain** [relative risk 0.80 (95% CI: 0.69, 0.93)], **had longer time to first dose of analgesic** [MD 12.06 min (95% CI: 0.80, 23.32)], **and shorter stays in the post-anaesthesia care unit** [MD -5.32 min (95% CI: -10.49 to -0.15)]. There was no dose-response with regard to the opioid-sparing effect. There was no increase in infection or delayed wound healing with dexamethasone, but blood glucose levels were higher at 24 h [MD 0.39 mmol litre(-1) (95% CI: 0.04, 0.74)]. A single i.v. perioperative dose of dexamethasone had small but statistically significant analgesic benefits.

NSAIDs, coxibs

We found one meta-analysis of randomized trials and one systematic review of randomized studies about NSAIDs and coxibs.

Meta-analysis about **ketorolac (13 studies, N=782):** The weighted mean difference (95% confidence interval [CI]) of combined effects showed a difference for ketorolac over placebo for early pain at rest of -0.64 (-1.11 to -0.18) but not at late pain at rest, -0.29 (-0.88 to 0.29) summary point (0-10 scale). **Opioid consumption was decreased by the 60-mg dose,** with a mean (95% CI) IV morphine equivalent consumption of -1.64 mg (-2.90 to -0.37 mg). **The opioid-sparing effects of ketorolac compared with placebo were greater when the drug was administered IM compared with when the drug was administered IV, with a mean difference** (95% CI) **IV morphine equivalent consumption of -2.13 mg** (-4.1 to -0.21 mg). **Postoperative nausea and vomiting were reduced by the 60-mg dose**, with an odds ratio (95% CI) of 0.49 (0.29-0.81). Single dose systemic ketorolac is an effective adjunct in multimodal regimens to reduce postoperative pain. Improved postoperative analgesia achieved with ketorolac was also accompanied by a reduction in postoperative nausea and vomiting. The 60-mg dose offers significant benefits but there is a lack of current evidence that the 30-mg dose offers significant benefits on postoperative pain outcomes.

Systematic review of **coxibs (22 studies, N=2246): Preoperative coxibs significantly reduced both postoperative pain and analgesic consumption** compared with preoperative placebo in 15/20 trials. In one further trial postoperative pain was reduced and in one analgesic consumption. There was **no significant difference in the incidence of postoperative nausea and vomiting** in 13/17 studies or when data were pooled. Postoperative antiemetic use was significantly reduced in all five trials reporting it; the NNT to prevent one patient using postoperative antiemetic was 10 (5.5 to 66). **No trial reported any significant difference in intraoperative blood loss or recovery from anaesthesia.** Patient satisfaction was significantly increased with preoperative coxib use. No conclusions could be drawn from the three trials comparing preoperative coxib with preoperative NSAID. One study reported significantly improved cost-efficacy with rofecoxib. Preoperative coxibs had clear benefits in terms of reduced postoperative pain, analgesic consumption and patient satisfaction compared with placebo. Effects on postoperative nausea and vomiting remain uncertain, as do those on recovery from surgery or economic benefit. Future trials should be larger and more pragmatic in nature.

NMDA receptor antagonists

We found two systematic reviews about NMDA receptor antagonists. **First one, which included 40 articles:** The evidence in favor of preventive analgesia was strongest in the case of dextromethorphan and ketamine, respectively with 67% and 58% of studies demonstrating a **reduction in pain, analgesic consumption**, or both beyond the clinical duration of action of the studied drug. **Second (70 studies, N=4701) review**: **Intravenous ketamine is an effective adjunct for postoperative analgesia**. Particular benefit was observed in painful procedures, including **upper abdominal, thoracic, and major orthopedic surgeries.** The analgesic effect of ketamine was independent of the type of intraoperative opioid administered, timing of ketamine administration, and ketamine dose.

Opioids

We did not find meta-analysis or systematic reviews about preemptive opioid administration. Some RCT–s have been performed focusing on administration of **tramadol** compared to placebo:

The first one included 42 patients and found that the administration of tramadol 100 mg i/v during the early preoperative period in patients undergoing abdominal hysterectomy provides a preventive analgesic effect of postoperative pain, thus reducing the need of supplementary analgesia with rescue medication.

Second study included 90 patients: Thirty patients (group I) were administered 100 mg of tramadol i/v before induction of general anesthesia (preemptive analgesia). Group II (30 patients) was administered 100 mg of tramadol i/v immediately after peritoneal closure (preventive analgesia) and control group (30 patients) received 100 mg of tramadol iv immediately after operation. Following the operation, all patients were administered tramadol in the PCA-i/v mode in order to treat postoperative pain. In the postoperative period, the following parameters were measured: pain intensity (using VAS), total consumption of tramadol, time until the first PCA activation, and frequency of side effects (drowsiness, nausea, vomiting). In patients of groups I and II who had received preemptive or preventive analgesia, a significantly lower total consumption of tramadol, as compared with control group, was observed in the early postoperative period. However, the time until the first PCA activation was significantly shorter in group I as compared to the other two groups. No significant differences between the groups were found regarding pain intensity and frequency of side effects.

Third study included 86 patients: Tramadol at a dosage of 100 mg in the preoperative period contributes to the reduction of the intensity of postoperative pain.

Gabapentin

They identified **eight placebo-controlled, randomized controlled trials and conducted a meta-analysis** using the primary outcomes of pain scores, total analgesia consumption, and side effects over a 24-hr period (N=907). Patients who **received gabapentin preoperatively reported significantly lower pain scores** (-11.9 at rest and -11.0 with movement on a 100-point visual analogue scale) **and opioid consumption** (-14.7 mg of morphine in 24 hr) with no difference in the incidence of side effects. **Although gabapentin given preoperatively decreases pain scores and analgesic consumption in the first 24 hr after surgery, the clinical significance of this finding has yet to be determined.** This meta-analysis could not demonstrate a significant reduction in the incidence of side effects. Due to the small numbers enrolled in the studies, larger randomized control trials are warranted.

References

Whether preemptive analgesic interventions are more effective than conventional regimens in managing acute postoperative pain remains controversial. We systematically searched for randomized controlled trials that specifically compared preoperative analgesic interventions with similar postoperative analgesic interventions via the same route. The retrieved reports were stratified according to five types of analgesic interventions: epidural analgesia, local anesthetic wound infiltration, systemic N-methyl-d-aspartic acid (NMDA) receptor antagonists, systemic nonsteroidal antiinflammatory drugs (NSAIDs), and systemic opioids. The primary outcome measures analyzed were the pain intensity scores, supplemental analgesic consumption, and time to first analgesic consumption. **Sixty-six studies with data from 3261 patients were analyzed.** Data were combined by using a fixed-effect model, and the effect size index (ES) used was the standardized mean difference. When the data from all three outcome measures were combined, the ES was most pronounced for **preemptive administration of epidural analgesia** (ES, 0.38; 95% confidence interval [CI], 0.28-0.47), local anesthetic wound infiltration (ES, 0.29; 95% CI, 0.17-0.40), and NSAID administration (ES, 0.39; 95% CI, 0.27-0.48). Whereas preemptive epidural analgesia resulted in consistent improvements in all three outcome variables, preemptive local anesthetic wound infiltration and NSAID administration improved analgesic consumption and time to first rescue analgesic request, but not postoperative pain scores. The least proof of efficacy was	Ong CK, Lirk P, Seymour RA, Jenkins BJ. *The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis.* Anesth Analg. 2005 Mar;100(3):757-73.

found in the case of systemic NMDA antagonist (ES, 0.09; 95% CI, -0.03 to 0.22) and opioid (ES, -0.10; 95% CI, -0.26 to 0.07) administration, and the results remain equivocal.	
OBJECTIVE: The purpose of this study was to determine whether **preemptive thoracic epidural analgesia (TEA)** initiated before surgical incision would reduce the severity of acute **post-thoracotomy pain and the incidence of chronic post-thoracotomy pain.** METHOD: Meta-analysis of randomized controlled trials (RCTs). SEARCH STRATEGY: MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE were searched from 1966 to December 2004 for prospective RCTs published in all languages using the following MeSH terms: post-thoracotomy pain, epidural analgesia, chronic pain, and preemptive analgesia. SELECTION CRITERIA: All RCTs that compared thoracic epidural analgesia initiated before surgical incision (preemptive group) versus thoracic epidural analgesia initiated after completion of surgery (control group) in adult patients undergoing unilateral thoracotomy. MEASUREMENTS AND MAIN RESULTS: Three authors reviewed all citations and simultaneously extracted data on sample size, patient characteristics, surgical and analgesic interventions, methods of pain assessment, and pain scores at 24 hours, 48 hours, and 6 months postoperatively. Six studies were included with a total of 458 patients. **Pooled analyses indicated that preemptive TEA was associated with a statistically significant reduction in the severity of acute pain on coughing at 24 and 48 hours** (weighted mean difference -1.17 [95% confidence interval (CI) -1.50 to -0.83] and -1.08 [95% CI -1.17 to -0.99]), respectively. Acute pain was a good predictor of chronic pain. However, there was no statistically significant difference in the overall incidence of chronic pain at 6 months between the preemptive TEA group (39.6%) and the control group (48.6%). CONCLUSION: Preemptive TEA appeared to reduce the severity of acute pain but had no effect on the incidence of chronic pain.	Bong, C.L.; Samuel, M.; Ng, J.M.; Ip-Yam, C. *Effects of preemptive epidural analgesia on post-thoracotomy pain.* J.Cardiothorac.Vasc.Anesth., 2005, 19, 6, 786-793, United States
BACKGROUND: This study aimed to determine the effect of **local anesthesia administered before laparoscopic surgery (preemptive anesthesia) on postoperative pain.** METHODS: The authors searched Medline, EMBase, and the Cochrane Central Register of Controlled Trials, as well as reference lists of textbooks and relevant articles. They , and data were extracted in duplicate. The data were pooled across studies using a random effects model. RESULTS: The 26 studies that met the inclusion criteria were included in the analysis. **Preemptive incisional local anesthetic was superior to placebo in terms of visual analog pain scores (VAS) at 4 h (weighted mean difference [WMD], -9.49 mm; 95% confidence interval [CI], -15.50 to -3.48) and 24 h (WMD, -4.75 mm; 95%CI, -8.90 to 0.60).** However, no difference was found between these measures and those for postoperative incision-site infiltration. **Preemptive intraperitoneal local anesthetic was superior to placebo in terms of VAS at 4 h** (WMD, 5.76 mm; 95%CI, -11.27 to -0.25), **8 h** (WMD, -9.64 mm; 95%CI, -13.68 to -5.60), **12 h** (WMD, -4.68 mm; 95%CI, -5.86 to -3.49), **and 24 h** (WMD, -5.57 mm; 95%CI, -8.35 to -2.79), and superior to postoperative anesthesia administration at 8 h (WMD, -7.42; 95%CI, -13.40 to -1.45), 12 h (WMD, -7.27 mm; 95%CI, -10.26 to -4.28), and 24 h (WMD, -7.95 mm; 95%CI, -12.33 to -3.56) CONCLUSION: Preemptive administration of local anesthetic at the incision site reduces postoperative pain compared with placebo but achieves an analgesic effect similar to that of postincisional anesthetic infiltration. Preemptive local anesthetic administered intraperitoneally decreases postoperative pain	Coughlin SM, Karanicolas PJ, Emmerton-Coughlin HM, Kanbur B, Kanbur S, Colquhoun PH. *Better late than never? Impact of local analgesia timing on postoperative pain in laparoscopic surgery: a systematic review and metaanalysis.* Surg Endosc. 2010 Dec;24(12):3167-76.

compared with both placebo and postoperative infiltration. Surgeons should use local analgesia in laparoscopic surgery to decrease postoperative pain, but the timing of administration is significant only for intraperitoneal infiltration.	
The use of **local anesthetics** to reduce acute postoperative pain has a long history, but recent reports have not been systematically reviewed. In addition, the need to include only those clinical studies that meet minimum standards for randomization and blinding must be adhered to. In this review, we have applied stringent clinical study design standards to identify publications on the use of perioperative local anesthetics. We first examined several types of peripheral nerve blocks, covering a variety of surgical procedures, and second, we examined the effects of intentionally administered IV local anesthetic (lidocaine) for suppression of postoperative pain. Thirdly, we have examined publications in which vascular concentrations of local anesthetics were measured at different times after peripheral nerve block procedures, noting the incidence when those levels reached ones achieved during intentional IV administration. Importantly, the very large number of studies using neuraxial blockade techniques (epidural, spinal) has not been included in this review but will be dealt with separately in a later review. The overall results showed a strongly positive effect of local anesthetics, by either route, for suppressing postoperative pain scores and analgesic (opiate) consumption. In only a few situations were the effects equivocal. Enhanced effectiveness with the addition of adjuvants was not uniformly apparent. The differential benefits between drug delivery before, during, or immediately after a surgical procedure are not obvious, and a general conclusion is that the significant antihyperalgesic effects occur when the local anesthetic is present during the acute postoperative period, and its presence during surgery is not essential for this action.	Barreveld A, Witte J, Chahal H, Durieux ME, Strichartz G. *Preventive analgesia by local anesthetics: the reduction of postoperative pain by peripheral nerve blocks and intravenous drugs*. Anesth Analg. 2013 May;116(5):1141-61.
BACKGROUND: The analgesic efficacy and adverse effects of a single perioperative dose of dexamethasone are unclear. We performed a systematic review to evaluate the impact of a single i.v. dose of dexamethasone on postoperative pain and explore adverse events associated with this treatment. METHODS: MEDLINE, EMBASE, CINAHL, and the Cochrane Register were searched for randomized, controlled studies that compared dexamethasone vs placebo or an antiemetic in adult patients undergoing general anaesthesia and reported pain outcomes. RESULTS: **Forty-five studies involving 5796 patients receiving dexamethasone 1.25-20 mg were included**. Patients receiving dexamethasone had lower pain scores at 2 h {mean difference (MD) -0.49 [95% confidence interval (CI): -0.83, -0.15]} and 24 h [MD -0.48 (95% CI: -0.62, -0.35)] after surgery. Dexamethasone-treated patients used less opioids at 2 h [MD -0.87 mg morphine equivalents (95% CI: -1.40 to -0.33)] and 24 h [MD -2.33 mg morphine equivalents (95% CI: -4.39, -0.26)], required less rescue analgesia for intolerable pain [relative risk 0.80 (95% CI: 0.69, 0.93)], had longer time to first dose of analgesic [MD 12.06 min (95% CI: 0.80, 23.32)], and shorter stays in the post-anaesthesia care unit [MD -5.32 min (95% CI: -10.49 to -0.15)]. There was no dose-response with regard to the opioid-sparing effect. There was no increase in infection or delayed wound healing with dexamethasone, but blood glucose levels were higher at 24 h [MD 0.39 mmol litre(-1) (95% CI: 0.04, 0.74)]. CONCLUSIONS: A single i.v. perioperative dose of dexamethasone had small but statistically significant analgesic benefits.	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 Anaesth. 2013 Feb;110(2):191-200.
We evaluated in a qualitative systematic review the effect of **N-methyl-D-aspartate (NMDA) receptor antagonists** on	McCartney CJ, Sinha A & Katz J.

reducing postoperative pain and analgesic consumption beyond the clinical duration of action of the target drug (preventive analgesia). Randomized trials examining the use of an NMDA antagonist in the perioperative period were sought by using a MEDLINE (1966-2003) and EMBASE (1985-2003) search. Reference sections of relevant articles were reviewed, and additional articles were obtained if they evaluated postoperative analgesia after the administration of NMDA antagonists. The primary outcome was a reduction in pain, analgesic consumption, or both in a time period beyond five half-lives of the drug under examination. Secondary outcomes included time to first analgesic request and adverse effects. Forty articles met the inclusion criteria (24 ketamine, 12 dextromethorphan, and 4 magnesium). The evidence in favor of preventive analgesia was strongest in the case of dextromethorphan and ketamine, with 67% and 58%, respectively, of studies demonstrating a reduction in pain, analgesic consumption, or both beyond the clinical duration of action of the drug concerned. None of the four studies examining magnesium demonstrated preventive analgesia. IMPLICATIONS: We evaluated, in a qualitative systematic review, the effect of N-methyl D-aspartate antagonists on reducing postoperative pain and analgesic consumption beyond the clinical duration of action of the target drug (preventive analgesia). Dextromethorphan and ketamine were found to have significant immediate and preventive analgesic benefit in 67% and 58% of studies, respectively.	*A qualitative systematic review of the role of N-methyl-D-aspartate receptor antagonists in preventive analgesia.* Anesth Analg 2004 May;98(5): 1385–400;
BACKGROUND: Preventive analgesia using non-opioid analgesic strategies is recognized as a pathway to improve postoperative pain control while minimizing opioid-related side effects. Ketorolac is a nonsteroidal antiinflammatory drug frequently used to treat postoperative pain. However, the optimal dose and route of administration for systemic single dose ketorolac to prevent postoperative pain is not well defined. We performed a quantitative systematic review to evaluate the efficacy of a single dose of perioperative ketorolac on postoperative analgesia. METHODS: We followed the PRISMA statement guidelines. A wide search was performed to identify randomized controlled trials that evaluated the effects of a single dose of systemic ketorolac on postoperative pain and opioid consumption. Meta-analysis was performed using a random-effects model. Effects of ketorolac dose were evaluated by pooling studies into 30- and 60-mg dosage groups. Asymmetry of funnel plots was examined using Egger regression. The presence of heterogeneity was assessed by subgroup analysis according to the route of systemic administration (IV versus IM) and the time of drug administration (preincision versus postincision). RESULTS: **Thirteen randomized clinical trials with 782 subjects were included.** The weighted mean difference (95% confidence interval [CI]) of combined effects showed a difference for ketorolac over placebo for early pain at rest of -0.64 (-1.11 to -0.18) but not at late pain at rest, -0.29 (-0.88 to 0.29) summary point (0-10 scale). **Opioid consumption was decreased by the 60-mg dose,** with a mean (95% CI) IV morphine equivalent consumption of -1.64 mg (-2.90 to -0.37 mg). The opioid-sparing effects of ketorolac compared with placebo were greater when the drug was administered IM compared with when the drug was administered IV, with a mean difference (95% CI) IV morphine equivalent consumption of -2.13 mg (-4.1 to -0.21 mg). **Postoperative nausea and vomiting were reduced by the 60-mg dose**, with an odds ratio (95% CI) of 0.49 (0.29-0.81). CONCLUSIONS: Single dose systemic ketorolac is an effective adjunct in multimodal regimens to reduce postoperative pain. Improved postoperative analgesia achieved with ketorolac was	De Oliveira GS Jr, Agarwal D, Benzon HT. *Perioperative single dose ketorolac to prevent postoperative pain: a meta-analysis of randomized trials.* Anesth Analg. 2012 Feb;114(2):424-33.

also accompanied by a reduction in postoperative nausea and vomiting. The 60-mg dose offers significant benefits but there is a lack of current evidence that the 30-mg dose offers significant benefits on postoperative pain outcomes.	
Preoperative use of coxibs has been claimed to reduce postoperative pain and analgesic consumption, and to affect other postoperative outcomes. METHODS: Systematic review of randomized trials comparing preoperative coxib with preoperative placebo, or active comparator. Searching of PubMed and Cochrane Library to August 2004. A qualitative and a quantitative analysis. RESULTS: **Twenty-two included trials with 2246 patients** had high reporting quality and validity scores, though treatment group sizes were small, with a median size of 30 patients. Most trials used oral preoperative rofecoxib (mainly 50 mg) or celecoxib (mainly 200 mg). Preoperative coxibs significantly reduced both postoperative pain and analgesic consumption compared with preoperative placebo in 15/20 trials. In one further trial postoperative pain was reduced and in one analgesic consumption. There was no significant difference in the incidence of postoperative nausea and vomiting in 13/17 studies or when data were pooled. Postoperative antiemetic use was significantly reduced in all five trials reporting it; the NNT to prevent one patient using postoperative antiemetic was 10 (5.5 to 66). No trial reported any significant difference in intraoperative blood loss or recovery from anaesthesia. Patient satisfaction was significantly increased with preoperative coxib use. No conclusions could be drawn from the three trials comparing preoperative coxib with preoperative NSAID. One study reported significantly improved cost-efficacy with rofecoxib. CONCLUSIONS: **Preoperative coxibs had clear benefits in terms of reduced postoperative pain, analgesic consumption and patient satisfaction compared with placebo**. Effects on postoperative nausea and vomiting remain uncertain, as do those on recovery from surgery or economic benefit. Future trials should be larger and more pragmatic in nature.	Straube S, Derry S, McQuay HJ, Moore RA. *Effect of preoperative Cox-II-selective NSAIDs (coxibs) on postoperative outcomes: a systematic review of randomized studies.* Acta Anaesthesiol Scand. 2005 May;49(5):601-13.
Purpose: **Perioperative intravenous ketamine** may be a useful addition in pain management regimens. Previous systematic reviews have included all methods of ketamine administration, and heterogeneity between studies has been substantial. This study addresses this issue by narrowing the inclusion criteria, using a random effects model, and performing subgroup analysis to determine the specific types of patients, surgery, and clinical indications which may benefit from perioperative ketamine administration. Source: We included published studies from 1966 to 2010 which were randomized, double-blinded, and placebocontrolled using intravenous ketamine (bolus or infusion) to decrease postoperative pain. Studies using any form of regional anesthesia were excluded. No limitation was placed on the ketamine dose, patient age, or language of publication. Principal findings: Ninety-one comparisons in seventy studies involving 4,701 patients met the inclusion criteria (2,652 in ketamine groups and 2,049 in placebo groups). Forty-seven of these studies were appropriate for evaluation in the core meta analysis, and the remaining 23 studies were used to corroborate the results. A reduction in total opioid consumption and an increase in the time to first analgesic were observed across all studies (P\0.001). The greatest efficacy was found for thoracic, upper abdominal, and major orthopedic surgical subgroups. Despite using less opioid, 25 out of 32 treatment groups (78%) experienced less pain than the placebo groups at some point postoperatively when ketamine was efficacious. This finding	Laskowski K, Stirling A, McKay WP, Lim HJ. *A systematic review of intravenous ketamine for postoperative analgesia* Can J Anesth/J Can Anesth 2011 Jul;58:911–923

implies an improved quality of pain control in addition to decreased opioid consumption. Hallucinations and nightmares were more common with ketamine but sedation was not. When ketamine was efficacious for pain, postoperative nausea and vomiting was less frequent in the ketamine group. The dose-dependent role of ketamine analgesia could not be determined. Conclusion: Intravenous ketamine is an effective adjunct for postoperative analgesia. Particular benefit was observed in painful procedures, including upper abdominal, thoracic, and major orthopedic surgeries. The analgesic effect of ketamine was independent of the type of intraoperative opioid administered, timing of ketamine administration, and ketamine dose.	
PURPOSE: **Gabapentin's** role in the treatment of chronic neuropathic pain is well known. What is less well established is its role for managing postoperative pain. In order to clarify whether gabapentin's utility in acute pain control is more than just theoretical, we conducted a meta-analysis of all randomized trials that addressed gabapentin's role in acute postoperative pain control. We specifically addressed whether gabapentin reduces pain scores, analgesia consumption, and/or analgesia-related side effects in the first 24 hr following surgery. SOURCE: We identified eight placebo-controlled, randomized controlled trials and conducted a meta-analysis using the primary outcomes of pain scores, total analgesia consumption, and side effects over a 24-hr period. PRINCIPLE FINDINGS: **Patients who received gabapentin preoperatively reported significantly lower pain scores** (-11.9 at rest and -11.0 with movement on a 100-point visual analogue scale) **and opioid consumption** (-14.7 mg of morphine in 24 hr) **with no difference in the incidence of side effects.** CONCLUSION: Although gabapentin given preoperatively decreases pain scores and analgesic consumption in the first 24 hr after surgery, the clinical significance of this finding has yet to be determined. This meta-analysis could not demonstrate a significant reduction in the incidence of side effects. Due to the small numbers enrolled in the studies, larger randomized control trials are warranted.	Seib RK, Paul JE. *Preoperative gabapentin for postoperative analgesia: a meta-analysis.* Can J Anaesth. 2006 May;53(5):461-9.

References of single studies

Objectives: The aim of our study was to determine whether the preoperative administration of **tramadol** may prevent postoperative pain. Based on the concept of 'preventive analgesia', the **preoperative administration of tramadol** was expected to prevent the central sensitization caused by the surgical incision, this reflected in a lower consumption of analgesics during the postoperative period. Material and Methods: We studied **42 patients** undergoing gynecologic surgery (abdominal hysterectomy), divided into two groups of 21 patients each. One group received tramadol 100 mg 30 minutes before surgery and the other group, placebo. In the early postoperative, PCA with tramadol was started in both groups and rescue analgesia with metamizol 2 g was also available. We studied different variable, including the visual analogic scale (VAS) and the simple verbal scale (SVS), hemodynamic variables (BP, HR), as well as endocrine variables (cortisol). Results: The results of this study did not show differences between the two groups regarding the total dose administered during the 24 hours of therapy and the number of bolus required. However, differences were observed in the number of patients requiring rescue analgesia with metamizol: 3 patients in the tramadol group and 10 patients in the placebo group. Conclusions: **The administration of tramadol 100 mg i.v. during the early preoperative period in patients**	Castro F, Barreto P, Gil R, Varela M, De la Iglesia A, Camba MA. *Double blind, comparative, randomized and controlled clinical trial for the assessment of the preventive effect of tramadol vs placebo in the management of postoperative gynecologic pain.* Revista de la Sociedad Espanola del Dolor. 7(4):214-219, 2000.

undergoing abdominal hysterectomy provides a preventive analgesic effect of postoperative pain, thus reducing the need of supplementary analgesia with rescue medication.	
The aim of this study was to assess the influence of iv **tramadol** on opioid requirement in the early postoperative period. **The subjects were 90 patients scheduled for colon surgery (hemicolectomy)** who received general anesthesia using the (N2O/O2) isoflurane technique. Thirty patients (group I) were administered 100 mg of tramadol iv before induction of general anesthesia (preemptive analgesia). Group II (30 patients) was administered 100 mg of tramadol iv immediately after peritoneal closure (preventive analgesia) and control group (30 patients) received 100 mg of tramadol iv immediately after operation. Following the operation, all patients were administered tramadol in the PCA-iv mode in order to treat postoperative pain. In the postoperative period, the following parameters were measured: pain intensity (using VAS), total consumption of tramadol, time until the first PCA activation, and frequency of side effects (drowsiness, nausea, vomiting). In patients of groups I and II who had received preemptive or preventive analgesia, a significantly lower total consumption of tramadol, as compared with control group, was observed in the early postoperative period. However, the time until the first PCA activation was significantly shorter in group I as compared to the other two groups. No significant differences between the groups were found regarding pain intensity and frequency of side effects.	Wordliczek J, Banach M, Garlicki J, Jakowicka-Wordliczek J, Dobrogowski J. *Influence of pre- or intraoperational use of tramadol (preemptive or preventive analgesia) on tramadol requirement in the early postoperative period.* Polish journal of pharmacology. 54(6):693-7, 2002 Nov-Dec.
Objective: To evaluate the analgesic effectiveness of **tramadol** in the prevention of postoperative pain in patients who underwent **acute appendicitis**. Material and methods: It harpvenedent tion of theryned i by ultrasound was carried out a controlled, double-blind, and randomized clinical study, on, patients who have been operated due to acute appendicitis at the hospital <<Guillermo Luis Fernandez Hernandez-Baquero>>, Moa, Holguin, Cuba, during the months going from October 2005 to May 2006; 86 patients were selected. They were divided into two groups of 43 patients each. Group I: tramadol 100 mg and; Group II: intravenous metamizol 2 g, both 30-minutes treatments were given before the surgery. General anesthesia was applied; and systolic blood pressure, cardiac rate and hemoglobin saturation (HbSat) were recorded during several stages of the anesthetic process: basal, transoperative, and at the first 180 minutes of the postoperative, as well as the most frequent adverse effects. Pain intensity was measured in the postoperative period through the Analogous Visual Scale (AVS). Results: Pain significantly decreased through the use of tramadol when compared with the placebo ($p < 0.05$); nausea was prevailing (16.3%), followed by vomits in the 13% of the patients who used tramadol. Conclusions: **Tramadol at a dosage of 100 mg in the preoperative period contributes to the reduction of the intensity of postoperative pain.**	De La Paz-Estrada C, Belette-Alpajon E. *Preventive effect 100 mg of tramadol for post-surgical pain.* Revista Mexicana de Anestesiologia. 31(4):278-81, 2008.

Guidelines

We reviewed 3 guidelines, all of them provide recommendations about preemptive administration of analgesics. These guidelines were:

1. Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine "Acute Pain Management: Scientific Evidence", 2010 (AU-10)

2. European Association of Urology "Guidelines on Pain Management and Palliative Care", 2013 (URO-13)

3. “Behandlung acuter perioperativer und postraumatischer Schmertzen”, 2009 (Schmertzen) (DE-07)

Australia and New Zealand 2010: The timing of a single analgesic intervention (preincisional rather than postincisional), defined as pre-emptive analgesia, has a significant effect on postoperative pain relief with epidural analgesia. There is evidence that some adjuvant analgesics like ketamine and dextromethorphan have an effect on postoperative pain and/or analgesic consumption that exceeds the expected duration of action of the drug, defined as preventive analgesia.

URO- 2013: This guideline defines pre-emptive or preventive analgesia as the administration of analgesia before surgical incision to prevent central sensitisation from incision or inflammatory injury, to achieve optimal postoperative pain control. Overall conclusion on the efficacy of pre-emptive and preventive analgesia is that results of clinical trials are controversial. This conclusion is based on 2 papers from 1999 and 2000 (Kissin, I).

Guideline provide 2 recommendations:

1. Administer clonidine preoperatively or epidurally postoperatively to reduce opioid requirements.

2. Gabapentin can be administered before as well as after surgery to decrease pain severity and need for analgesic supplementation.

Deutsche 2007: Guideline evaluates postoperative pain treatment methods by type of surgery.

Conclusions:

-Preoperative epidural ananlgesia is effective method to reduce acute postopertive pain.

-There is not enough evidence to recommend use of preoperative systematic analgesia.

-Use of gabapentin before operation is recommended.

-Preoperative NSAIDs and opioids is not recommended for total hip and knee arthroplasties , no recommendations were provided for other types of surgery

References from guidelines

Author, year	Patients	Intervention	Results
Suzuki 2006	49 pt, thoracotomy	Epidural + i/v ketamine vs epidural + i/v placebo	At 1 and 3 months: pain scores ↓
Duale 2009	86 pt, thoracotomy	Preoperative ketamine until 24 h postop vs placebo	Acute pain↓, chronic pain ↔
Dahl 2004	Review		
Katz 2008	Review		
Katz 2002	Review		
Lavand`homme 2005	85 pt, colonic resection	Intraoperative I/v ketamine + epidural and i/v combinations postoperatively	Intraop epidural + ketamine more effective vs i/v treatment
Kissin 2000, 1996	Review		
Farmery 2009	66 pt, spinal surgery	Epidural clonidine vs placebo	Opioid consumption ↓, nausea ↓
Clivatti 2009	17 RCTs, 2066 pt	Gabapentin preop	Pain scores and opioid consumption ↓
Zhang 2011	11 RCTs , 899 pt	Pregabalin for postoperative pain	Pain ↔, opioid consumption and adverse effects ↓
Lui 2011	Review		