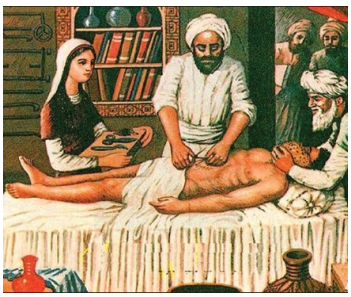
Anestesia ilman opioideja

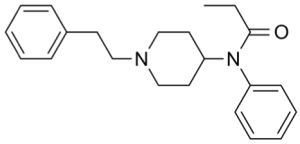
Matias Rantanen
29.3.2019

Tausta & sidonnaisuudet

- kliininen opettaja, Turun yliopisto
- anestesiologian ja tehohoidon erikoislääkäri, Tyks leikkausosasto TG4
- luento- ja koulutuspalkkioita
  - Nuorten Lääkärien Yhdistys ry, Suomen Anestesiasairaanhoitajat ry, CSL Behring
- koulutusmatka
  - MSD
- apurahaa
  - Lastentautien tutkimussäätiö, Suomen Lääkäriliitto
- luottamustoimia
  - Suomen Lääkäriliitto, Nuorten Lääkärien Yhdistys

TYKS TURUN YLIOPISTO





THE LANCET

Volume 329, Issue 8527, 31 January 1987, Pages 243–248
Originally published as Volume 1, Issue 8527

RANDOMISED TRIAL OF FENTANYL ANAESTHESIA IN PRETERM BABIES UNDERGOING SURGERY: EFFECTS ON THE STRESS RESPONSE

K.J.S. Anand[1,*], W.G. Sippell[b], A.Aynsley Green[c]

In a randomised controlled trial, preterm babies undergoing ligation of a patent ductus arteriosus were given nitrous oxide and d-tubocurarine, with (n = 8) or without (n = 8) the addition of fentanyl (10 μg/kg intravenously) to the anaesthetic regimen. Major hormonal responses to surgery, as indicated by changes in plasma adrenaline, noradrenaline, glucagon, aldosterone, corticosterone, 11-deoxycorticosterone, and 11-deoxycortisol levels, in the insulin/glucagon molar ratio, and in blood glucose, lactate, and pyruvate concentrations were significantly greater in the non-fentanyl than in the fentanyl group. The urinary 3-methylhistidine/creatinine ratios were significantly greater in the non-fentanyl group on the second and third postoperative days. Compared with the fentanyl group, the non-fentanyl group had circulatory and metabolic complications postoperatively. The findings indicate that preterm babies mount a substantial stress response to surgery under anaesthesia with nitrous oxide and curare and that prevention of this response by fentanyl anaesthesia may be associated with an improved postoperative outcome.

Opioidien perioperatiiviset haitat

- hengityslama
- uniapnea
- sedaatio
- huimaus
- suolilama
- pahoinvointi
- kutina
- virtsaumpi

Rapid Development of Tolerance to Analgesia During Remifentanil Infusion in Humans

H. Ronald Vinik, MD*, and Igor Kissin, MD, PhD†

(Anesth Analg 1998;86:1307–11)

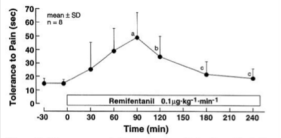


Figure 1. Time course of the analgesic effect of remifentanil (constant-rate infusion of 0.1 mg · kg^{-1} · min^{-1}) as determined by using a cold water pain tolerance test. *$P < 0.0001$ versus Time 0; †$P < 0.05$ versus 90 min; ‡$P < 0.0001$ versus 90 min.

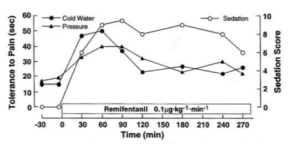
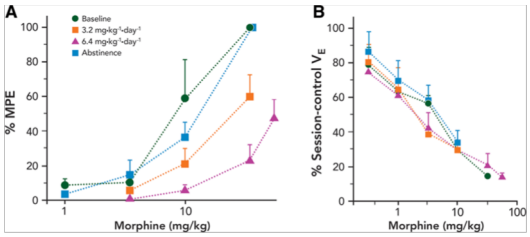


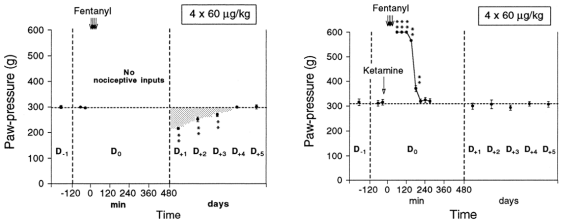
Figure 3. Individual time course for the analgesic and sedative effects of remifentanil administered as a constant-rate infusion in one of the volunteers.

Differential tolerance

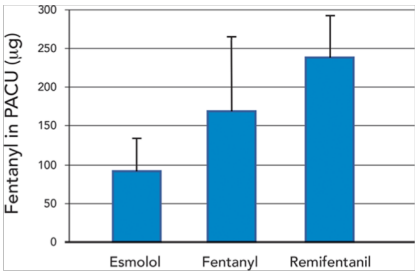


Differential Opioid Tolerance and Opioid-induced Hyperalgesia:A Clinical Reality
Anesthes. 2016;124(2):483-488.

Hyperalgesia



E Célèrier et al. Long-lasting hyperalgesia induced by fentanyl in rats: Preventive effect of ketamine.
Anesthesiology. (2000). 92 465–72



Intraoperative Esmolol Infusion in the Absence of Opioids Spares Postoperative Fentanyl in Patients Undergoing Ambulatory Laparoscopic Cholecystectomy
Collard et al. Anesth Analg 2007; 105:1255–62.

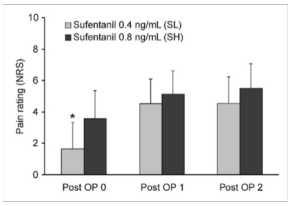
The impact of intra-operative sufentanil dosing on post-operative pain, hyperalgesia and morphine consumption after cardiac surgery

J. Fechner, H. Ihmsen, J. Schüttler, C. Jeleazcov

Eur J Pain **17** (2013) 562–570

Table 2 Cumulative post-operative opioid consumption in the first 48 h.

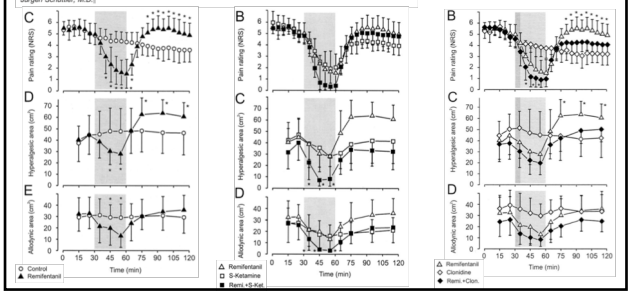
	Sufentanil target concentration		
	0.4 ng/mL	0.8 ng/mL	*p*-value
Opioids (mg/kg) until extubation	0.18 (0–0.36)	0.15 (0–0.42)	0.48
Morphine PCA (mg/kg) after extubation	0.68 ± 0.21	0.96 ± 0.44	0.03



Differential Modulation of Remifentanil-induced Analgesia and Postinfusion Hyperalgesia by S-Ketamine and Clonidine in Humans

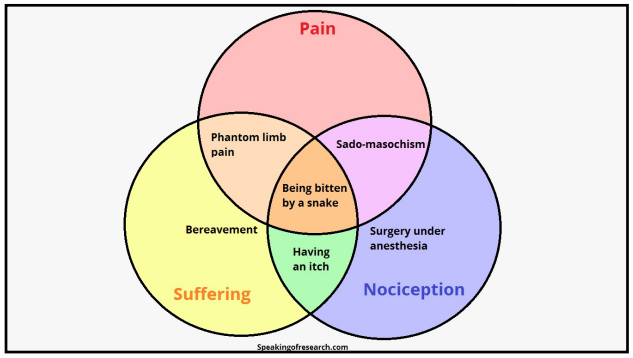
Anesthesiology 2003; 99:152–9

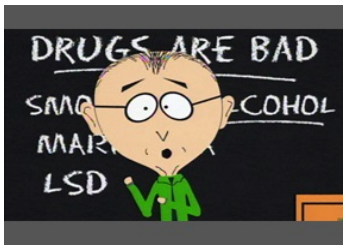
Wolfgang Koppert, M.D., Reinhard Sittl, M.D.,† Karin Scheuber, M.D.,‡ Monika Alsheimer, M.D.,† Martin Schmelz, M.D.,§ Jürgen Schüttler, M.D.‖*



Opioidihaittojen minimointi

- Multimodaalinen kivun hoito
  - regionaalitekniikat, adjuvantit
- Intraoperatiivisen opioidin vähentäminen
  - sympaattisen hermoston vasteen salpaus ei-opioidilääkkeillä
  - toleranssin ja hyperalgesian välttäminen





Opioid-free anaesthesia?

Kenelle?
- obeesi potilas
- keuhkosairaus, uniapnea
- opioidien väärinkäyttäjä
- krooninen kipu
- aiemmat opioidihaitat

Kenelle ei?
- AV-katkos, bradyarytmiat
- sokki, hypovolemia
- epästabiili sydänsairaus
- akuutti hypertensio
- ortostatismi

Rev Bras Anestesiol. 2015;65(3):191–199

Opioid-free total intravenous anesthesia with propofol, dexmedetomidine and lidocaine infusions for laparoscopic cholecystectomy: a prospective, randomized, double-blinded study☆

Mefkur Bakan[a,*], Tarik Umutoglu[a], Ufuk Topuz[a], Harun Uysal[a], Mehmet Bayram[b], Huseyin Kadioglu[c], Ziya Salihoglu[a]

Table 4 Postoperative pain intensity analysis.

	Group RF $n = 40$	Group DL $n = 40$	p
Postoperative fentanyl consumption			
0–2 h (μg)	120 ± 94 (110)	75 ± 59 (60)	0.04
0–4 h (μg)	185 ± 143 (160)	123 ± 100 (120)	NS
0–6 h (μg)	235 ± 175 (220)	162 ± 142 (150)	NS
Max-NRS	4 (2–6)	3 (2–4)	0.028
Max-NRS-cough	5.5 (3–7)	4 (3–5)	0.015
Shoulder pain (n)	7 (18%)	10 (25%)	NS
Rescue analgesic need (n)	19 (48%)	9 (23%)	0.034

Data are presented as mean ± standard deviation (median), median (25th–75th percentile), or absolute number of patients (percentage). NS, not significant, Max-NRS, maximal numeric rating scale score for pain intensity at the surgical ward after PCA was discontinued.

Adjuvantit

- (S-)ketamiini
  - bolus 0,1-0,35 mg/kg, infuusio 0,2-0,5 mg/kg/h
- α_2-agonistit
  - deksmedetomidiini 0,1-0,7 µg/kg/h, 1-2 µg/kg i.n.
  - klonidiini 150 µg i.v./i.m.
- lidokaiini
  - bolus 1-2 mg/kg, infuusio 1-3 mg/kg/h
- magnesiumsulfaatti
  - bolus 30-50 mg/kg, infuusio 5-20 mg/kg/h
- anti-inflammatoriset lääkkeet
- gabapentinoidit

The Use of Intravenous Infusion or Single Dose of Low-Dose Ketamine for Postoperative Analgesia: A Review of the Current Literature

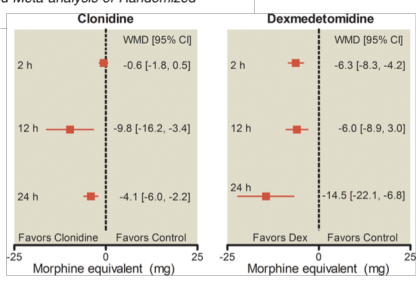
Julie Jouguelet-Lacoste, MSc,*[1]
Luca La Colla, MD,*[2] Dennis Schilling, PharmD,[†]
and Jacques E. Chelly, MD, PhD, MBA*

Results. Low-dose IV ketamine reduces opioid consumption by 40%. It also lowers pain scores, but these findings are less clear. No major complications have been reported with low-dose IV infusion of ketamine when given up to 48 hours after surgery. While our review lends support to using low-dose IV infusion of ketamine in the management of perioperative pain, its optimal dose and regimen remain to be determined.

Pain Medicine 2015; 16: 383–403

Effect of Perioperative Systemic $\alpha 2$ Agonists on Postoperative Morphine Consumption and Pain Intensity

Systematic Review and Meta-analysis of Randomized Controlled Trials



Anesthesiology 2012; 116:1312–22

Huang et al. BMC Anesthesiology (2015) 15:21
DOI 10.1186/s12871-015-0004-1

BMC Anesthesiology

RESEARCH ARTICLE Open Access

Dexmedetomidine versus remifentanil in postoperative pain control after spinal surgery: a randomized controlled study

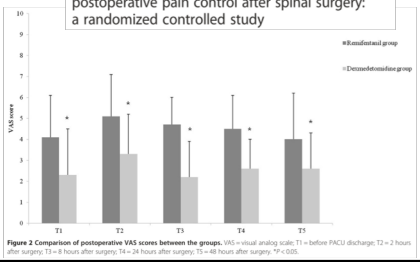


Figure 2 Comparison of postoperative VAS scores between the groups. VAS = visual analog scale; T1 = before PACU discharge; T2 = 2 hours after surgery; T3 = 8 hours after surgery; T4 = 24 hours after surgery; T5 = 48 hours after surgery. *P < 0.05.

Anesthesiology
55:578–581, 1981

Lidocaine before Endotracheal Intubation: Intravenous or Laryngotracheal?

James F. Hamill, M.D.,* Robert F. Bedford, M.D.,† David C. Weaver, M.D.,‡
Austin R. Colohan, M.D.‡

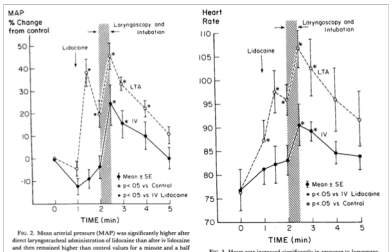
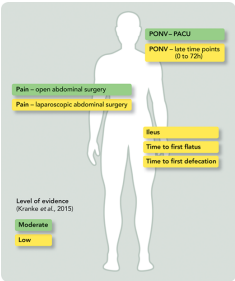


FIG. 2. Mean arterial pressure (MAP) was significantly higher after direct laryngotracheal administration of lidocaine than after iv lidocaine and then remained higher than control values for a minute and a half after intubation. After intravenous lidocaine MAP was significantly increased for less than a minute after intubation was completed.

FIG. 3. Heart rate increased significantly in response to laryngotracheal injection of lidocaine, and peak heart rate after endotracheal intubation was significantly higher than that in the intravenous lidocaine group.



Cochrane Database of Systematic Reviews

Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery

Cochrane Systematic Review - **Intervention** | Version published: 16 July 2015

There is low to moderate evidence that this intervention, when compared to placebo, has an impact on pain scores, especially in the early postoperative phase, and on postoperative nausea. There is limited evidence that this has further impact on other relevant clinical outcomes, such as gastrointestinal recovery, length of hospital stay, and opioid requirements. So far there is a scarcity of studies that have systematically assessed the incidence of adverse effects; the optimal dose; timing (including the duration of the administration); and the effects when compared with epidural anaesthesia.

Cochrane Database of Systematic Reviews

Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery in adults

Cochrane Systematic Review - **Intervention** | Version published: 04 June 2018 see what's new

We are uncertain whether IV perioperative lidocaine, when compared to placebo or no treatment, has a beneficial impact on pain scores in the early postoperative phase, and on gastrointestinal recovery, postoperative nausea, and opioid consumption. The quality of evidence was limited due to inconsistency, imprecision, and study quality. Lidocaine probably has no clinically relevant effect on pain scores later than 24 hours. Few studies have systematically assessed the incidence of adverse effects. There is a lack of evidence about the effects of IV lidocaine compared with epidural anaesthesia in terms of the optimal dose and timing (including the duration) of the administration. We identified three ongoing studies, and 18 studies are awaiting classification; the results of the review may change when these studies are published and included in the review.

Perioperative Use of Intravenous Lidocaine
Anesthes. 2017;126(4):729-737.

PAIN 159 (2018) 1696–1704

Perioperative lidocaine infusions for the prevention of chronic postsurgical pain: a systematic review and meta-analysis of efficacy and safety

Martin Bailey[a,b,*], Tomas Corcoran[a,c,d], Stephan Schug[a,c], Andrew Toner[a]

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Jendoubi 2017	1	20	9	20	5.1%	0.06 [0.01, 0.58]
Grigoras 2012	2	17	9	19	8.3%	0.15 [0.03, 0.83]
Choi 2016	6	41	16	43	21.8%	0.29 [0.10, 0.84]
Terkawi 2014	4	34	8	27	13.9%	0.32 [0.08, 1.20]
Kendall 2017	8	62	17	59	28.4%	0.37 [0.14, 0.93]
Kim 2017	7	39	14	39	22.5%	0.39 [0.14, 1.11]
Total (95% CI)		**213**		**207**	**100.0%**	**0.29 [0.18, 0.48]**
Total events	28		73			

Heterogeneity: Tau² = 0.00; Chi² = 2.98, df = 5 (P = 0.70); I² = 0%
Test for overall effect: Z = 4.84 (P < 0.00001)

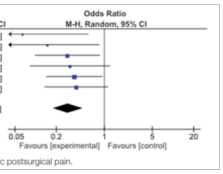


Figure 2. Effect of perioperative lidocaine infusions on CPSP in all surgery types. CPSP, chronic postsurgical pain.

Intravenous infusion of lidocaine significantly reduces propofol dose for colonoscopy: a randomised placebo-controlled study

C. Forster[1], A. Vanhaudenhuyse[2,3], P. Gast[4], E. Louis[4], G. Hick[1], J.-F. Brichant[1] and J. Joris[1,*]

Methods: Forty patients undergoing colonoscopy were included in this randomised placebo-controlled study. After titration of propofol to produce unconsciousness, patients were given i.v. lidocaine (1.5 mg kg^{-1} then 4 mg kg^{-1} h^{-1}) or the same volume of saline. Sedation was standardised and combined propofol and ketamine. The primary endpoint was propofol requirements. Secondary endpoints were: number of oxygen desaturation episodes, endoscopists' working conditions, discharge time to the recovery room, post-colonoscopy pain, fatigue.
Results: Lidocaine infusion resulted in a significant reduction in propofol requirements: 58 (47) *vs* 121 (109) mg (P=0.02). Doses of ketamine were similar in the two groups: 19 (2) *vs* 20 (3) mg in the lidocaine and saline groups, respectively. Number of episodes of oxygen desaturation, endoscopists' comfort, and times for discharge to the recovery room were similar in both groups. Post-colonoscopy pain (P<0.01) and fatigue (P=0.03) were significantly lower in the lidocaine group.
Conclusions: Intravenous infusion of lidocaine resulted in a 50% reduction in propofol dose requirements during colonoscopy. Immediate post-colonoscopy pain and fatigue were also improved by lidocaine.

British Journal of Anaesthesia, 121 (5): 1059–1064 (2018)

VOL 13 NO 2 ANÆSTHESIA APRIL 1958

Intravenous lignocaine anæsthesia

S. G. DE CLIVE-LOWE, TD, MB, ChB, FFARCS, DA
Consultant Anæsthetist, Guildford Group of Hospitals
J. DESMOND, MB, BS, MD (Canada), DA
Consultant Anæsthetist, RCAF
J. NORTH, FFARCS, MRCS, LRCP, DA
Consultant Anæsthetist, Guildford Group of Hospitals

The aim of the modern anæsthetist is to produce, at the minimum cost to the subject, the maximum protection from the traumatic onslaughts of the surgeon, both during operative procedures and in the immediate postoperative phase. This must necessarily be combined with the optimum operating conditions for the surgeon and be applicable to young and old, good and bad operative risks alike.

All drugs used in anæsthesia are to a greater or less degree toxic to the subject, and depend to a very large extent, in their toxicity, upon the skill of the anæsthetist in their application.

Induktioon tiopentaali 500 mg + lidokaiini 60 mg + suksametoni 50 mg

1 h: lidokaiini 40 mg 5 min välein
2 h: lidokaiini 20 mg 5 min välein
3 h: lidokaiini 20 mg 10 min välein

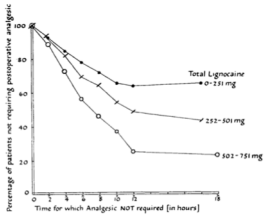


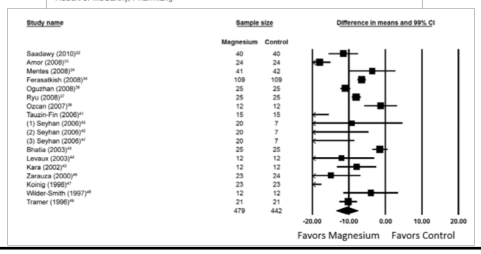
FIG. 2

Perioperative Systemic Magnesium to Minimize Postoperative Pain

A Meta-analysis of Randomized Controlled Trials

Anesthesiology 2013; 119:178-90

Gildasio S. De Oliveira, Jr., M.D., M.S.C.I.,* Lucas J. Castro-Alves, M.D.,† Jamil H. Khan, B.S.,‡ Robert J. McCarthy, Pharm.D.§

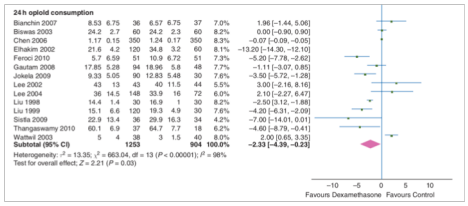


British Journal of Anaesthesia **110** (2): 191–200 (2013)
Advance Access publication 5 December 2012 · doi:10.1093/bja/aes431

BJA

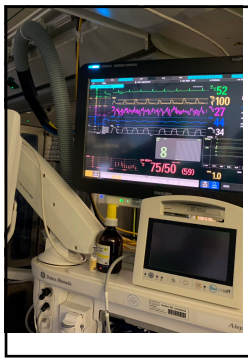
Impact of perioperative dexamethasone on postoperative analgesia and side-effects: systematic review and meta-analysis

N. H. Waldron, C. A. Jones, T. J. Gan, T. K. Allen and A. S. Habib*



AZ Sint-Jan OFA protocol (J. Mulier & I Zadonsky)

- esilääke pregabaliini 150 – 300 mg p.o.
- deksmedetomidiini 0,2 µg / kg i.v. 10 min ennen induktiota
- induktio- ja ylläpitoseos ”Mullimix”
  - deksmedetomidiini 50 µg = 1 µg/ml
  - ketamiini 50 mg (/ S-ketamiini 25 mg) = 1 mg/ml
  - lidokaiini 500 mg (25 ml 2 %) = 10 mg/ml
  - NaCl 0,9 % ad 50 ml



Induktio

- 1 ml / 10 kg IBW induktio- ja ylläpitoseosta
  - = dex 0,1 µg/kg, ketamiini 0,1mg/kg, lidokaiini 1 mg/kg
- propofoli
- rokuroni 1 mg/kg
- deksametasoni 10 mg
- magnesiumsulfaatti 2,5 g (~40 mg/kg)
- DHBP 0,625 – 1,25 mg
- ketorolaakki 30 mg

Ylläpito

- sevofluraani 1,0 MAC / propofoli-TCI
  - BIS
- 1 ml / 10 kg IBW / h induktio- ja ylläpitoseosta
  - = dex 0,1 µg/kg/h, ketamiini 0,1mg/kg/h, lidokaiini 1 mg/kg/h
- rokuroni-infuusio
  - PTC < 5 bariatrisessa kirurgiassa
- korkeisiin verenpaineisiin nikardipiini- tai metoprololibolus
- mataliin verenpaineisiin efedriini tai fenyyliefriini
- nesteytys pulssiaallon variaation ohjaamana

Toimenpiteen loppu

- 15 min ennen loppua ylläpitoinfuusio lasketaan 0,5 ml / 10 kg / h
  - jatkuu heräämössä
- parasetamoli 2 g i.v.
  - jatkoon 1 g x 4
- relaksaation kumoaminen
  - sugammadeksin annostelu LBW + 20-40 %
  - neostigmiinin annostelu LBW + 60-80 %
- heräämössä tarvittaessa morfiini i.v.
- osastolle prokaiini-infuusio, parasetamoli ja NSAID, tarv. opioidi p.o.

OFA aloittelijoille

- etene asteittain
- yhdistä aina regionaalitekniikkaan, jos mahdollista
- vähennä intraoperatiivisia opioidiannoksia
- kaasu on helpompi kuin TIVA
- pidä annokset alle sedatiivisen tason

1. ketamiini
2. lidokaiini
   - ei toimi, jos suuri opioidiannos
3. deksmedetomidiini

Mitä ei tiedetä?

- Optimaaliset lääkeannokset ja –yhdistelmät
- Lisää näyttöä hyödyistä
  - eri potilasryhmät
  - eri toimenpiteet
- Lisää turvallisuusnäyttöä