Atypical intravenous analgesics

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Declaration of interests

- I have received payment for presentations and advisory board membership from Pfizer and Grunenthal
- I have received financial support from Astellas Pharma for a conference visit

What am I talking about?

- The probable mechanisms and evidence for the efficacy of iv atypical analgesics in acute pain…
- And a bit about the prevention of PPP
- I’m not talking about gabapentinoids as they have very poor evidence for acute pain…
- And minimal evidence for prevention of PPP
- I’m not talking about clonidine, dexmedetomidine or steroids – because I haven’t got time
- So that leaves… ketamine, magnesium and lidocaine

ERAS http://erassociety.org

- Henrik Kehlet – Copenhagen, late 90's
- Aim is risk free pain free surgery
- Ask each day "what is keeping this patient in hospital?"
- Initially simple few interventions to improve recovery
- However has now got really complicated with many unneccessary additions
- Risk assessment needs to link surgical and non-surgical complications
- Need to re focus on the underlying problem after surgery – the pro inflammatory state that is the stress response

The trouble with epidurals

- Epidural analgesia is becoming uncommon – why?
- Provides superior analgesia for first 48 hours and reduces respiratory complications Rigg, J.R.A., et al., Lancet. 2002. p. 1276–1282. but…
- Neurological complications Cook, T.M., et al., BJA. 2009. p. 179-190.
  - NAP3 looked at perioperative, obstetric and chronic pain
  - Highest risk of serious neurological complications with perioperative epidural
  - 8-17/100000 with 60% recovering within 12 months
  - Is it appropriate to abandon epidural anaesthesia on the basis of safety?
- What about the risk of perioperative death or other complications?

Epidural meta-analysis

Annals of Surgery Volume 259, Number 6, June 2014

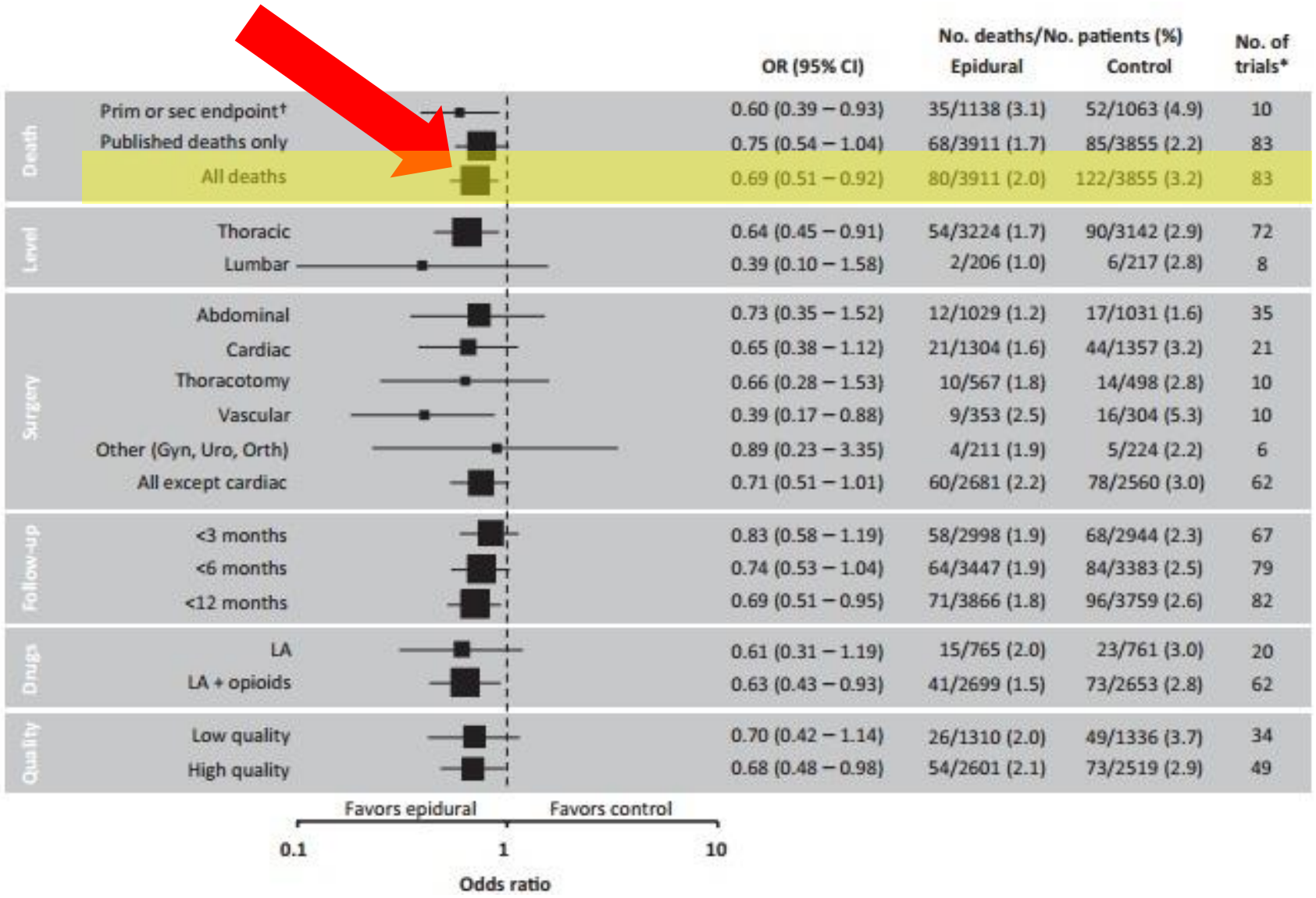
Impact of Epidural Analgesia on Mortality and Morbidity After Surgery

Systematic Review and Meta-analysis of Randomized Controlled Trials

Daniel M. Pöpping, MD, Nadia Elia, MD, MSc,† Hugo K. Van Aken, MD,* Emmanuel Marret, MD,‡ Stephan A. Schug, MD,§ Peter Kranke, MD, MBA,¶ Manuel Wenk, MD,* and Martin R. Tramèr, MD, DPhil‖*

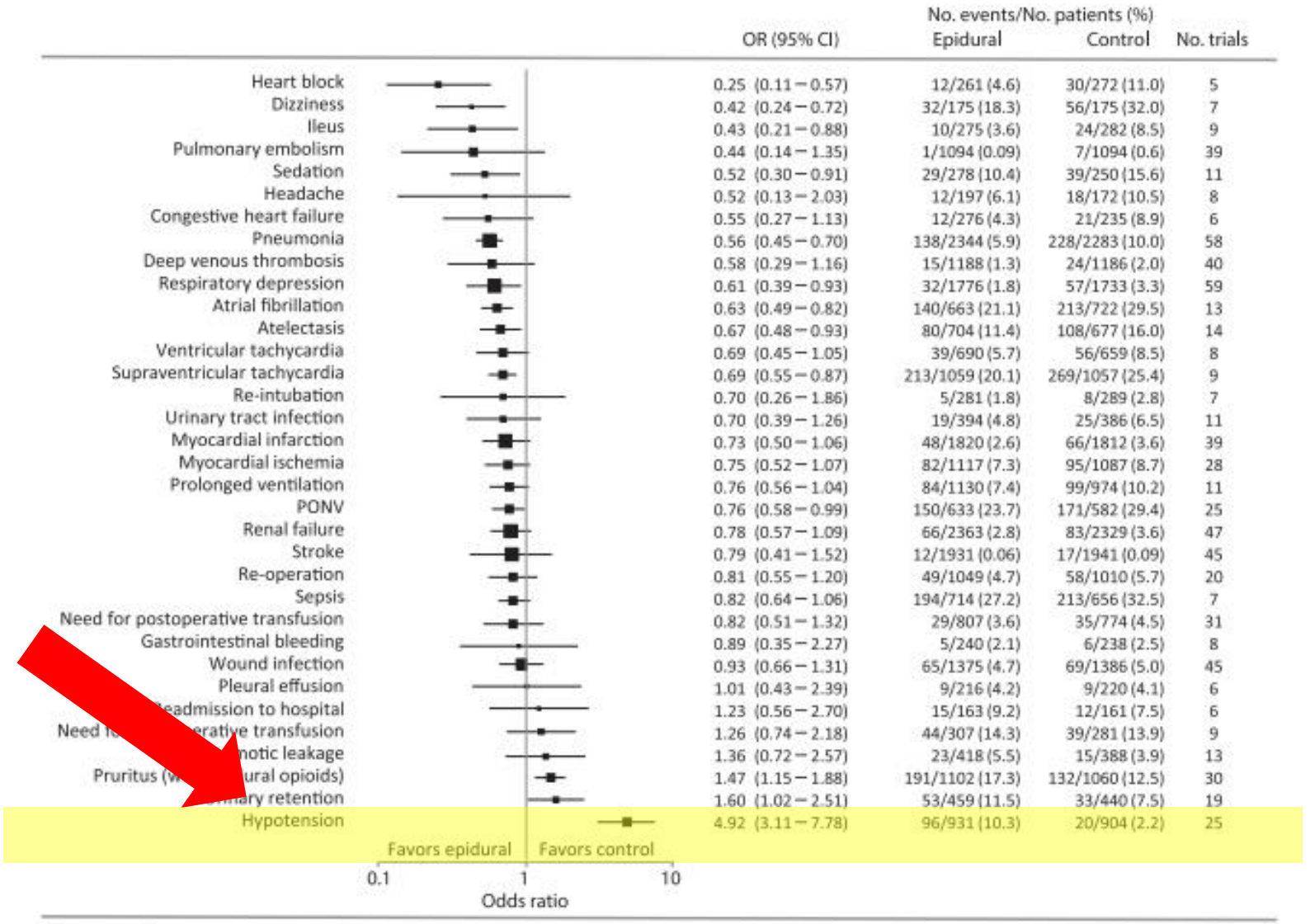
- 125 trials n=9044 surgery under GA
- Epidurals with local anaesthesia for > 24 hours
- Versus systemic analgesia

Post-operative mortality



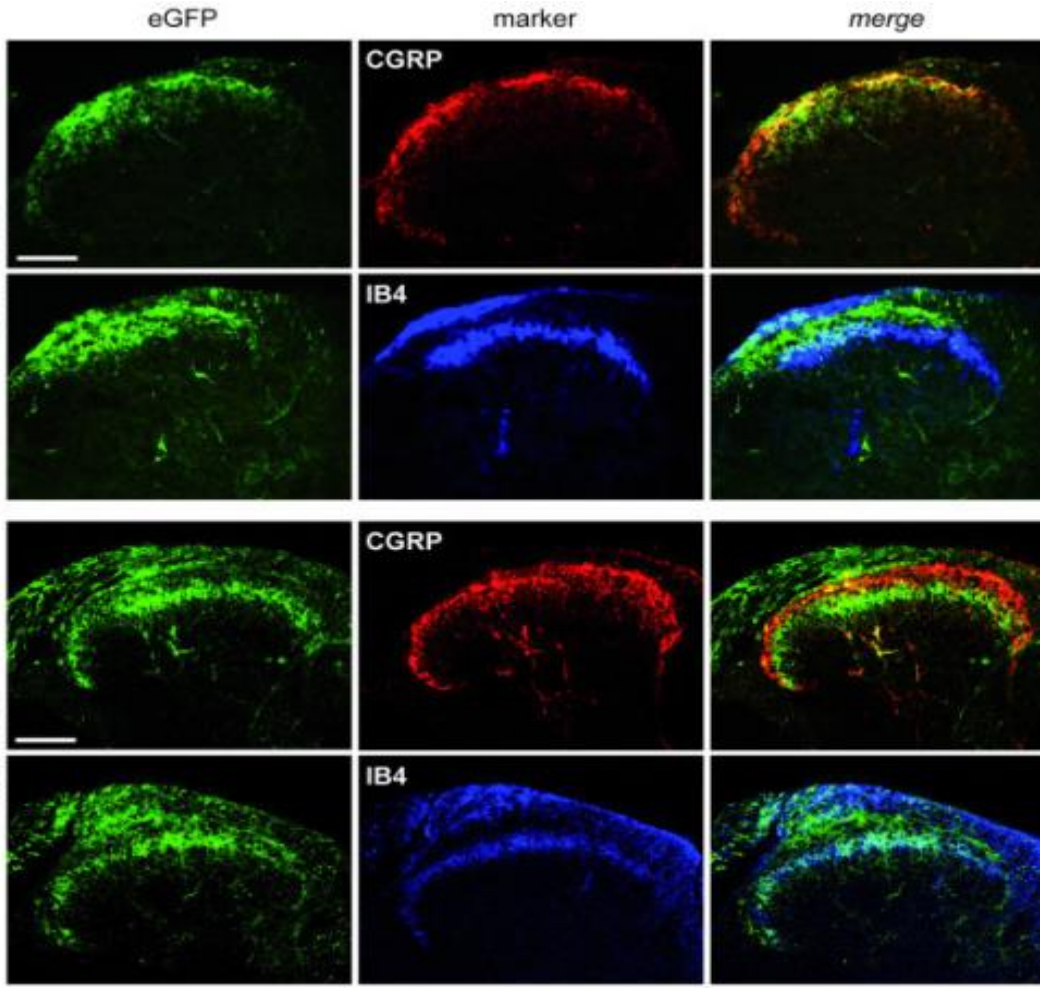
		OR (95% CI)	No. deaths/No. patients (%) Epidural	No. deaths/No. patients (%) Control	No. of trials*
Death	Prim or sec endpoint†	0.60 (0.39 – 0.93)	35/1138 (3.1)	52/1063 (4.9)	10
	Published deaths only	0.75 (0.54 – 1.04)	68/3911 (1.7)	85/3855 (2.2)	83
	All deaths	0.69 (0.51 – 0.92)	80/3911 (2.0)	122/3855 (3.2)	83
Level	Thoracic	0.64 (0.45 – 0.91)	54/3224 (1.7)	90/3142 (2.9)	72
	Lumbar	0.39 (0.10 – 1.58)	2/206 (1.0)	6/217 (2.8)	8
Surgery	Abdominal	0.73 (0.35 – 1.52)	12/1029 (1.2)	17/1031 (1.6)	35
	Cardiac	0.65 (0.38 – 1.12)	21/1304 (1.6)	44/1357 (3.2)	21
	Thoracotomy	0.66 (0.28 – 1.53)	10/567 (1.8)	14/498 (2.8)	10
	Vascular	0.39 (0.17 – 0.88)	9/353 (2.5)	16/304 (5.3)	10
	Other (Gyn, Uro, Orth)	0.89 (0.23 – 3.35)	4/211 (1.9)	5/224 (2.2)	6
	All except cardiac	0.71 (0.51 – 1.01)	60/2681 (2.2)	78/2560 (3.0)	62
Follow-up	<3 months	0.83 (0.58 – 1.19)	58/2998 (1.9)	68/2944 (2.3)	67
	<6 months	0.74 (0.53 – 1.04)	64/3447 (1.9)	84/3383 (2.5)	79
	<12 months	0.69 (0.51 – 0.95)	71/3866 (1.8)	96/3759 (2.6)	82
Drugs	LA	0.61 (0.31 – 1.19)	15/765 (2.0)	23/761 (3.0)	20
	LA + opioids	0.63 (0.43 – 0.93)	41/2699 (1.5)	73/2653 (2.8)	62
Quality	Low quality	0.70 (0.42 – 1.14)	26/1310 (2.0)	49/1336 (3.7)	34
	High quality	0.68 (0.48 – 0.98)	54/2601 (2.1)	73/2519 (2.9)	49

Post operative complications



Alternatives to epidural analgesia

- Hypotension is bad
- Epidurals (can be) bad
- Without epidurals we use more opioids (which are bad)…
- So what are the alternatives??
- Understanding the neuroplastic processes occurring after surgery aids understanding of how and where alternative analgesics (and antihyperalgesics) might work…



Mechanisms of post-surgical pain

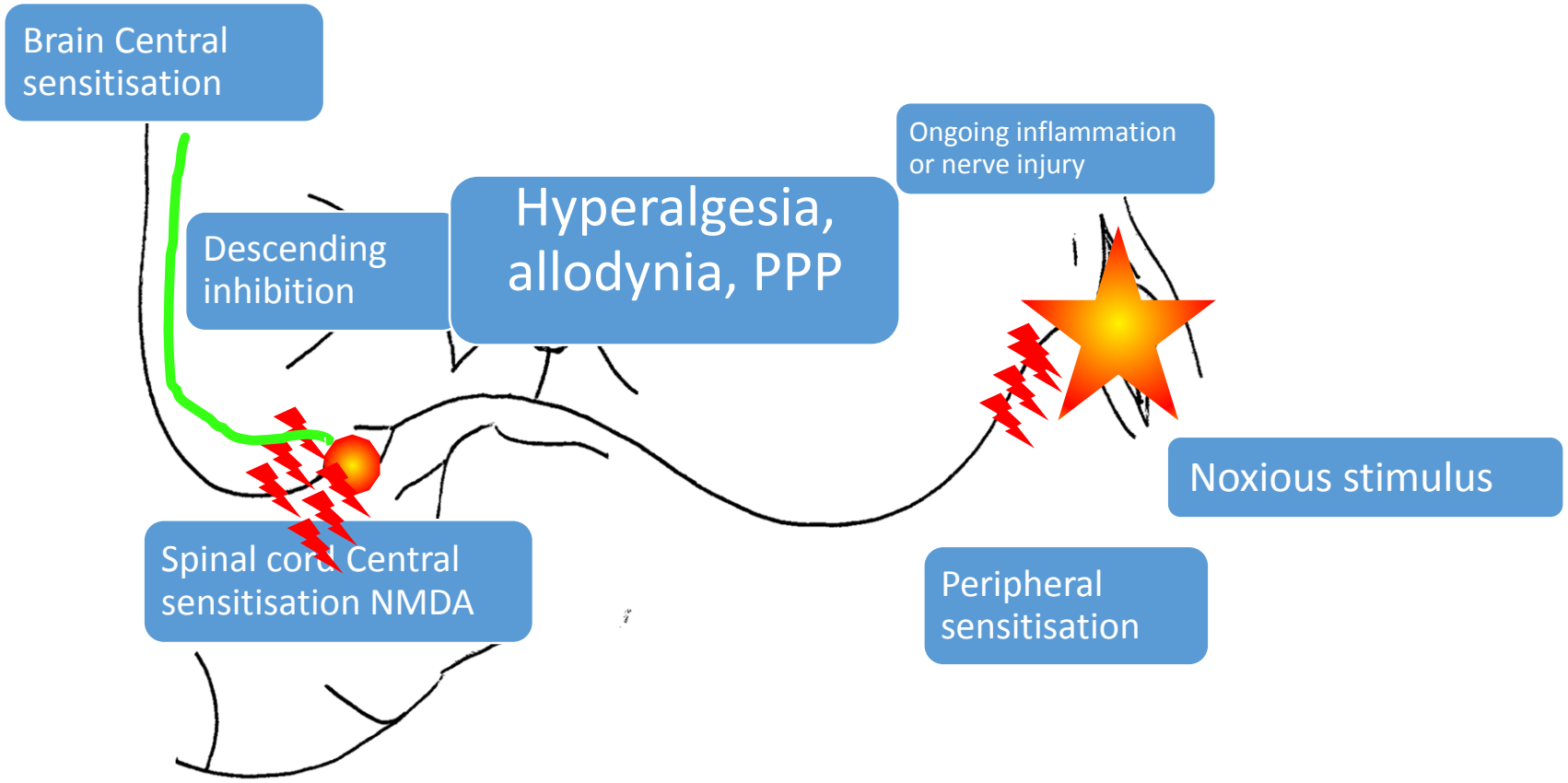
Nociception, peripheral and central sensitisation – what are the potential targets for atypical analgesics (antihyperalgesics)

What happens after surgery?

The neurobiology of post surgical pain

- Inflammatory response (IL1 TNFα BK PGs etc..)
- Nerve injury
- Peripheral sensitisation
  - Increased responsiveness and reduced threshold of nociceptive neurons in the periphery to the stimulation of their receptive fields
- Central sensitisation
  - Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input

Neuroplastic processes occurring after surgery

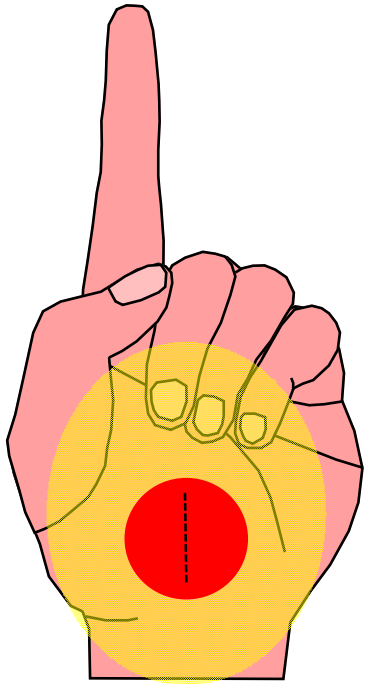


Clinical findings following surgical trauma

Arendt-Nielsen 2006 Anaesthesiology 104:601-607

- Primary hyperalgesia (mechanical and heat)
- Allodynia
- Spontaneous pain

- Secondary hyperalgesia (mechanical only) – represents central sensitisation
- Apply anti-hyperalgesic drug



Peripheral injury

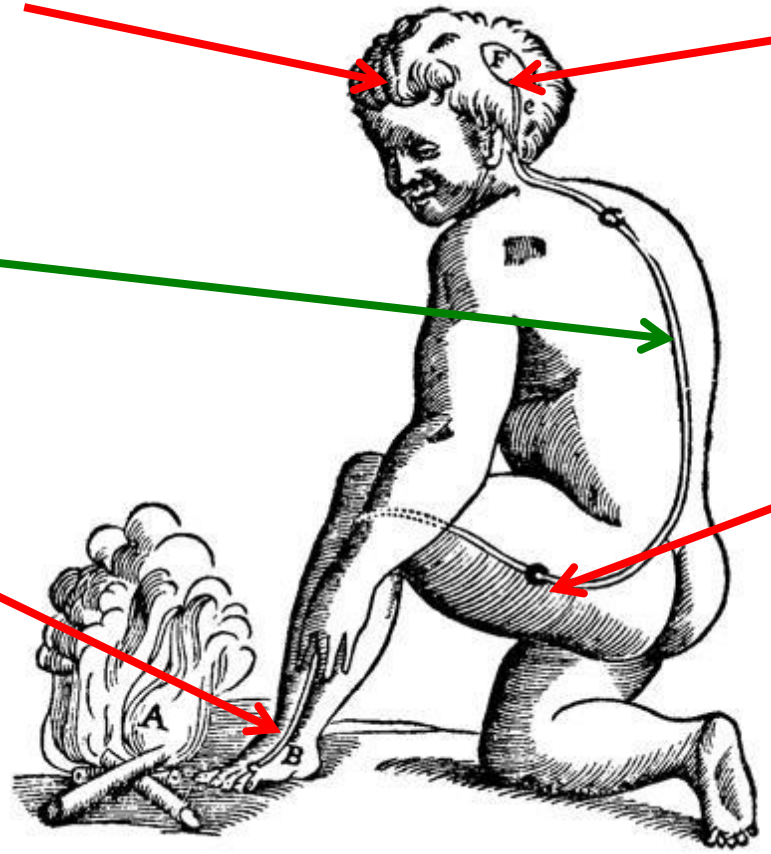
Warncke, T., Stubhaug, A., & Jorum, E. (1997). Ketamine, an NMDA receptor antagonist, suppresses spatial and temporal properties of burn-induced secondary hyperalgesia in man: a double-blind, cross-over comparison with morphine and placebo. Pain, 72(1-2), 99–106.

Neuroplasticity in acute pain

Pain perception modulated by peripheral and central (psychological) events

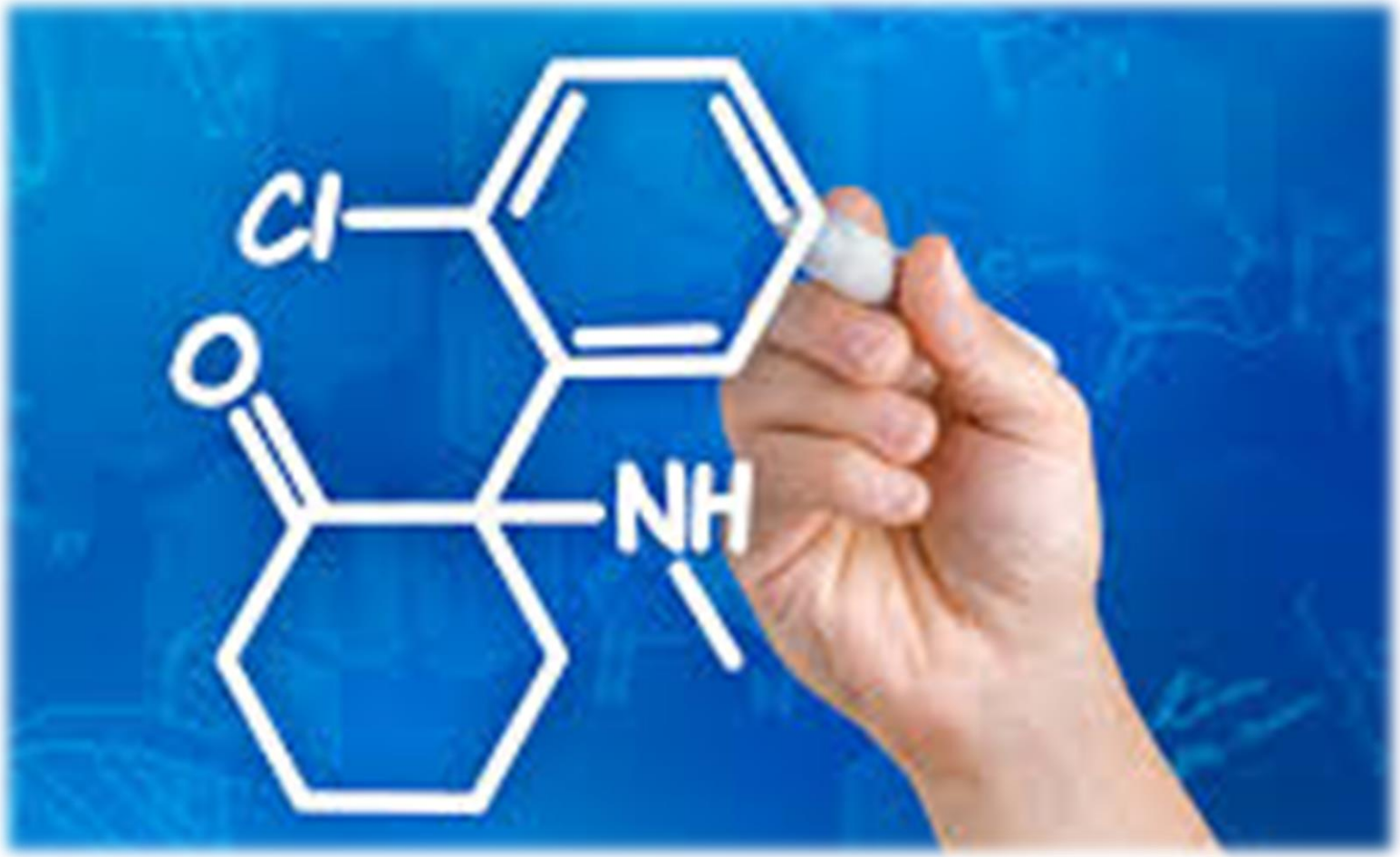
Descending inhibition modulates central sensitisation

Inflammation / nerve injury drives peripheral sensitisation



Brain central sensitisation depends on balance of excitation / inhibition

Increased afferent barrage drives spinal cord central sensitisation

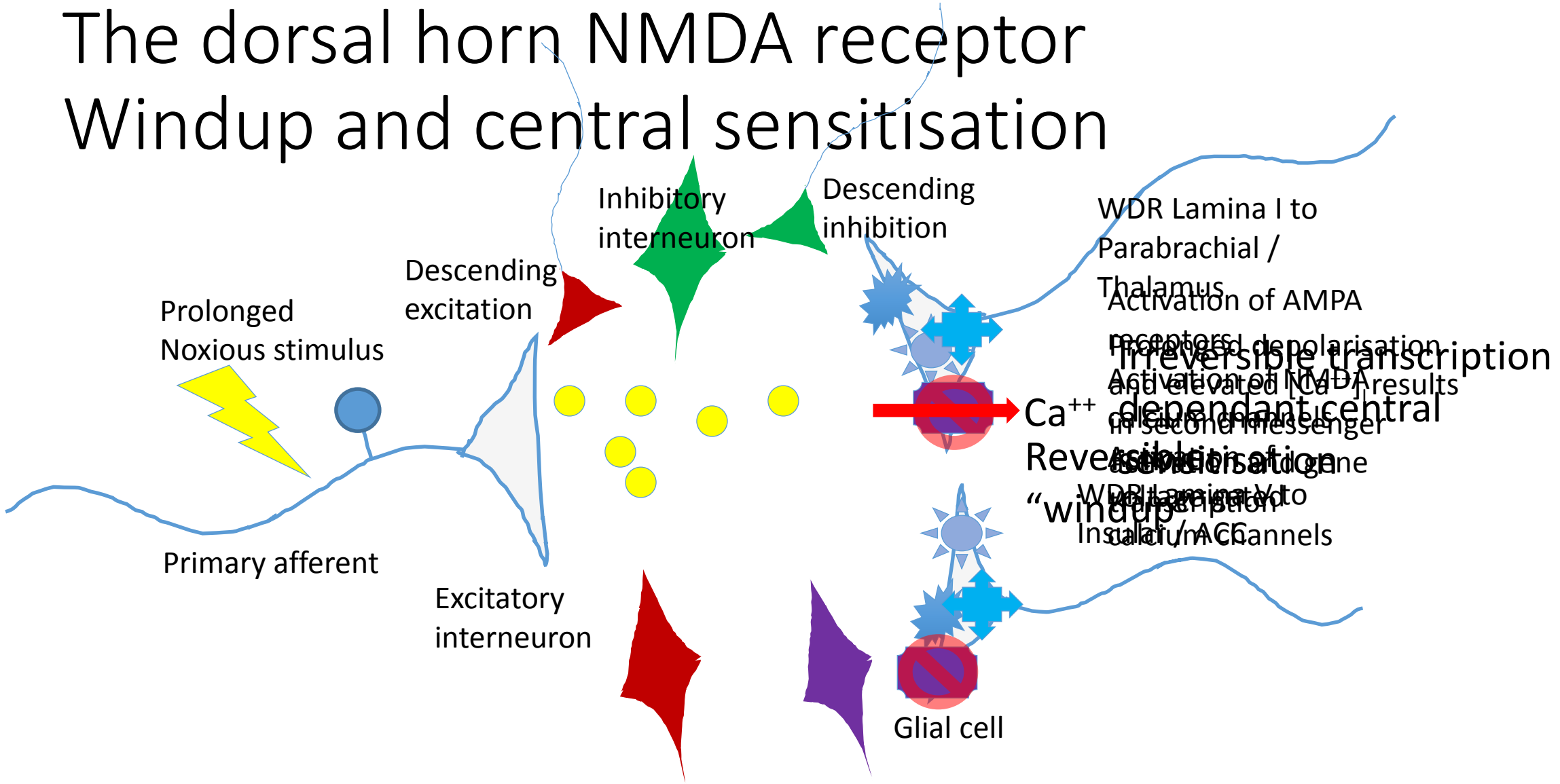


Ketamine

Introduction

- Ketamine is a phencyclidine derivative first synthesised in 1963
- It was first approved for clinical use in 1970 as a ‘dissociative anaesthetic’
- It’s primary target, the NMDA receptor is implicated in central sensitisation, resulting in hyperalgesia and allodynia as well as opioid i tolerance and opioid induced hyperalgesia
- NMDA glutamatergic neurotransmission is also implicated in learning and memory, cognition, neural development, neuroplasticity, excitotoxicity, addiction, and psychiatric disorders

The dorsal horn NMDA receptor Windup and central sensitisation



Mechanism of ketamine analgesia

- Non-competitive antagonism of the NR2B NMDA sub-unit is probably the most important anti-nociceptive effect
- In addition to its well-known NMDA blockade, ketamine affects a wide range of intracellular neuronal processes
- The analgesic effects of ketamine appear to involve both short term and long term disturbance of cellular function
- Immediate analgesic effects mediated by a combination of opioid system sensitisation and descending aminergic anti-nociception (via serotonergic and noradrenergic activation and inhibition of their re-uptake)
- Anti-neuropathic effect: may rely on immediate receptor mediated action and initiation of longer lasting cell signalling cascades (synaptic plasticity / apoptosis)
- Anti-inflammatory effect: inhibiting inflammatory cell recruitment, cytokine production and down-regulating inflammatory mediators

Ketamine side-effects

- Ketamine induces visual hallucinations and out of body experiences which has led to its increasing recreational abuse (dose related psychotomimetic effects)
- Case reports of chronic abusers have demonstrated multiple neuropsychiatric complications including cognitive impairment and schizophrenia-like symptoms
- About 20-30% of chronic ketamine abusers report urinary tract symptoms due to ketamine-induced vesicopathy +/- hydroureter (Tawfic 2013)
- Hepatotoxicity +/- cholangiopathy and corneal oedema with endothelial cell loss is also reported in chronic users
- In general these complications are reversible and cessation of abuse is the best treatment (Tawfic 2013)

Specific roles for ketamine as an antihyperalgesic

- Ketamine acts as an adjuvant in the treatment of pain associated with central sensitisation (an anti-hyperalgesic):
  - Severe acute pain
  - Neuropathic pain
  - “Opioid-resistant” pain
- Due to its effects on long lasting neuroplastic events, it is likely ketamine also impacts on persistent post surgical pain (a preventive analgesic):
  - Meta-analysis found benefit in reducing the incidence of PPP at 3 months (NNT 12) and 6 months (NNT 14) but not at 12 months postoperatively (Chaparro 2013 Cochrane 14 RTCs n=1388)

Can J Anesth/J Can Anesth (2011) 58:911–923
DOI 10.1007/s12630-011-9560-0

REPORTS OF ORIGINAL INVESTIGATIONS

A systematic review of intravenous ketamine for postoperative analgesia

Revue méthodique de l'utilisation de la kétamine intraveineuse pour l'analgésie postopératoire

Kevin Laskowski, MD · Alena Stirling, MD · William P. McKay, MD · Hyun J. Lim, MD

Received: 9 November 2010 / Accepted: 8 July 2011 / Published online: 20 July 2011

- Perioperative use of ketamine (70 trials n=4701)
- From 1966 to 2010 randomized, double-blinded, and placebo controlled
- Using intravenous ketamine (bolus or infusion) to decrease postoperative pain
- Studies using any form of regional anaesthesia were excluded.
- No limitation on the ketamine dose, patient age, or language of publication

Meta-analysis of analgesic effects

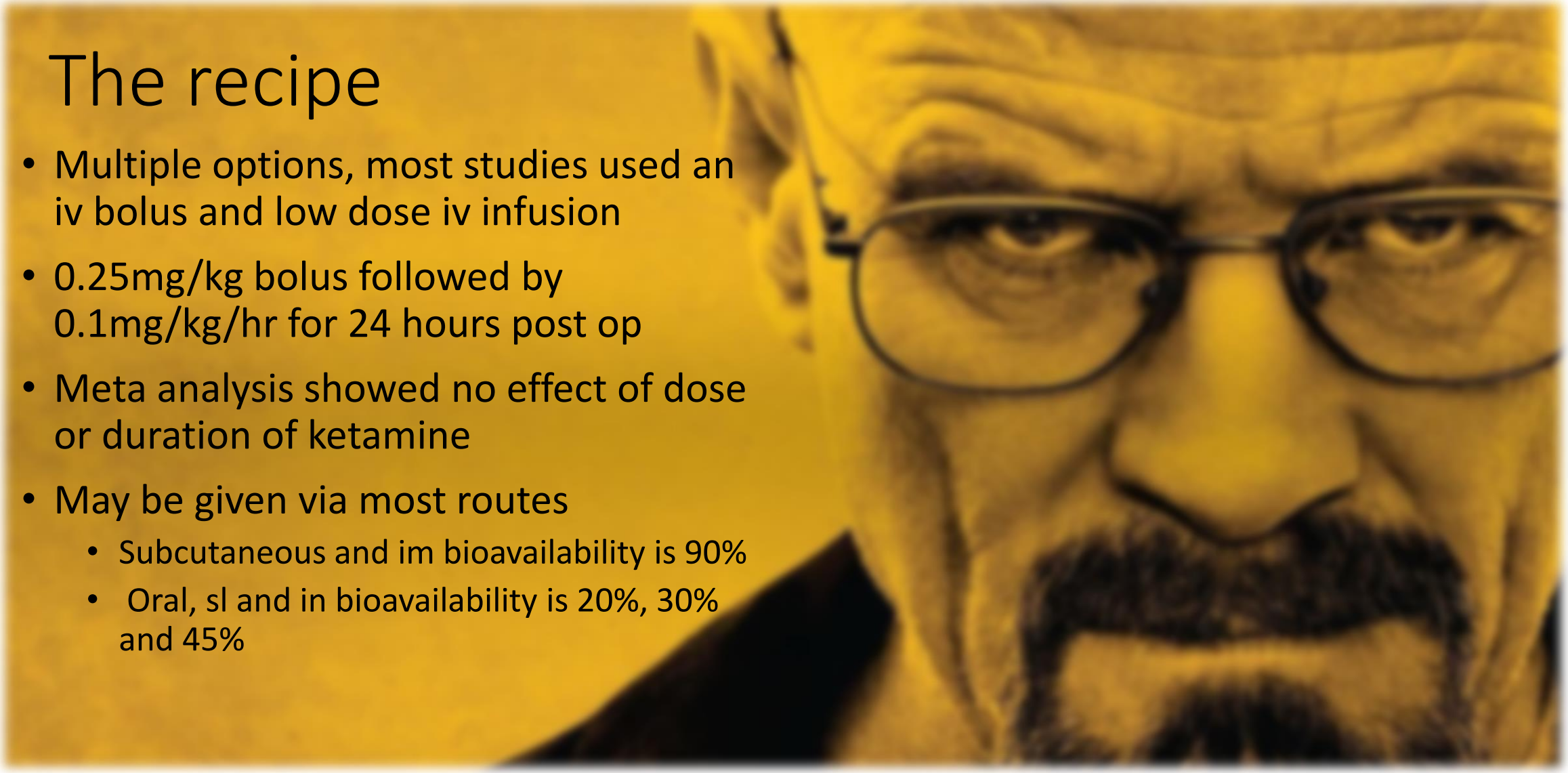
- Reduced total opioid consumption and an increase in the time to first analgesic were observed across all studies ($P<0.001$).
- Opioid sparing was highest in painful procedures with a max VAS of 7 or more.
- 37.5% of studies showed a significant decrease in early pain scores (30 min-4 hr)
- 25% showed a significant decrease in late pain scores (24-72 hr).
- 78% of the placebo groups experienced significantly more pain (with more opioid)
- Greatest efficacy was found for thoracic, upper abdominal, and major orthopaedic surgical subgroups

Meta-analysis of side effects

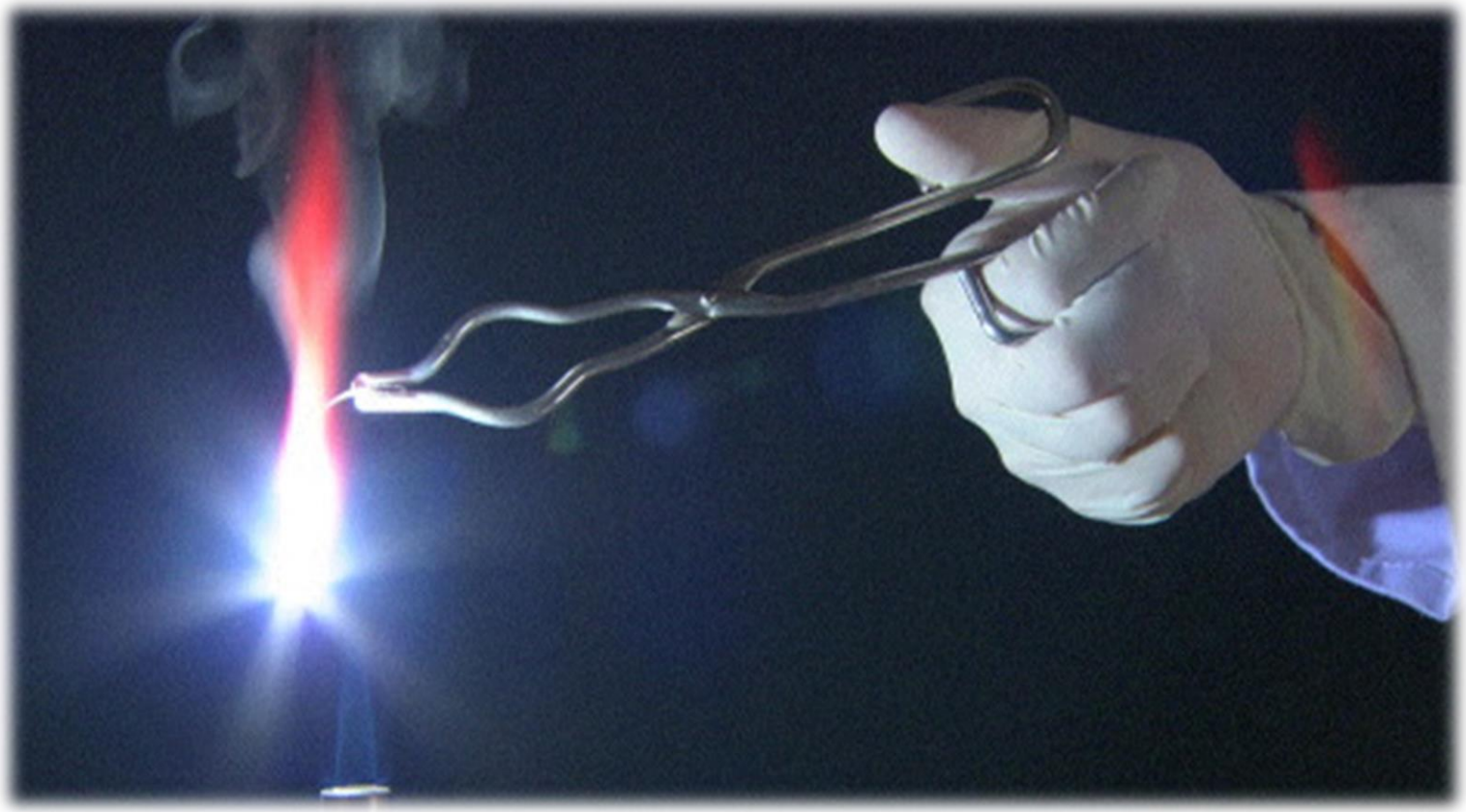
- Increased neuropsychiatric effects (P = 0.018)
- Decreased PONV (P = 0.018)
- No difference in sedation (P = 0.99)
- For efficacious studies alone, neuropsychiatric effects were more significant (P<0.001), and PONV was significantly decreased (P<0.001)
- No difference in the incidence of pruritis, urinary retention, or other reported side effects.

The recipe

- Multiple options, most studies used an iv bolus and low dose iv infusion
- 0.25mg/kg bolus followed by 0.1mg/kg/hr for 24 hours post op
- Meta analysis showed no effect of dose or duration of ketamine
- May be given via most routes
  - Subcutaneous and im bioavailability is 90%
  - Oral, sl and in bioavailability is 20%, 30% and 45%



Breaking Bad Netflix 2014



Magnesium

Background

- Magnesium is the fourth most common cation in the body and the second most common intracellular ion
- First isolated in 1808 by the English chemist, Sir Humphrey Davy
- An essential constituent of over 300 enzyme systems, especially those involved in energy generation and modulates key physiological processes such as nucleic acid synthesis, receptor-binding and ion flux
- Given its diverse actions within the body magnesium salts have been used to treat a variety of clinical conditions
- The first randomised controlled trial exploring its analgesic properties was published relatively recently in 1996 (Trammer 1996).

Uses of magnesium

Table 3. This table shows the potential therapeutic uses of magnesium.

System	Condition	Evidence base
Central nervous system	Acute pain	• Perioperative IV magnesium reduced opiate consumption postoperatively and led to reduced pain scores [46]
	Chronic pain	• IV and PO magnesium increased range of movement and reduced pain scores in chronic back pain with a neuropathic component [48]
	Memory dysfunction	• Increased brain magnesium enhanced learning and memory in rats [72] but no research in humans to date
	Neuromuscular blockade	• Potentiates the effects of non-depolarising neuromuscular blocking agents [73]-[76] • Blunts the serum potassium rise induced by suxamethonium [77]
	Postoperative shivering and thermoregulation	• Reduction in hypothermic shivering threshold from 36.6˚C to 36.3˚C (not clinically significant) [78], some reports of reduced postoperative shivering [79]-[81] but not borne out in a systematic review [82]
	Insomnia	• PO supplementation gave improved sleep quality, sleep time and ease of getting to sleep [49]
Cardiovascular system	Arrhythmias	• Treatment for torsades de pointes, digoxin toxicity, most atrial and ventricular arrhythmias where hypokalaemia is present [50] • Superior to amiodarone in cardioversion of atrial tachyarrhythmias in intensive care [51]
	Myocardial infarction	• Reduced infarct size in canine model [83] • LIMIT-2 study showed reduced 28-day mortality in magnesium treated group [84] • Larger and more recent ISIS-4 and MAGIC-2 trials showed no survival benefit [85] [86]
	Cardiothoracic surgery	• Prophylactic magnesium reduced incidence of postoperative atrial fibrillation from 28% to 18% [53] and ventricular arrhythmias by 48% [54] • Magnesium in cardioplegic solution reduced postoperative ischaemia [55]
	Phaeochromocytoma anaesthesia	• Case series reported 15 out of 17 cases with good haemodynamic stability at induction and tracheal intubation, with 4 cases requiring additional pharmacological support for blood pressure control during tumour handling [59]
Respiratory system	Acute severe asthma	• Scottish Intercollegiate Guidelines Network (SIGN) and British Thoracic Society (BTS) 2012 recommend intravenous magnesium for patients with acute asthma, non-respondent to inhaled short-acting beta-2 agonists, inhaled anticholinergics, corticosteroids and oxygen [60] • Reduced admission rates in acute severe asthma but not in non-severe [61]
	Respiratory muscle weakness	• Improved respiratory muscle power in hypomagnesaemic patients given supplementation [62]
Gastrointestinal system	Mendelson's syndrome	• Magnesium trisillicate is superior to cimetidine in achieving a higher gastric pH [66] in prophylaxis against Mendelson's syndrome (pulmonary aspiration of gastric contents in obstetric anaesthesia)
Obstetrics	Eclampsia	• Reduced risk of maternal death and seizure recurrence compared to diazepam [67]
	Pre-eclampsia	• Reduced risk of developing eclampsia compared to placebo, phenytoin and nimodipine [68]

Mechanism of analgesic action

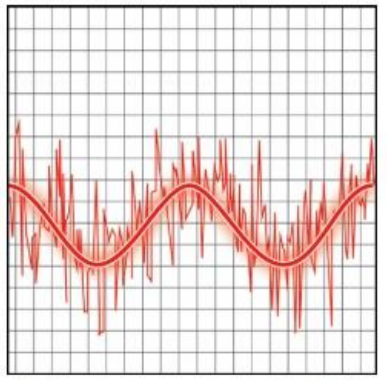
1. Action at NMDA receptor: non-competitive NMDA-receptor antagonist at the spinal cord (synergistic to ketamine and effective iv, PO and IT)
2. However, IV magnesium seems not to increase CSF magnesium (Mercieri 2012) – is it limiting central sensitization by a pre-synaptic mechanism?
3. Anti inflammatory effects: reduces IL-6 and TNF-alpha plasma levels in the postoperative setting (Aryana 2014)
4. Hypomagnesaemia can activate pro-inflammatory neuro-endocrine pathways (Lezhitsa 2011), therefore some anti inflammatory effects may be due to the treatment of subclinical hypomagnesaemia which is prevalent in patients following colorectal surgery
5. Calcium channel blockade: inhibition of calcium-mediated neuroendocrine secretion has been demonstrated (the release of catecholamines during intubation – James 1989)
6. Alpha adrenergic antagonistic effects in baboons & humans (James 2009)

Magnesium safety and side effects

- Mg++ causes a dose dependent pre-synaptic inhibition of ACh release at the neuromuscular junction
- Clinically significant hypermagnesaemia can occur in renal failure or after prolonged and excessive intravenous infusion.

Magnesium Concentration	Features
0.75-0.95 mmol/L (1.7-2.2 mg/dL)	Normal range
2-3.5 mmol/L (5-8 mg/dL)	Flushing, ECG changes
4-5 mmol/L (9-12 mg/dL)	Drowsiness, slurred speech, absent deep tendon reflexes
More than 6 mmol/L (more than 15 mg/dL)	Muscle paralysis, respiratory depression
More than 8 mmol/L (more than 20 mg/dL)	Cardiac arrest

Evidence for analgesic efficacy of Mg^{++}



"There is a signal in the noise! Magnesium does something. Is that something useful?"

- **Two meta analyses in 2013**
- De Oliveira 20 RCTs, n=1257 – 1 point reduction in pain scores and opioid sparing ranging from 5-85% (mean 30%).
- Murphy 22 RCTs, n=1177 - improved pain scores at 4-6 hours (WMD = -0.67 p = 0.003). However, there was no difference in pain scores at 20-24 hours after surgery (WMD = -0.25 p = 0.17). Opioid sparing WMD 7.4mg (95% CI -9.4 to -5.4).
- No change in PONV in either meta-analysis (Murphy RR = 0.76; 95% CI: 0.52 to 1.09, p = 0.14)
- However, opioid sparing is a desirable endpoint in itself – neuroendocrine effects and ongoing inappropriate use

- **Other study findings:**
- Prolonged the duration of sensory block from spinal anaesthesia (level 2) IV and IT
- Prolonged time to first rescue analgesia (level 2)
- Prevented remifentanil-induced acute tolerance & hyperalgesia (level 2)
- Better quality of recovery (QoR) scores at 24 h & reduced opioid requirements after discharge (level 2)
- Attenuates tourniquet pain (level 2)

Other Mg^{++} study results

– evidence for synergy with ketamine and a dose response effect

- Ketamine + IV magnesium reduced 48 h morphine consumption by 30% compared to ketamine alone after scoliosis surgery (Jabbour 2014 Level II, n=50). Pain scores were not different, sleep quality and patient satisfaction were improved with the combination treatment.
- IV magnesium prevented remifentanil-induced hyperalgesia after thyroidectomy (Song 2011 Level II, n=90).
- Magnesium may also have other beneficial effects on postoperative recovery:
  - Breast WLE in an outpatient setting, patients receiving IV magnesium had better quality of recovery (QoR) scores at 24 h compared with the saline group (MD 24/40; 99%CI 3 to 33; P<0.001) and reduced opioid requirements after discharge (De Oliveira 2013a Level II, n=50, JS 5).

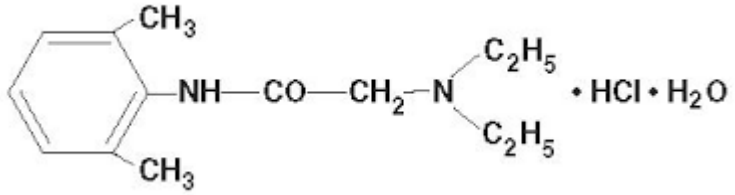
Magnesium recipe

- Most of the trials included in the meta-analyses used a 30–50mg/ kg bolus during surgery and some continued with a maintenance infusion
- A potentially important finding is that those studies that continued magnesium infusion postoperatively showed a greater reduction of late pain at rest and greater opioid sparing
- Typical doses were by a 0.16 mmol/kg loading dose and an infusion of 0.04 mmol/kg per hour (1g = 4.06mmol) 2.7g then 0.7g/hr for 70kg
- One limitation of the meta-analyses is that it did not include the plasma magnesium concentrations measured in many of the studies

Lidocaine


LIDOCAINE HCl
INJECTION, USP
1%
2 mL
LIDOCAINE HCl
INJECTION, USP
1%
(10 mg/mL)
10 mL
Multiple Dose Vial
LIDOCAINE HCl
INJECTION, USP
2%
100 mg
(20 mg/mL)
5 mL Single Dose Vial
LIDOCAINE HCl
INJECTION, USP
2%
2 mL

Pharmacology



- Lidocaine (lignocaine - 2-(diethylamino)-N-(2,6-dimethyl phenyl)-acetamide) was developed in 1948 and was the first amide-type local anaesthetic
- In 1958, Clive-Lowe et al published the first paper on intravenous Lidocaine analgesic effect
- Pharmacokinetics:
- 60-80% protein binding
- 90% metabolised by liver (<10% unchanged in urine) to Mono-ethylglycinexylidide (MEGX)
- Elimination half-life of 1-2h (Baselt, 2008).
- Therapeutic plasma concentration 2-5mcg/ml
- Follows multi-compartment kinetics. Steady state concentrations are reached after 3–4 h of infusion in normal subjects (McCarthy et al 2010).

Potential mechanisms of lidocaine analgesia

- Inactivation of peripheral and central voltage-gated Na channels i.e. A-delta and C-fibre nociceptors
  - However, plasma levels when given IV are too low to block sodium channels directly (de Oliveira, 2010)
  - Damaged nerve fibres may be more sensitive and local blockade at the site of injury may decrease neurogenic inflammation (important in ileus)
- Stimulation of inhibitory descending pain pathways
  - Increase in ACh in CSF via Muscarinic (M3) & Nicotinic receptors (Abelson & Hoglund 2002 – Rat studies)
- Anti-inflammatory effects
  - Inhibits NMDA receptors (Sugimoto 2003)
  - It inhibits the migration of granulocytes and release of lysosomal enzymes and consequently leads to decreased release of pro- and anti-inflammatory cytokines (Ramaswamy 2012)
  - Inhibits NF-kB signaling and pro-inflammatory cytokine production
- Inhibition of nociceptive transmission
  - Mono-ethylglycinexylidide (MEGX) inhibits Glycine Transporter 1 → increased extracellular Glycine
  - Glycine is an inhibitory neurotransmitter at the dorsal horn
- These effects will limit peripheral and central sensitization, accounting for the anti-hyperalgesic effect

Evidence for efficacy – recent meta-analysis 2015

BJA

British Journal of Anaesthesia, 116 (6): 770–83 (2016)

doi: 10.1093/bja/aew101
Review Article

Cochrane Library

Cochrane Database of Systematic Reviews

Efficacy and safety of intravenous lidocaine for postoperative analgesia and recovery after surgery: a systematic review with trial sequential analysis†

S. Weibel[1,*], J. Jokinen[1], N. L. Pace[2], A. Schnabel[1], M. W. Hollmann[3], K. Hahnenkamp[4], L. H. J. Eberhart[5], D. M. Poepping[6], A. Afshari[7] and P. Kranke[1]

Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery (Review)

Kranke P, Jokinen J, Pace NL, Schnabel A, Hollmann MW, Hahnenkamp K, Eberhart LHJ, Poepping DM, Weibel S

Kranke Cochrane Library 2015

Cochrane Library
Cochrane Database of Systematic Reviews

Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery (Review)

Kranke P, Jokinen J, Pace NL, Schnabel A, Hollmann MW, Hahnenkamp K, Eberhart LHJ, Poepping DM, Weibel S

- 45 RCTs (n=2802)
- Subgroup analysis effective in laparoscopic or open abdominal surgery only
- Also limited evidence of positive effects of lidocaine on postoperative gastrointestinal recovery, opioid requirements, postoperative nausea and vomiting, and length of hospital stay

Lidocaine efficacy

- Lidocaine reduced early postoperative pain 0.8 points at 1-4 hours, 0.3 points up to 24 hours, no effect at 48 hours.
- Perspective – most RCTS show that epidurals have a 1-2 point benefit over opioid techniques
- Perhaps as good as TEA in lap surgery MD -1.14, 95% CI -1.51 to -0.78

Adverse effects and clinical tips

- Lidocaine is the LA of choice for continuous intravenous administration
- Low plasma levels are required, in contrast to the therapy of chronic pain diseases
- Free lidocaine concentration will depend on the patient's plasma protein concentration and acid base status
- Drug accumulation may occur because of delayed elimination due to hepatic or renal insufficiency
- Lidocaine is metabolized to active metabolites by the liver, limited by liver perfusion
- No evidence that intravenous lidocaine was associated with an increased risk of adverse effects such as death, arrhythmias, or signs of lidocaine toxicity (Kranke et al 2015)
- Subcutaneous lidocaine can result in stable therapeutic plasma lidocaine concentrations and may be safer than IV (Weinberg 2016 – Online ahead of print)
- When Lidocaine is given as a prolonged infusion there is hepatic competition for the metabolism of lidocaine by MEGX (metabolite)
- Therefore reduce IVI by 20% if given for >24hr

The recipe

- Bolus dose, infusion rate and duration not clear from latest meta-analysis
- 1.5mg/kg as a bolus and an infusion of 1.33mg/kg/hr seemed free of side effects, but didn’t take account of hepatic or renal dysfunction

Summary

- Ketamine, magnesium and lidocaine all have small but significant effects on opioid use and post operative pain scores
- Also moderate to weak evidence for positive effect on other aspects of recovery (lidocaine)
- Where a regional / neuraxial analgesic approach is not helpful (eg: laparoscopic colorectal surgery), there is probably a role for these modalities
- Some evidence for a synergistic effect of ketamine and magnesium
- Unknown additional effect of lidocaine
- Some effects on longer term pain outcomes, preventive analgesia, may reflect activity on central sensitisation (antihyperalgesic)

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Thank you for your attention…
Any questions?