TECHNIQUES TO REDUCE POSTOPERATIVE OPIOID REQUIREMENTS

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OVERVIEW

- **Problems with opioids**

Hypothesis: if I improve analgesia with non-opioids, I can give less opioid, reduce opioid side-effects, improve patient satisfaction, and shorten length of stay.

- **Pain physiology review**
- **Intraoperative techniques**

How can I modify a general anesthetic to reduce post-operative opioid requirements?

INTRAOPERATIVE TECHNIQUES

- Prevent opioid hyperalgesia
- Wound infiltration or regional anesthesia
- Limit spinal cord wind-up
  - NMDA antagonists, NSAIDs, methadone
- Administer intravenous lidocaine
- Administer β-adrenergic receptor antagonists
- Play music

PROBLEMS WITH OPIOIDS

- **Pharmacogenetic**
- **Organ-specific side effects**
- **Physiologic effects**
  - Hyperalgesia, tolerance, addiction
- **Inadequate pain relief**
  - Adverse physiologic responses
  - Postoperative chronic pain states

PHARMACOGENETIC ISSUES WITH OPIOIDS

- Cytochrome P450 enzyme CYP2D6
  - Normal (extensive metabolizers) convert:
    - Codeine (inactive) -> morphine (active)
    - Hydrocodone (inactive) -> hydromorphone
      - At age 5 yrs. – only 25% of adult level
  - Poor metabolizers (genetic variants)
    - 7-10% Caucasians, African-Americans
    - Codeine, hydrocodone (Vicodin) ineffective

ORGAN-SPECIFIC SIDE EFFECTS WITH OPIOIDS - 1

- GI
  - Stomach: decreased emptying, nausea, vomiting
  - Gallbladder: biliary spasm
  - Small intestine: minimal effect
  - Colon: ileus, constipation (Mostafa. Br J Anaesth 2003; 91:815), fecal impaction

ORGAN-SPECIFIC SIDE EFFECTS WITH OPIOIDS - 2

- Respiratory
  - Hypoventilation, decreased ventilatory response to hypoxia & hypercarbia, respiratory arrest, (cough suppression)

ORGAN-SPECIFIC SIDE EFFECTS WITH OPIOIDS - 3

- GU – urinary retention
- CNS – dysphoria, hallucinations, coma
- Cardiac - bradycardia
- Other
  - Pruritus, chest wall rigidity, immune suppression

REVERSING OPIOID SIDE EFFECTS - 1

- **Symptomatic therapy**
  - Nausea, vomiting: 5-HT_3 antagonists
  - Ileus: lidocaine, Constipation: laxatives
  - Urinary retention: Foley catheter
  - Respiratory depression: antagonists, agonist/antagonist, doxapram
  - Pruritus: antihistamines

REVERSING OPIOID SIDE EFFECTS - 2

- **Systemic antagonists** – reverse analgesia
- **Peripheral antagonists** (in development)
  - Do not cross BBB
  - Improved GI, less pruritus
  - Methylnaltrexone, Alvimopan
  - Bates et al, Anesth Analg 2004;98:116
- **Dose reduction** - this presentation

UNDESIRABLE PHYSIOLOGIC EFFECTS OF OPIOIDS

- Hyperalgesia
  - NMDA receptor
- Tolerance
  - NMDA receptor
- Addiction

PATIENT PERCEPTION of PAIN after OUTPATIENT SURGERY

- Apfelbaum. A-1
  - At home after surgery
    - 82% - moderate to extreme pain
    - 21% - analgesic side effects

EXCESSIVE PAIN after AMBULATORY SURGERY

- Chung F. *Anesth Analg* 1999; 89: 1352-9
  - Excessive pain
    - 9.5%
    - 22% longer stay in recovery

POSTOPERATIVE CHRONIC PAIN STATES - 1

- Perkins, Kehlet. Chronic pain as an outcome of surgery. Anesthesiology 2000; 93:1123-33
  - Amputation: phantom limb pain 30-81%, stump pain 5-57%
  - Postthoracotomy pain syndrome 22-67%
  - Chronic pain after groin surgery 11.5% (0-37%)

POSTOPERATIVE CHRONIC PAIN STATES - 2

- Perkins, Kehlet. Chronic pain as an outcome of surgery. Anesthesiology 2000; 93:1123-33
  - Postmastectomy pain syndrome
    - Breast/chest pain 11-57%, phantom breast pain 13-24%, arm/shoulder pain 12-51%
  - Postcholecystectomy syndrome
    - Open 7-48%, laparoscopic 3-54%

PAIN PHYSIOLOGY REVIEW

- Potential sites of intervention
  - Peripheral nerve ending
  - Peripheral nerve transmission
  - Dorsal horn
  - Spinal cord
  - Brain

PERIPHERAL NERVE ENDINGS

- Pain receptor (nociceptor) stimulation
  - Incision, traction, cutting, pressure
- Nociceptor sensitization
  - Inflammatory mediators
  - Primary hyperalgesia
    - Area of surgery or injury (umbra)
  - Secondary hyperalgesia
    - Area surrounding injury (penumbra)

PERIPHERAL NERVE TRANSMISSION

- Normal
  - A-δ fibers (sharp) + c-fibers (dull)
    - 70-90% of peripheral nerve; reserve:total = ?%
- Peripheral sensitization
  - A-δ fibers + c-fibers
    - Normal + reserve traffic
  - A-α fibers (spasm) + A-β fibers (touch)
    - New traffic – terminate at different levels of dorsal horn than A-δ fibers & c-fibers

DORSAL HORN

- Termination of nociceptor input
  - Lamina I – A-δ fibers
  - Lamina II (substantia gelatinosa) – c-fibers
  - Deeper laminae – A-β fibers
- Synapses
  - Ascending tracts
  - Descending tracts
  - Within dorsal horn at entry level
  - Dorsal horns above and below entry level

SPINAL CORD

- Ascending tracts
  - Supraspinal reflexes – surgical stress response
- Descending tracts
  - Opioids, α_2-agonists
- Spinal cord “wind-up”
  - Central sensitization
    - NMDA receptors (post-synaptic cell membrane)
      - NR1 & NR2 subunits
    - c-fos induction -> fos protein production (cell nucleus)

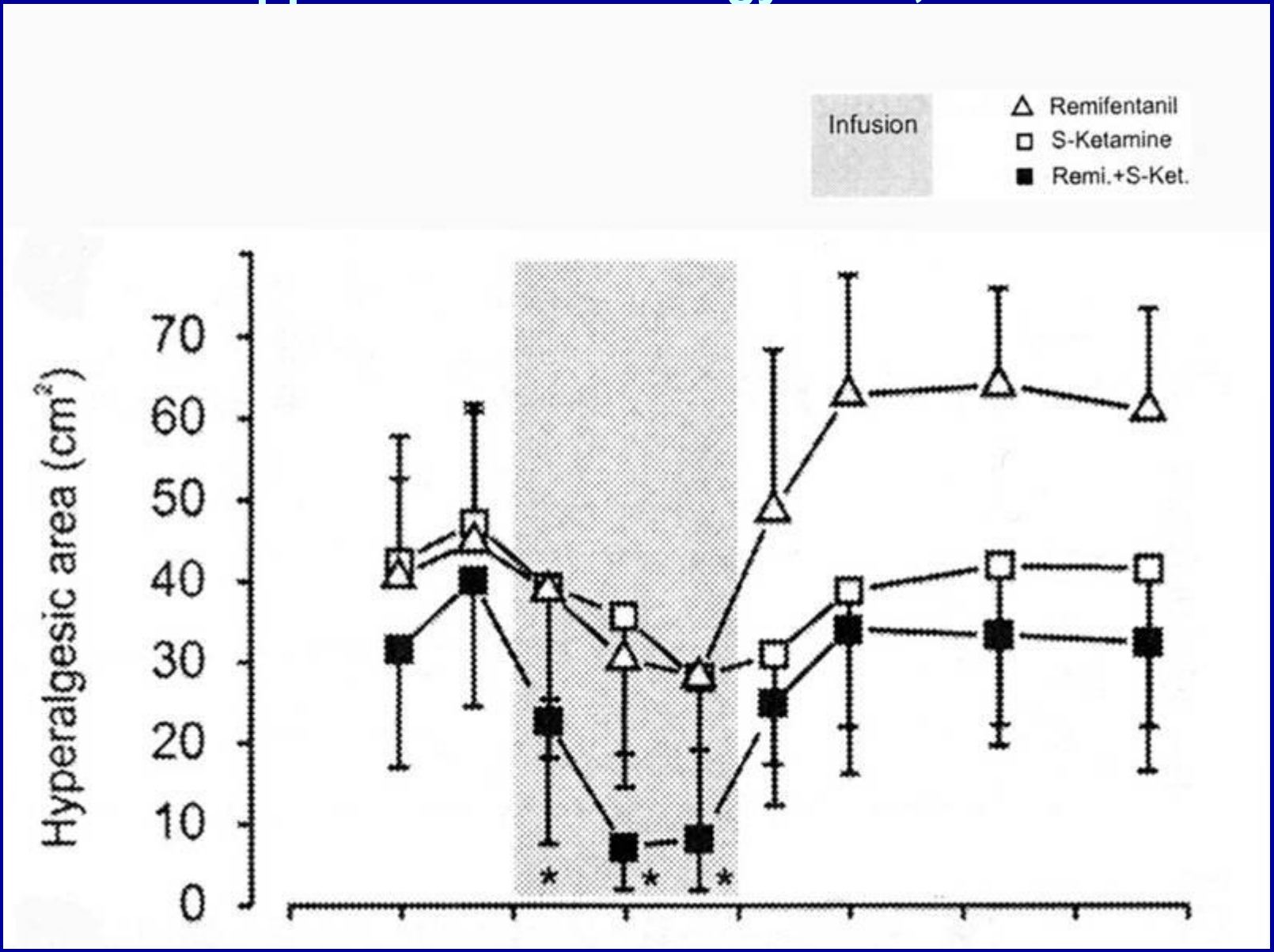
OPIOID HYPERALGESIA

- Vinik. Anesth Analg 1998;86:1307
  - Rapid Development of Tolerance to Analgesia during Remifentanil Infusion in Humans
- Guignard. Anesthesiology 2000;93:409
  - Acute Opioid Tolerance: Intraoperative Remifentanil Increases Postoperative Pain and Morphine Requirements
- Remember the days of “industrial dose” fentanyl for “stress-free” cardiac anesthesia – Did we create hyperalgesia?

PREVENT OPIOID HYPERALGESIA

- Luginbuhl. Anesth Analg 2003;96:726
  - Modulation of Remifentanil-induced Analgesia, Hyperalgesia, and Tolerance by Small-Dose Ketamine in Humans
- Koppert. Anesthesiology 2003;99:152
  - Differential modulation of Remifentanil-induced Analgesia and Postinfusion Hyperalgesia by S-Ketamine and Clonidine in Humans

Koppert. Anesthesiology 2003;99:152



WOUND INFILTRATION – BLOCK NERVE ENDINGS

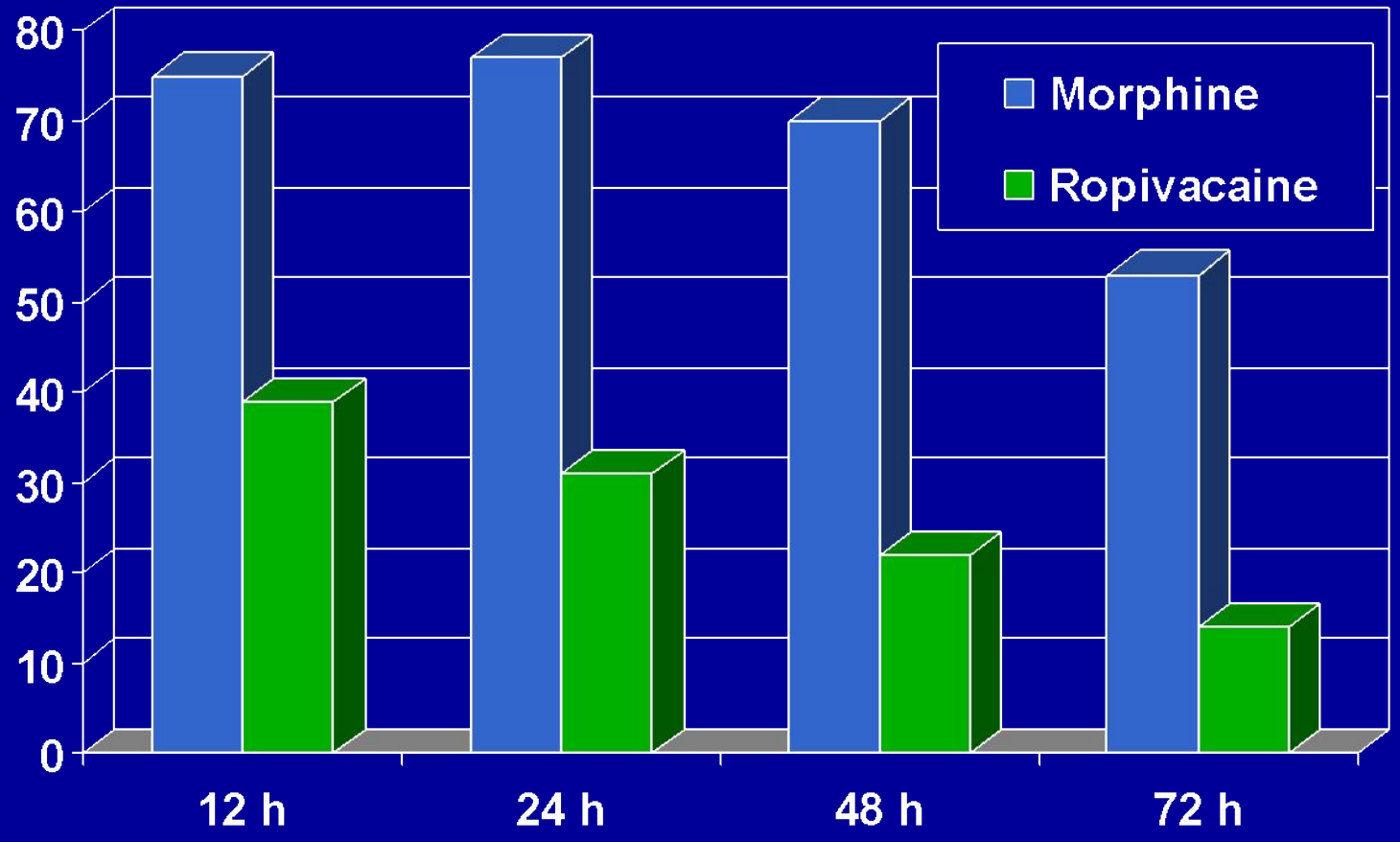
REGIONAL ANESTHESIA – BLOCK NERVE TRANSMISSION

WOUND INFILTRATION – BLOCK NERVE ENDINGS

- Bianconi. Anesth Analg 2004; 98:166
  - Pharmacokinetics & Efficacy of Ropivacaine Continuous Wound Instillation after Spine Fusion Surgery (n = 38)
  - Morphine group: baseline infusion + ketorolac
  - Ropivacaine group: wound infiltration 0.5% + continuous infusion 0.2% 5 ml/h via subq multihole 16-gauge catheter

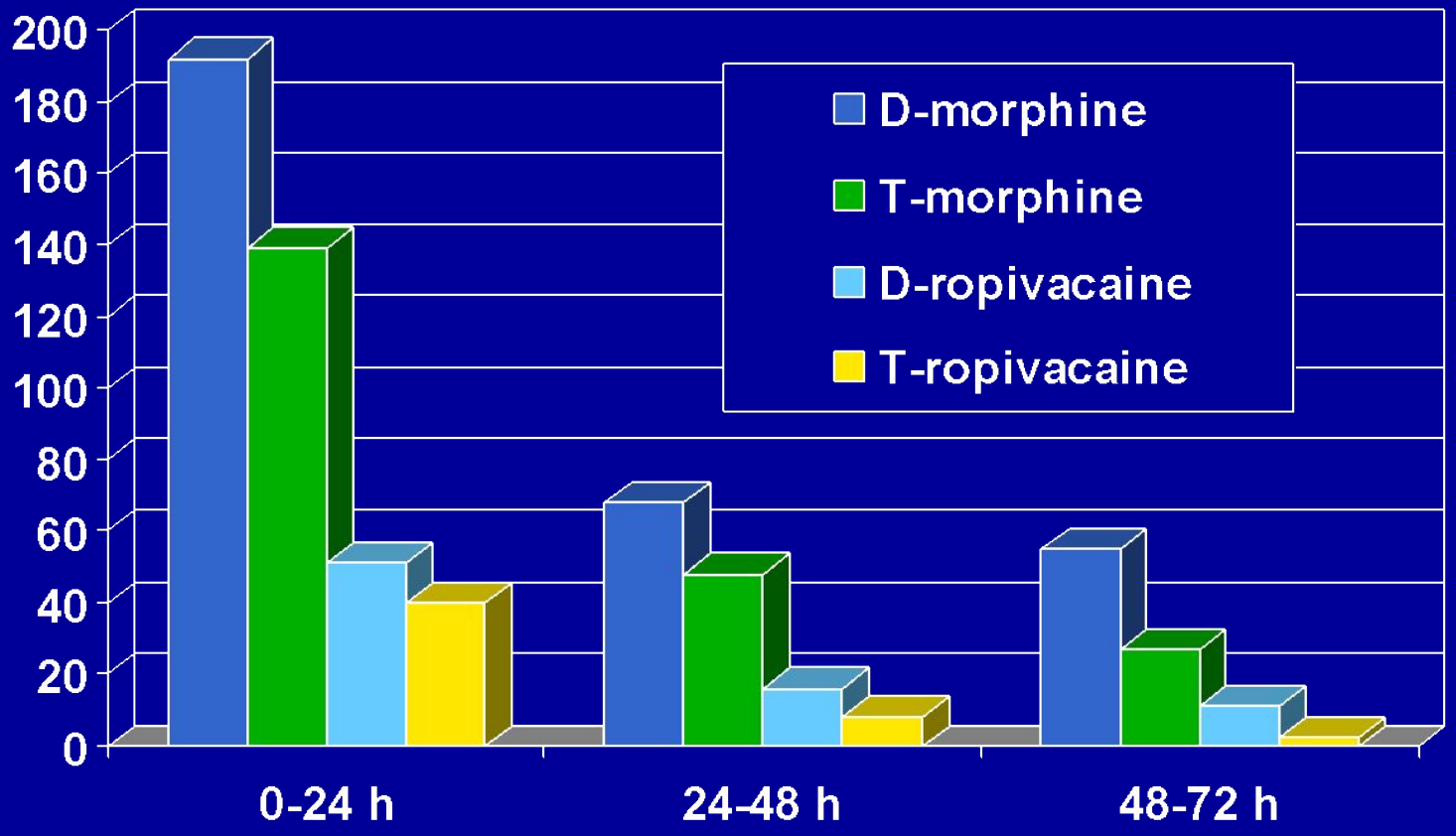
VAS during Passive Mobilization after Spine Surgery

Bianconi. Anesth Analg 2004;98:166



Diclofenac (mg, im) & Tramadol (mg, iv) Rescue after Spine Surgery

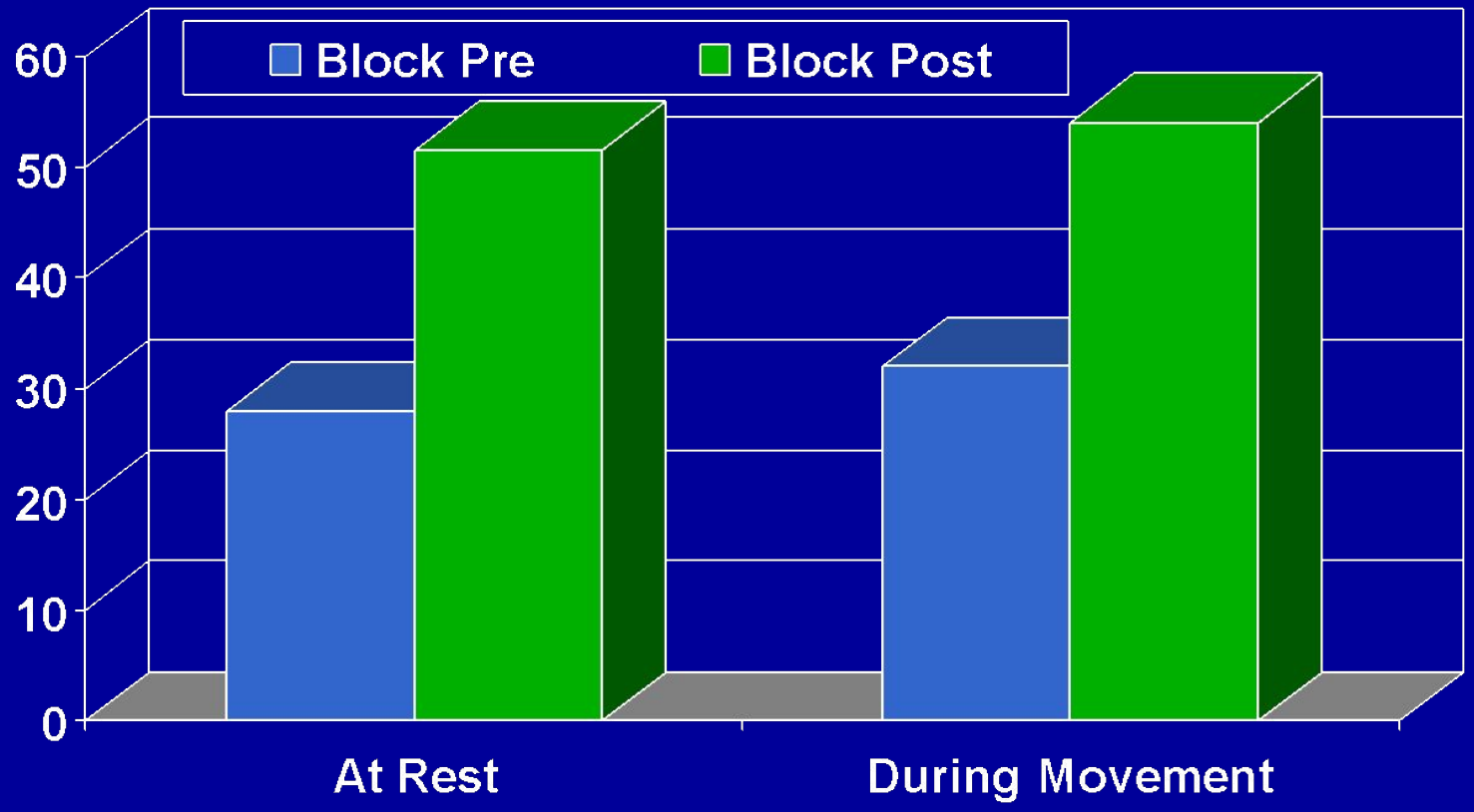
Bianconi. Anesth Analg 2004;98:166



Maximum Pain Scores after Elective Shoulder Surgery

Wurm. ANESTH ANALG 2003;97:1620

Pre- vs Postop Interscalene Block



REGIONAL ANALGESIA initiated during surgery DECREASES OPIOID DEMAND after inpatient surgery

- Wang. A-135
- Capdevila. *Anesthesiology* 1999; 91: 8-15
  - TKR, epidural *vs* femoral nerve block *vs* PCA
- Borgeat. *Anesthesiology* 1999; 92: 102-8
  - Shoulder, Patient controlled iv *vs* interscalene
- Stevens. *Anesthesiology* 2000; 93: 115-21
  - THR, lumbar plexus block

LIMIT SPINAL CORD WIND-UP

- NMDA antagonists
  - Magnesium
  - Ketamine
- NSAIDS
- Local anesthetics iv

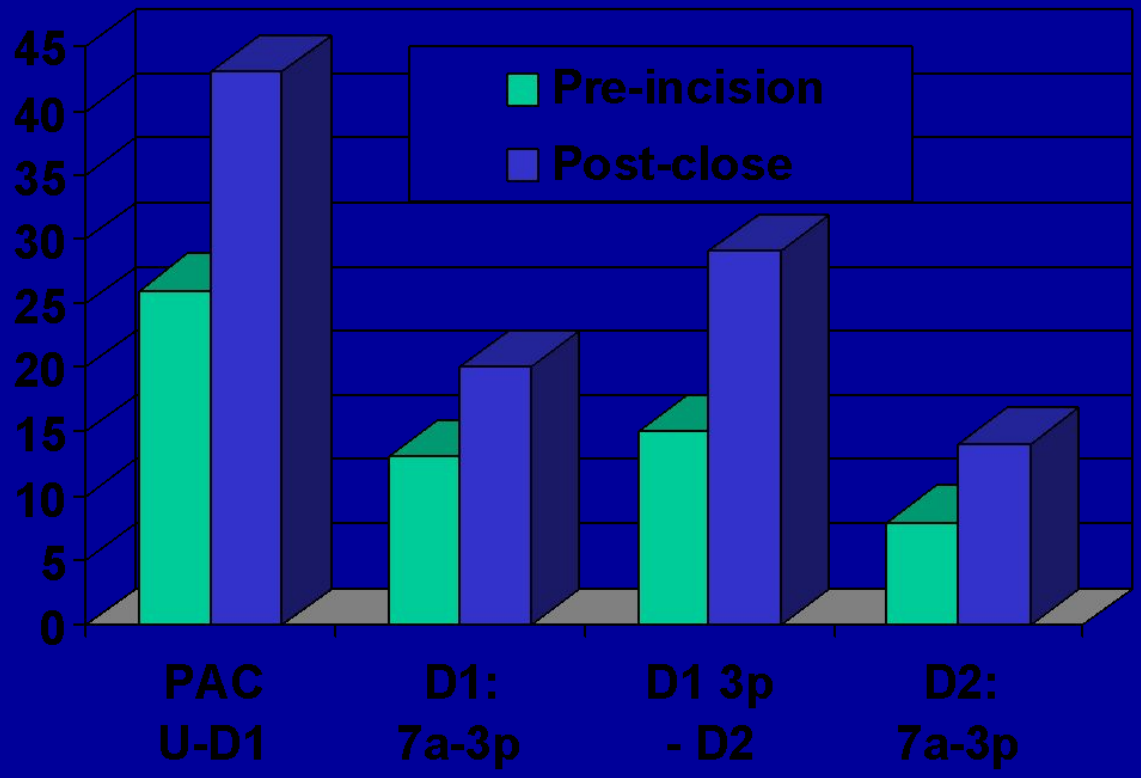
Ketamine: Pre-incision vs. Pre-emergence

Fu. Anesth Analg 1997; 84:1086

- Ketamine administration
  - Pre-incision group
    - 0.5 mg/kg bolus before incision + 10 ug/kg/min infusion until abdominal closure = **164 +/- 88 mg over 141 +/- 75 min**
  - Pre-emergence group
    - none until abdominal closure, then 0.5 mg/kg bolus = **41 +/- 9 mg**

Ketamine: Pre-incision vs. Pre-emergence Effect on Morphine (mg) Administered

Fu. Anesth Analg 1997; 84:1086

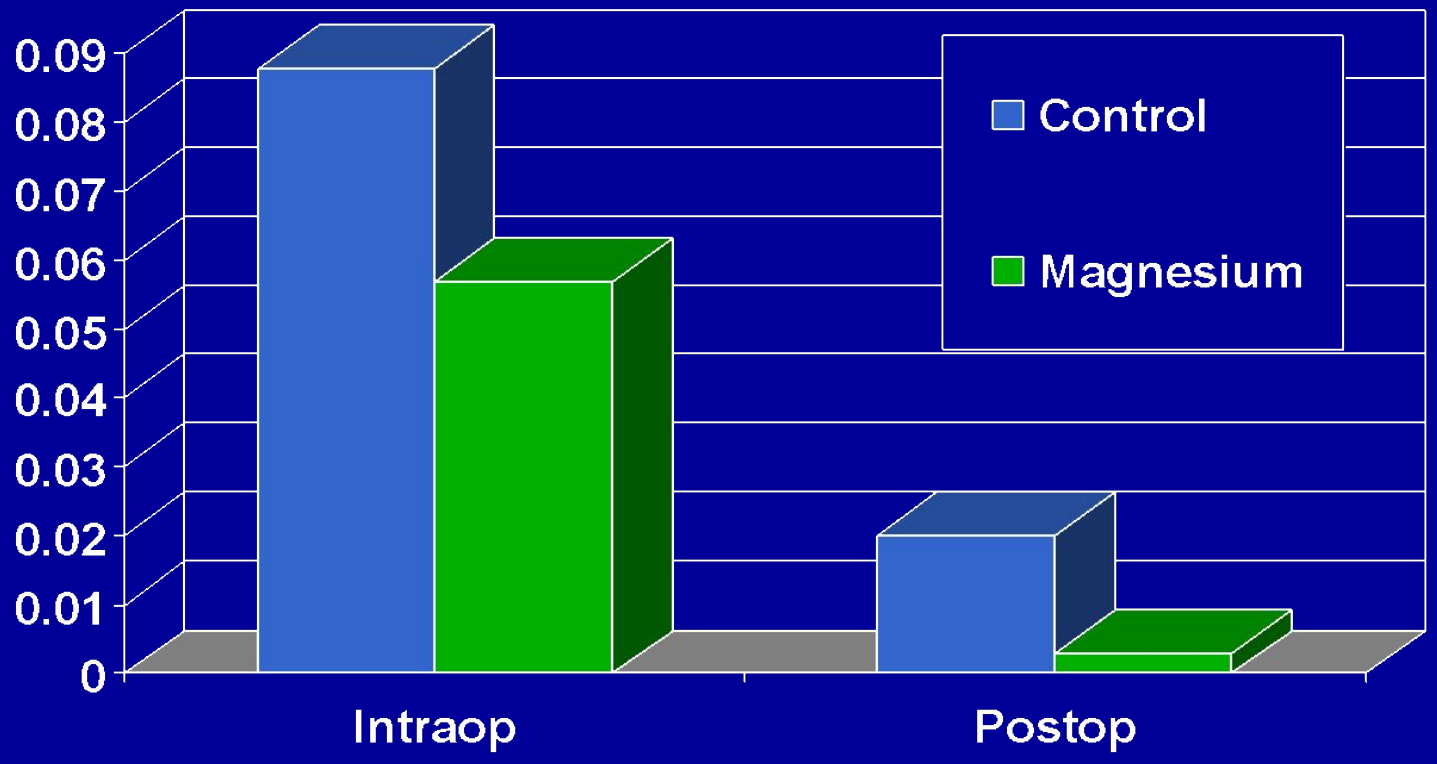


Intraoperative $MgSO_4$ Reduces Fentanyl Requirements During and After Knee Arthroscopy

- **Konig. Anesth Analg 1998; 87:206**
- **$MgSO_4$ administration**
  - Magnesium group
    - 50 mg/kg pre-incision +7 mg/kg/h
  - No magnesium group
    - Saline - same volume as in Mg group

Effect of $MgSO_4$ on Fentanyl Administration (µg/kg/min)

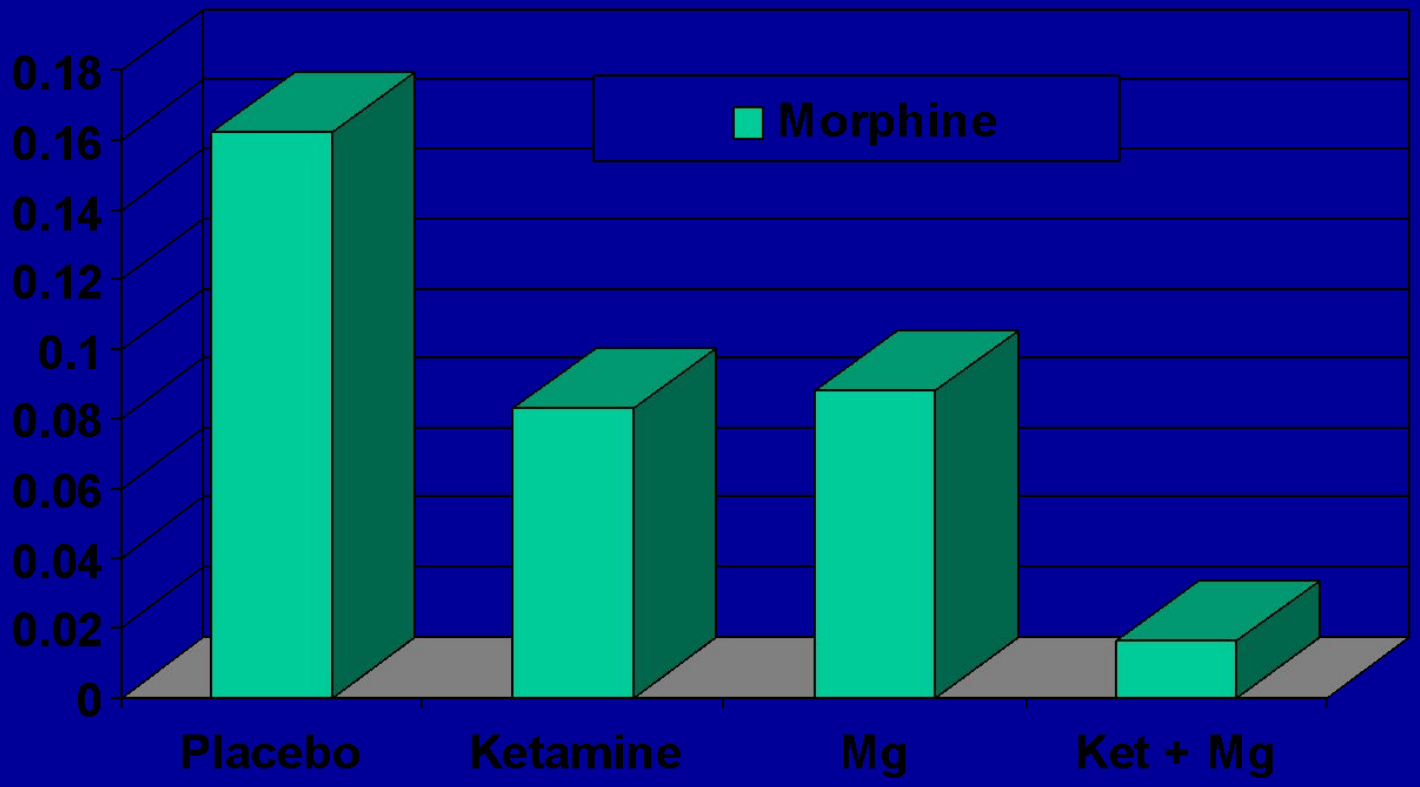
Konig. Anesth Analg 1998;87:206



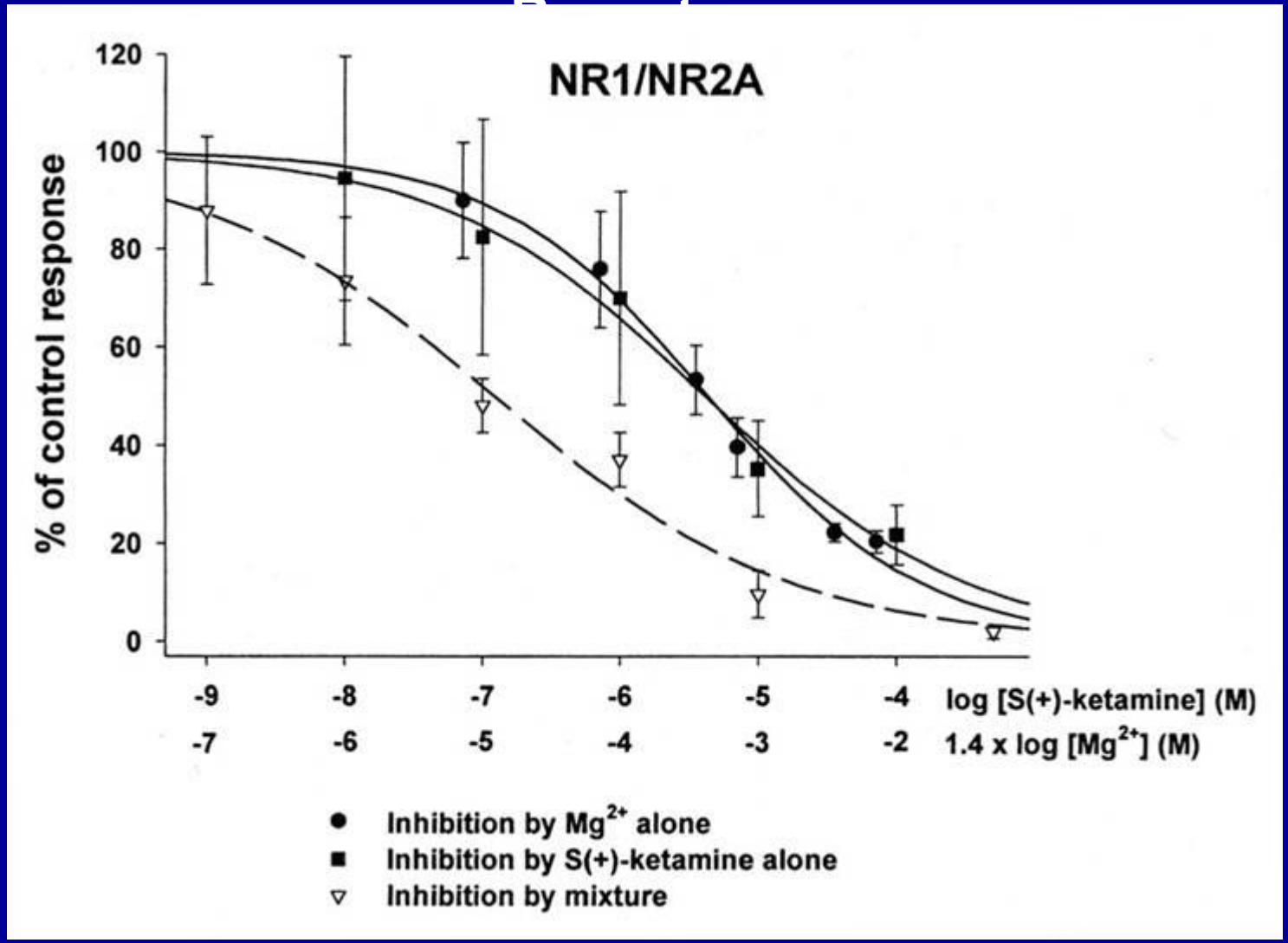
$MgSO_4$ 30 mg/kg + Ketamine 0.15 mg/kg Gynecologic Surgery

Lo. Anesthesiology 1998; 89:A1163

Morphine (mg/kg/1st 2 hrs postop)



Liu. Anesth Analg 2001;92:1173
Super-additive Interactions between Ketamine and Mg^{2+} at NMDA



NMDA ANTAGONISTS - MAGNESIUM

- O'Flaherty, *et al.* A-1265
  - Pain after tonsillectomy, 40 patients 3-12 yrs
  - Monitored fentanyl dose (mcg/kg) in PACU
  - Mg 0.20 *vs* 0.91, P=0.009
  - Ketamine 0.43 *vs* 0.91, P=0.666
  - Combination - no synergism

NEUROMUSCULAR BLOCKADE & Mg^{2+}

- Fuchs-Buder. Br J Anaesth 1995; 74:405
  - Mg^{2+} 40 mg/kg
  - Reduces vecuronium ED_{50} 25%
  - Shortens onset time 50%
  - Increases recovery time 100%
- Fawcett. B J Anaesth 2003; 91:435
  - Mg^{2+} 2 gms in PACU (for dysrhythmia) 30 min after reversal of cisatracurium produced recurarization and need to reintubate.

NMDA ANTAGONISTS - METHADONE

- **Byas-Smith, *et al.* Methadone produces greater reduction than fentanyl in post-operative morphine requirements, pain intensity for patients undergoing laparotomy. A- 848**

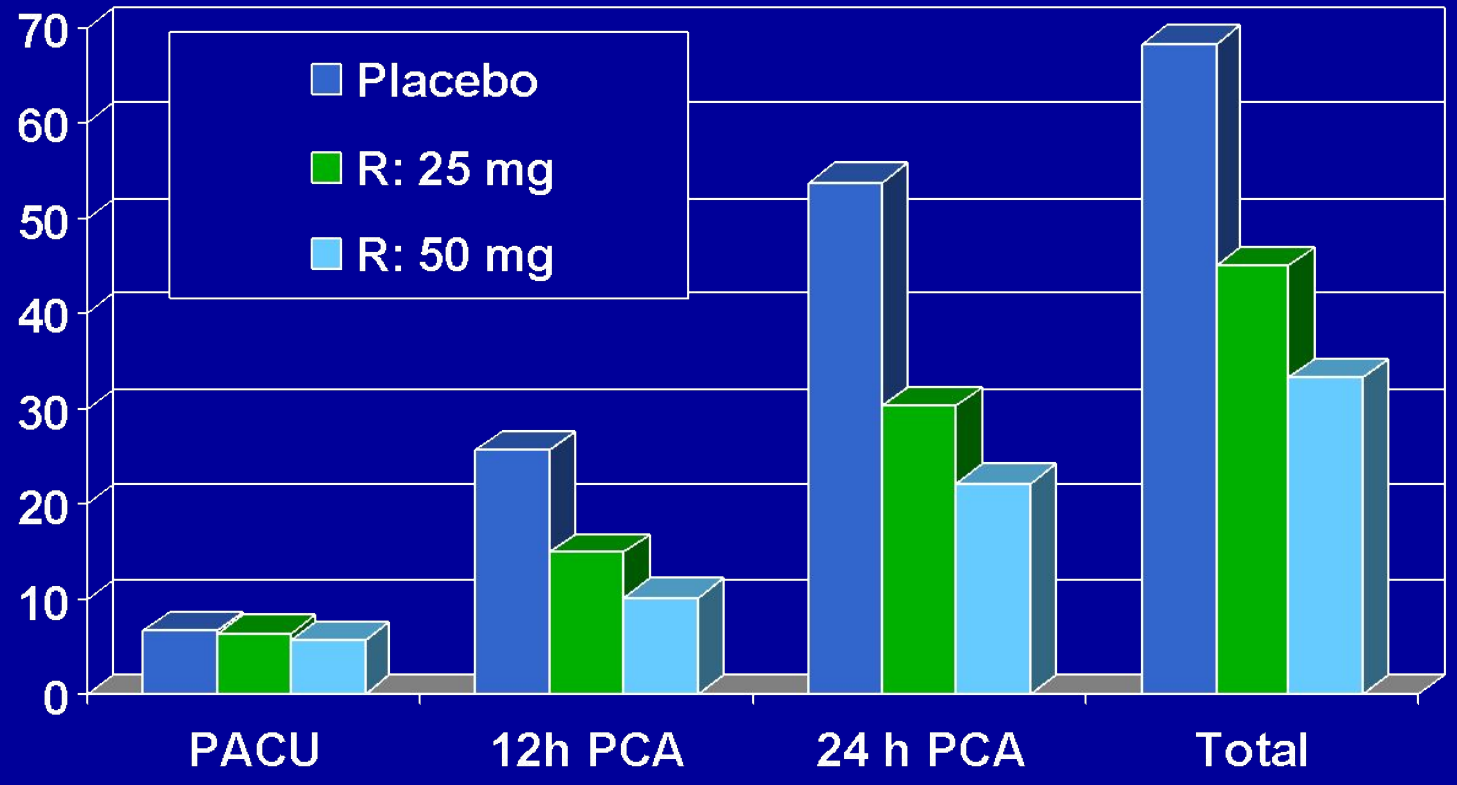
PREOPERATIVE ADMINISTRATION OF ORAL NSAIDS DECREASES POSTOPERATIVE ANALGESIC DEMANDS

- **Sinatra. Anesth Analg 2004; 98:135**
  - Preoperative Rofecoxib Oral Suspension as an Analgesic Adjunct after Lower Abdominal Surgery
- **Buvendendran. JAMA 2003; 290:2411**
  - Effects of Peroperative Administration of Selective Cyclooxygenase Inhibitor on Pain Management after Knee Replacement

Preoperative Rofecoxib Oral Suspension as an Analgesic after Lower Abdominal Surgery

Sinatra. Anesth Analg 2004; 98:135

Postoperative Morphine (mg)



Buvendendran. JAMA 2003;290:2411

- Anesthesia for TKR
  - Epidural bupivacaine/fentanyl + propofol
- “Traditional analgesia” (VAS < 4)
  - Basal epidural + PCEA bupivacaine/fentanyl x 36-42 h
  - Hydrocodone 5 mg p.o. q 4-6 h thereafter
- Rofecoxib
  - 50 mg 24 h and 6 h preop, daily postop x 5 d
  - 25 mg daily PODs 6-14

Buvendendran. JAMA 2003;290:2411

- Rofecoxib group (vs placebo)
  - Less opioid asked for – PCEA and oral
  - Fewer opioid side effects
    - Nausea, vomiting, antiemetic use,
  - Lower VAS pain scores
  - Less sleep disturbance postop nights 1-3
  - Greater range of motion
    - At discharge and at 1 month
  - Greater patient satisfaction

IV LIDOCAINE - 1

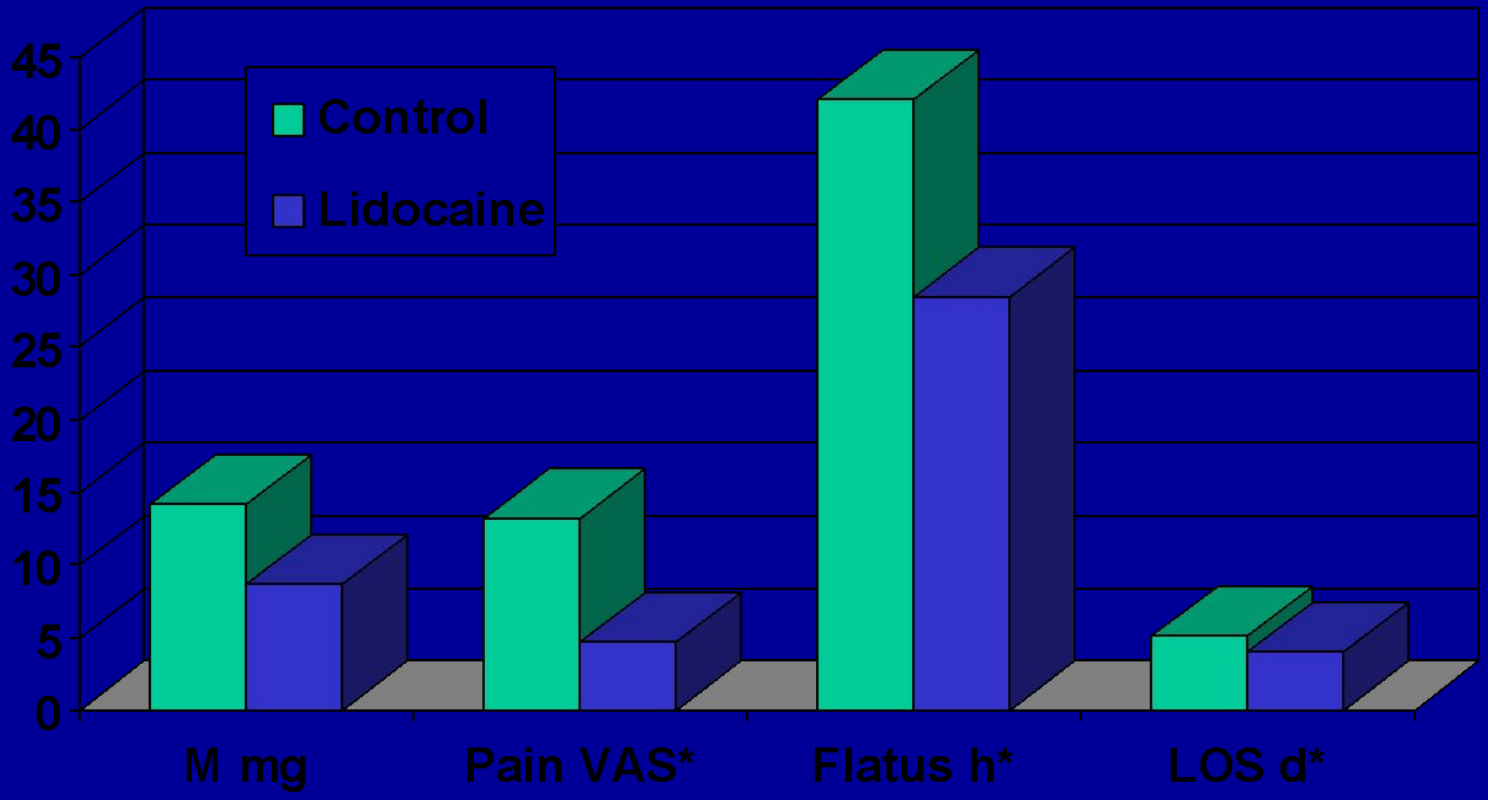
- **Groudine. Anesth Analg 1998; 86:235-9**
  - Radical retropubic prostatectomy, 64-yr-olds
  - Isoflurane-N2O-opioid anesthesia
  - **Lidocaine: none vs bolus (1.5 mg/kg) + infusion (3 mg/kg) throughout surgery & PACU**
  - Ketorolac: 15 mg iv q 6 h starting in PACU
  - Morphine for “breakthrough” pain

IV LIDOCAINE - 2

- **Groudine. Anesth Analg 1998; 86:235-9**
  - Postoperative advantages
    - Lower VAS pain scores
    - Less morphine
    - Faster return of bowel function
    - Shorter length of stay

Lidocaine (intraop) + Ketorolac (postop)

Groudine. Anesth Analg 1998; 86:235



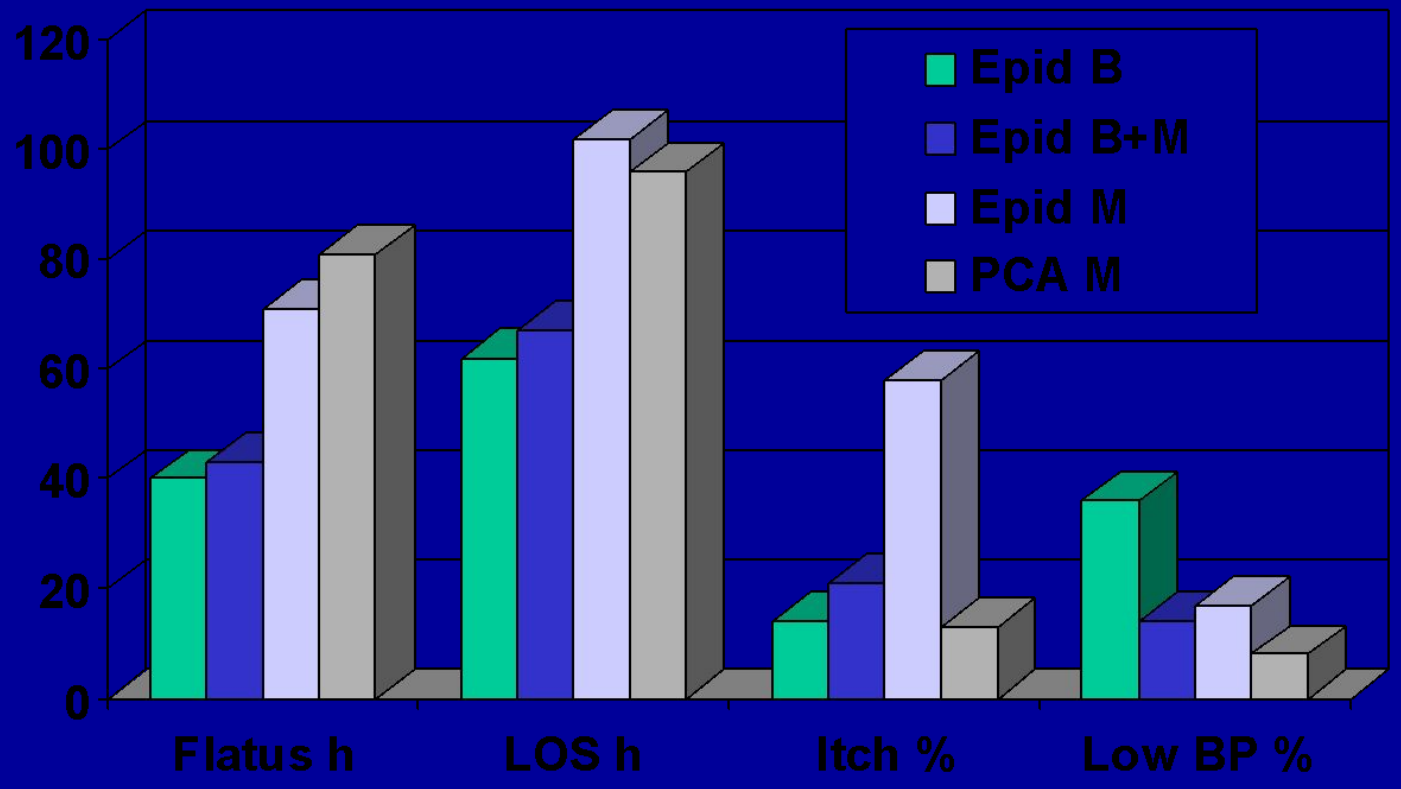
IV LIDOCAINE - 3

- **Koppert. Anesthesiology 2000;93:A855**
  - Abdominal surgery
  - Lidocaine: none vs 1.5 mg/kg/hr surgery/PACU
  - **Total morphine (P < 0.05)**
    - **146 mg (none) vs 103 mg (lidocaine)**
  - Nausea: less in lidocaine group
  - 1st BM: no difference

Epidural Analgesia after Partial Colectomy

Liu. Anesthesiology 1995; 83:757

What if [iv-lidocaine ± ketorolac + PCA-morphine] group?



β-ADRENERGIC RECEPTOR ANTAGONISTS REDUCE POSTOPERATIVE OPIOID REQUIREMENTS

- Zaugg. Anesthesiology 1999; 91:1674
- White. Anesth Analg 2003; 97:1633

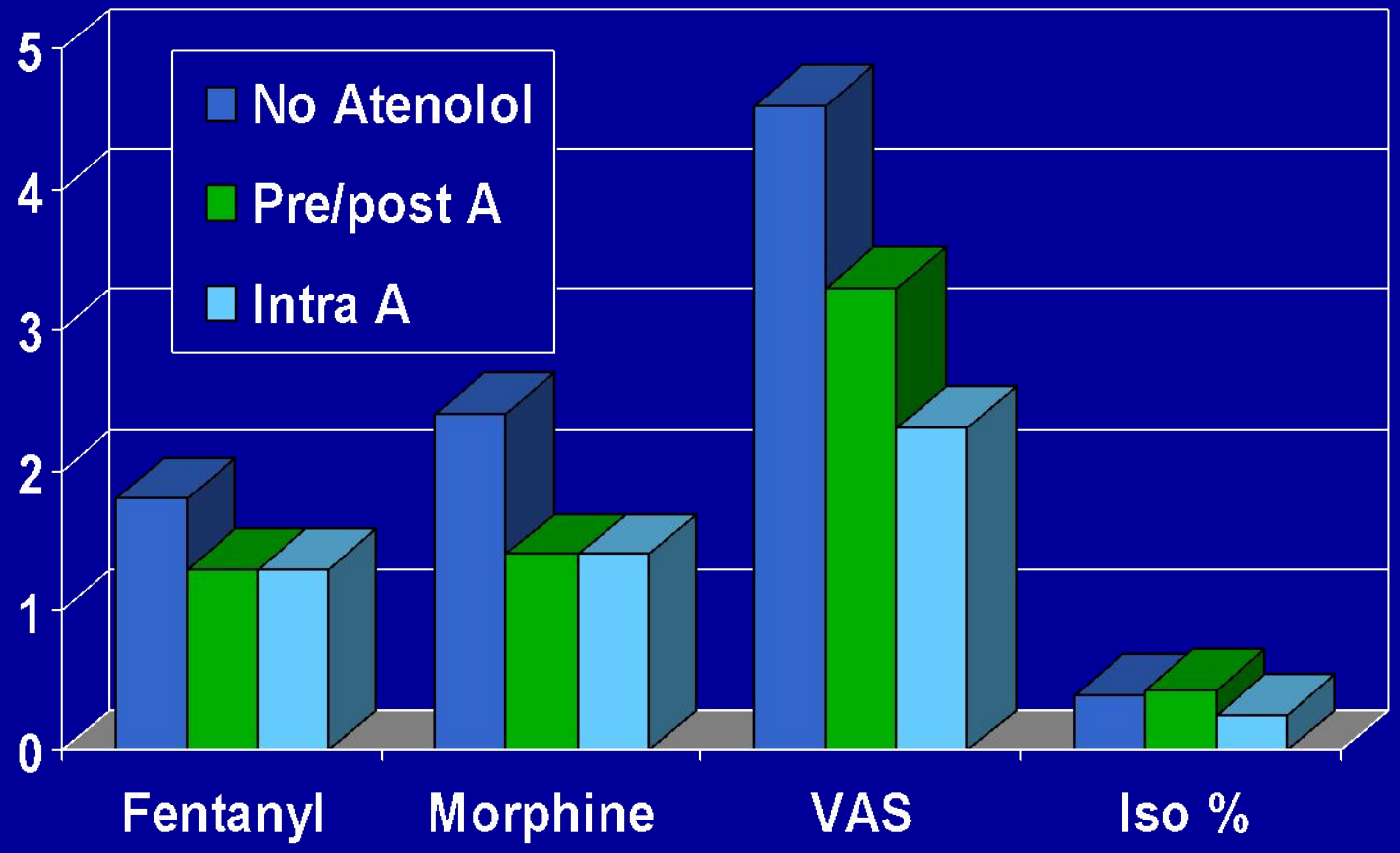
β-BLOCKERS REDUCE MORPHINE ADMINISTRATION

Zaugg. Anesthesiology 1999;91:1674

- **75-yr-olds, major abdominal surgery**
- **Fentanyl-isoflurane anesthesia**
- **Atenolol administration (iv)**
  - Group 1: **none**
  - Group 2: 10 mg **preop** + 10 mg **PACU** if HR > 55 bpm, SBP > 100 mmHg; none intraop
  - Group 3: 5 mg increments q 5 min for HR > 80 bpm, **intraop** only
    - limited fentanyl 2 μg/kg/h, isoflurane 0.4%

Atenolol Reduces Fentanyl (µg/kg/h) Intraop & Morphine (mg) in PACU

Zaugg. Anesthesiology 1999; 91:1674



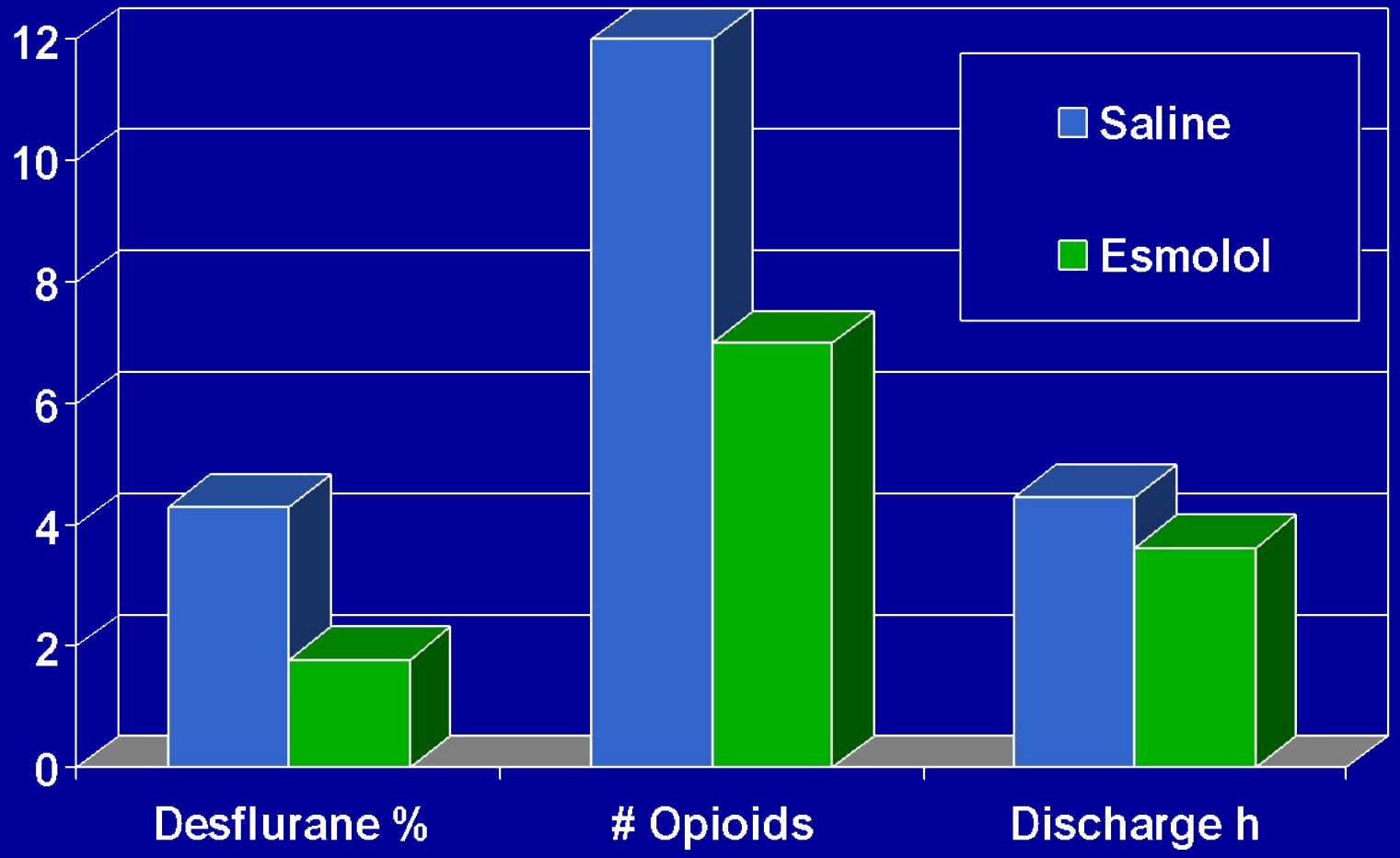
Esmolol Infusion Intraop Reduces # of Patients Requiring Analgesia

White. Anesth Analg 2003;97:1633

- Gyn laparoscopy
  - Induction: midazolam 2 mg, fentanyl 1.5 µg/kg, propofol 2 mg/kg
  - Maintenance: desflurane-N_2O (67%), vecuronium
- Esmolol
  - None vs 50 mg + 5 µg/kg/min (92 ± 97 mg)

Esmolol Reduces Anesthetic Requirements, Need for Postop Analgesia, & LOS

White. Anesth Analg 2003;97:1633



DOES MUSIC AFFECT ANESTHESIA OR POSTOPERATIVE ANALGESIA?

- Fentanyl (HR, BP), isoflurane (BIS 50)
- **Yes**
  - Hemispheric synchronization, Δ 15 dec
  - Bariatric surgery, ⅓ less fentanyl intraop
    - Lewis. Anesth Analg 2004; 98:533-6

DOES MUSIC AFFECT ANESTHESIA OR POSTOPERATIVE ANALGESIA?

- **No (patient-selected CD or Hemi-Sync)**
  - Lumbar laminectomy (Hemi-Sync)
    - Lewis. Anesth Analg 2004; 98:533-6
  - TAH-BSO (catechols, cortisol, ACTH)
    - Migneault. Anesth Analg 2004; 98:527-32

SUMMARY

- Considerable research activity addressing
  - Basic - new pain mechanisms
  - Translational - new drugs based on these mechanisms
  - Clinical – new applications for newer & older drugs
- Keeping up with current literature can change your practice!
- Small doses make big differences

WHAT DO I DO DIFFERENTLY?

If general anesthesia and not regional or combined regional-general, I use:

- Lopressor, labetalol aggressively
- Ketamine – 10 mg pre-incision, 5-10 mg q1h
- $MgSO_4$ – 2 gm pre-incision, 0.5 gm q1h
- Lidocaine – 100 mg load, 2 mg/min/OR
- Less inhaled agent (BIS 50-60), less fentanyl, more morphine intraop
- [COX-2 preoperatively]

WOUND INFILTRATION VS. SYSTEMIC LOCAL ANESTHETICS

- **EMLA CREAM -> DECREASED POSTOPERATIVE PAIN**
  - **Fassoulaki, *et al.* EMLA reduces acute and chronic pain after breast surgery for cancer. *Reg Anesth Pain Med* 2000; 25: 350-5**
  - **Hollmann & Durieux. Prolonged actions of short-acting drugs: local anesthetics and chronic pain. *Reg Anesth Pain Med* 2000; 25: 337-9 [editorial]**

α-ADRENERGIC RECEPTOR AGONISTS REDUCE POSTOPERATIVE OPIOID REQUIREMENTS

- Locus ceruleus (sedation)
- Dorsal horn (analgesia)
- Arain. Anesth Analg 2004; 98:153 – 30 min before end of surgery:
  - Dexmedetomidine: 1 μg/kg over 10 min + 0.4 μg/kg/h for 4 h OR
  - Morphine: 0.08 mg/kg

Effect of Dexmedetomidine on Total PACU Morphine (mg) Administration

Arain. Anesth Analg 2004;98:153