



Groupe francophone de Réhabilitation
Améliorée après Chirurgie

NSAIDs and steroids intraoperatively: more than analgesic?

Jean Joris



Department of Anesthesiology
CHU Liège, University of Liège,
Belgium





1. Nonsteroidal antiinflammatory drugs

Analgesic properties of NSAIDs

Table 1 Pairwise comparisons for primary morphine-related outcomes. The first treatment is the intervention and the second is the control. A negative mean difference indicates that the intervention was more effective than the control treatment. An OR < 1 indicates that the intervention has performed better than the control. *Adjusted for baseline morphine consumption

Comparison	Morphine consumption, unadjusted, mean difference, mg (95% CrI)	Morphine consumption, adjusted,* mean difference, mg (95% CrI)	Nausea and PONV, pairwise OR (95% CrI)	Sedation, pairwise OR (95% CrI)
Paracetamol vs placebo	-6.34 (-9.02, -3.65)	-8.68 (-11.43, -5.94)	1.00 (0.60, 1.53)	1.62 (0.32, 5.02)
NSAID vs placebo	-10.18 (-11.65, -8.72)	-9.45 (-10.90, -8.01)	0.70 (0.53, 0.88)	0.53 (0.20, 1.01)
COX-2 vs placebo	-10.92 (-12.77, -9.08)	-10.67 (-12.42, -8.94)	0.88 (0.61, 1.25)	0.63 (0.18, 1.49)
NSAID vs paracetamol	-3.85 (-6.80, -0.89)	-0.77 (-3.75, 2.21)	0.74 (0.44, 1.17)	0.51 (0.08, 1.63)
COX-2 vs paracetamol	-4.58 (-7.83, -1.35)	-1.99 (-5.24, 1.24)	0.93 (0.51, 1.63)	0.63 (0.07, 2.33)
COX-2 vs NSAID	-0.74 (-3.03, 1.56)	-1.22 (-3.43, 1.00)	1.28 (0.81, 1.97)	1.40 (0.30, 4.31)
Number of arms; residual deviance	116; 186	116; 114	86; 97	31; 41

- NSAIDs reduce:
 - Opioid consumption
 - Opioid-induced side effects (PONV, ileus)
 - Pain scores (at rest and on movement)

Dahl J. and Kehlet H., BJA 1991
 Marret E. et al., Anesthesiology 2005
 Elia N. et al., Anesthesiology 2005
 Maund E. et al., BJA 2011

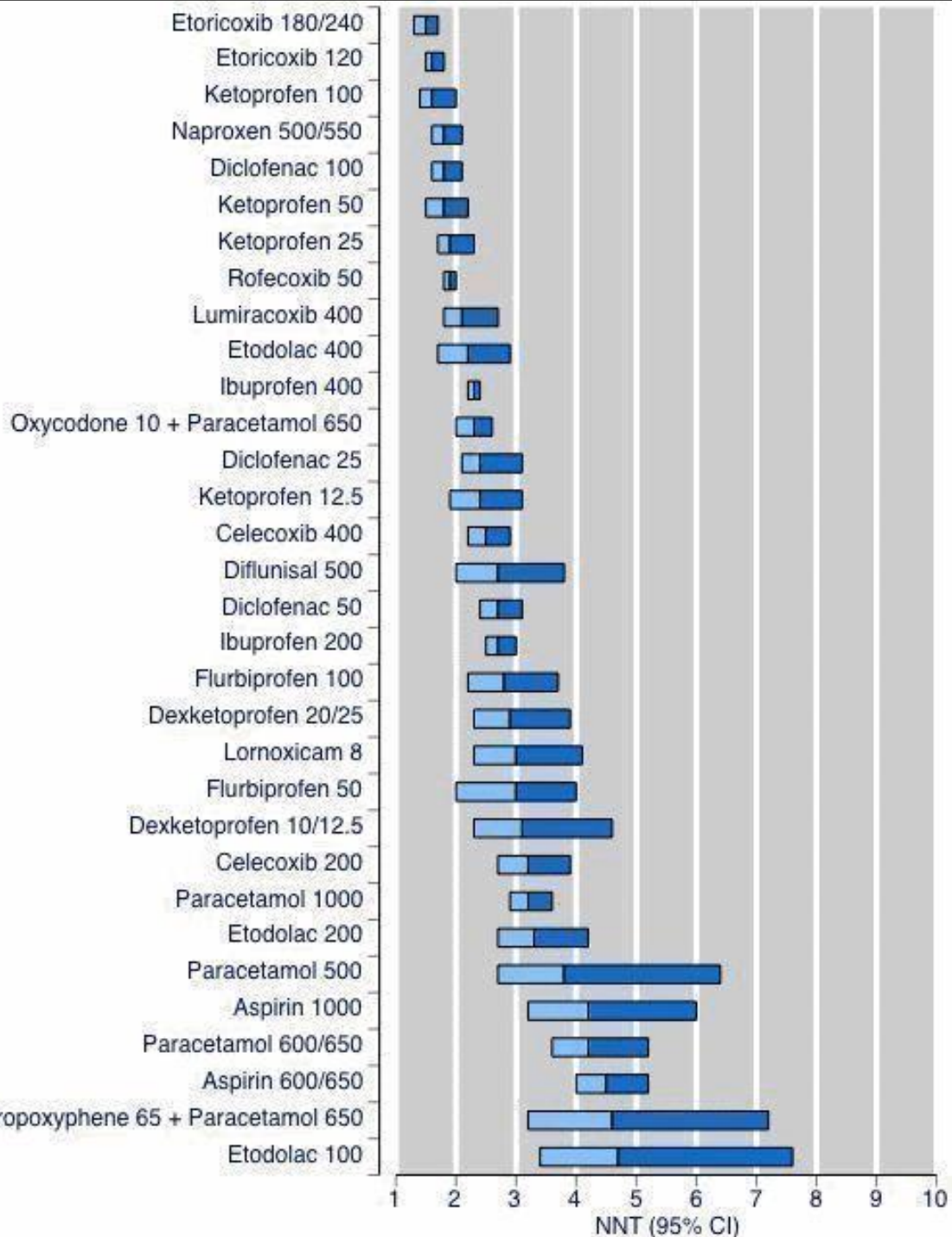
NSAIDs : not all the same?

AINS	analgésie	anti-inflammatoire	antipyrétique
kétorolac	0.7	2	0.9
indométhacine	3	4	2.1
diclofenac	8	7	0.4
naproxène	13	56	0.5
ibuprofen	45	10	7
piroxicam	100	3	1.7
tenoxicam	100	5	1.7
aspirine	228	162	18

ED50 = mg/kg

Greyn J. et al., Acta Anaesth Belg 1998

NSAID: different efficacy!!



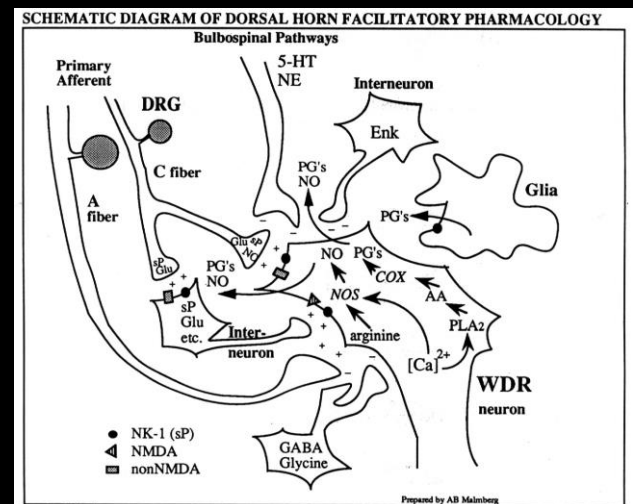
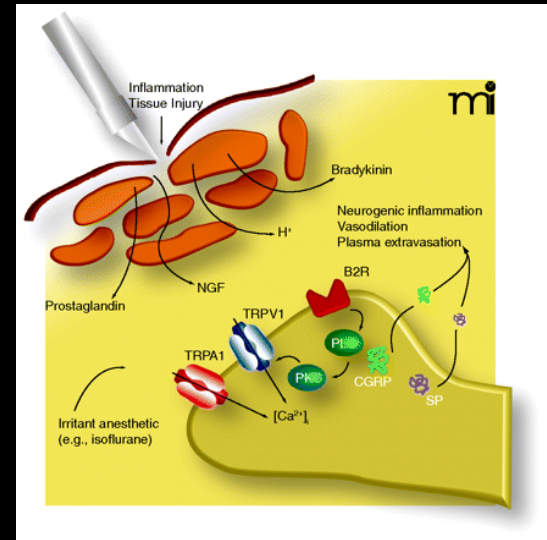
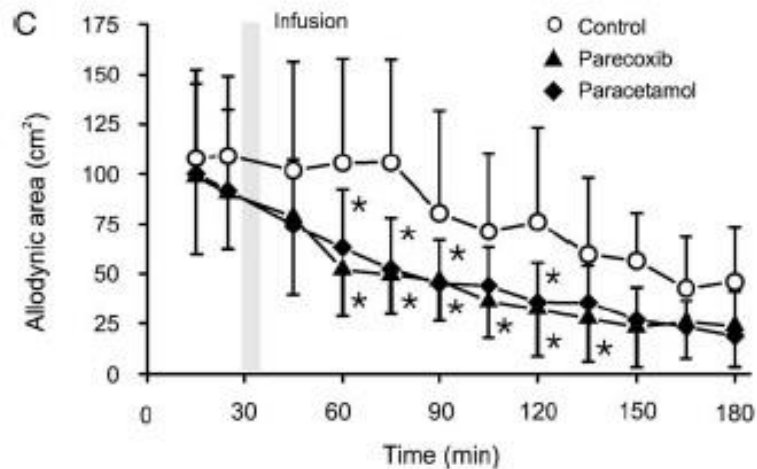
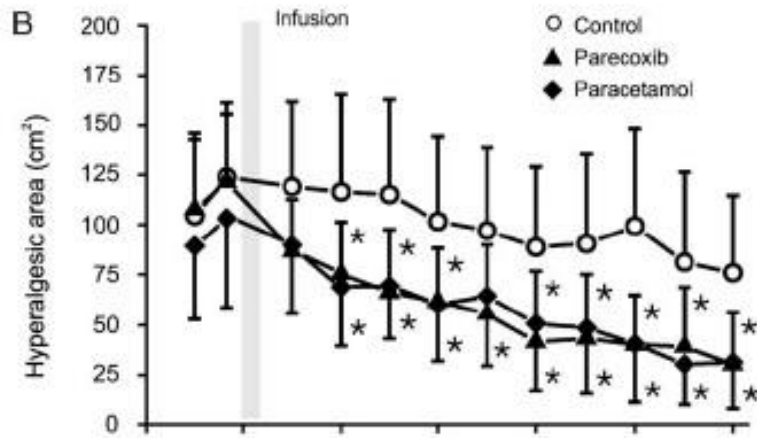
Single dose oral analgesics for acute postoperative pain in adults.

Moore, Andrew R; Derry, Sheena; McQuay, Henry J; Wiffen, Philip J

Cochrane Database of Systematic Reviews. Issue 9, 2011.

Figure : Dental pain: NNT for at least 50% maximum pain relief over four to six hours compared with placebo, by rank order.

Anti-hyperalgesic action of NSAID



Side effects of NSAIDs !

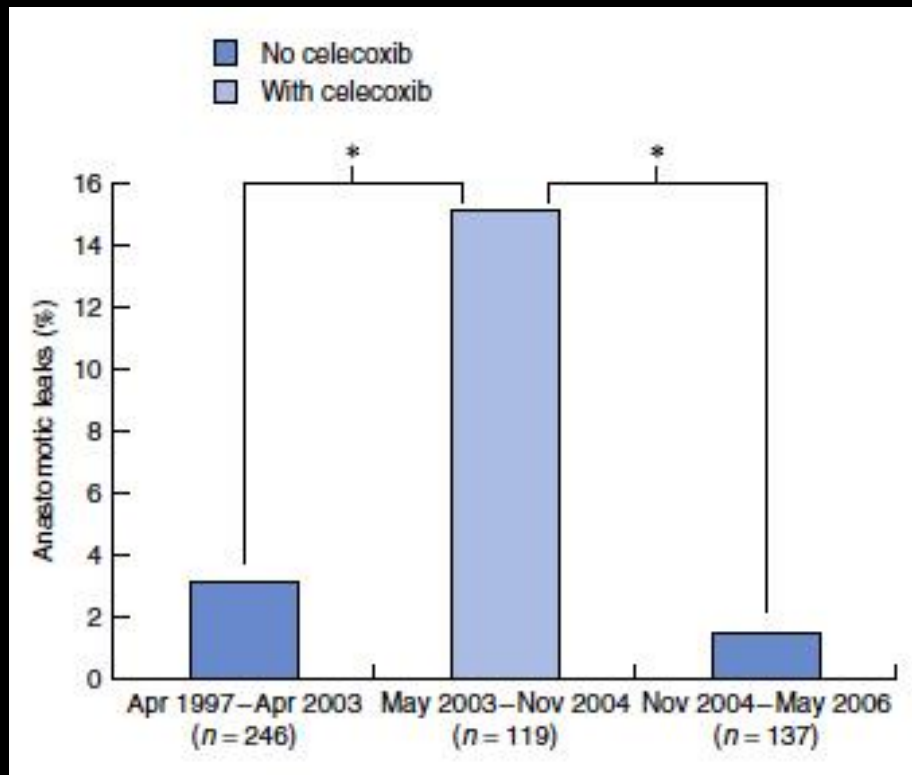
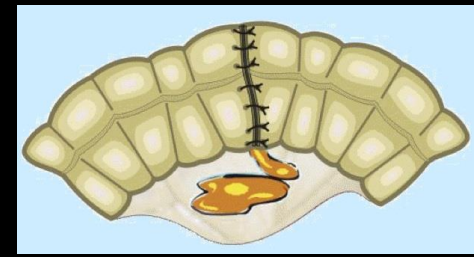
- Very low incidence of the « usual » side effects of postoperative NSAID in case of short duration administration. Forrest J. et al., BJA 2003
- Risk of cardiovascular side effects!
Fosbol E. et al., Clin Pharm Ther 2009; CNT collaboration, Lancet 2013
 - COXIB ~ diclofenac (5-10 fold COX-2 selective!)
 - Reduced risk with naproxen and ibuprofen (≤ 1200 mg/day)
 - But, reduction of postoperative myocardial infarction with ketorolac ! Beatie W. et al., AA 1997, Engoren M. et al., Ann Thor Surg 2011

NSAIDs and interference with inflammation !



- Inflammation necessary for healing processes.
 - Risk of GI anastomotic leakage ?
 - Risks of pseudarthrosis, fracture non-union ?
- Inflammation can have deleterious effects:
 - Reduction of postoperative cancer recurrence?
 - Prevention of postoperative peritoneal adhesions.
Arung W. et al., World J Gastroenterol 2011; J Invest Surg 2013
 - Reduction of peritoneal inflammation and ileus.
Grass J et al., Anesthesiology 1993, Ferraz A. et al., Am Surg 1995
 - Effects on fatigue, convalescence, cognitive dysfunction?

COXIBs and anastomotic leakage?

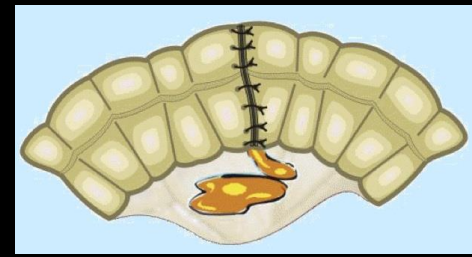


- Risk of anastomotic leakage increased with diclofenac
- Use of ibuprofen does not increase this risk
- COX-2 selective NSAIDs should be used with caution after colorectal surgery

Holte K. et al., BJS 2009

Klein M. et al., BMJ 2012

NSAIDs and anastomotic leakage?



- Use of IV ketorolac increases postoperative complications after gastrointestinal surgery
Kotagal M. et al., Ann Surg 2015
- No statistical increase in anastomotic leakage for patients undergoing elective colorectal surgery
Paulasir S. et al., DCR 2015
- Postoperative NSAID not associated with increased risk for AL among patients undergoing elective colorectal resection and *bariatric surgery*.
Hakkarainen T. et al., JAMA Surg 2015

NSAIDs and colorectal surgery !

- Recommended by ERAS and GRACE in fast track surgery protocols
- Short duration treatment : 1-2 days
- Avoid COXIB and diclofenac
- Avoid NSAID if additional:
 - Medical risk factors
 - Surgical risk factors



NSAIDs and complications after major gastro-intestinal surgery

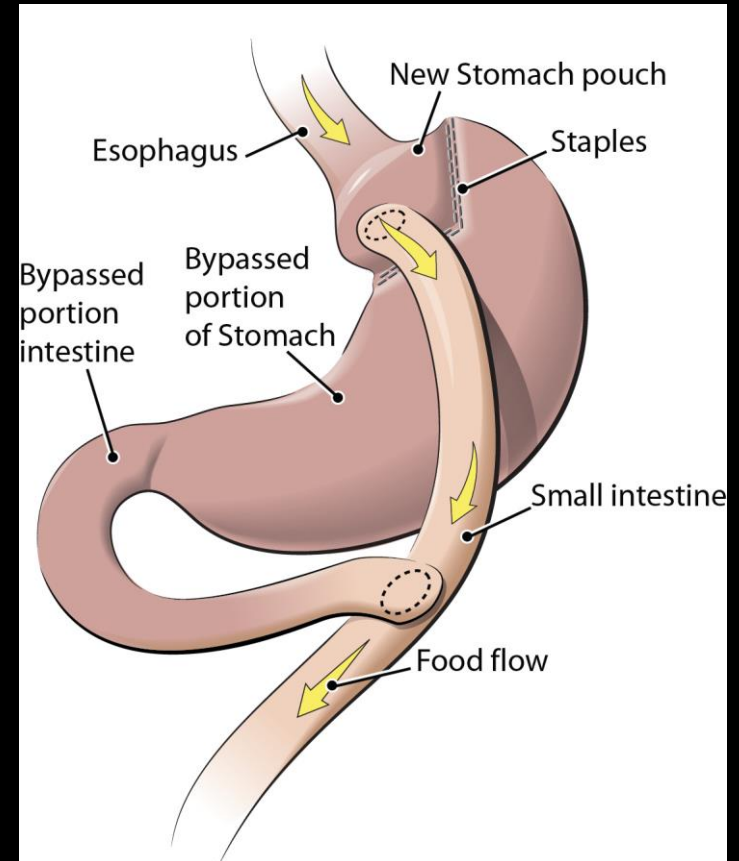
« Early use of NSAIDs is associated with a reduction in postoperative adverse events following major gastro-intestinal surgery »

STARSurge collaborative,
BJS 2014

NSAID dose	Complication type	Odds ratio	<i>P</i>
Any dose	All	0.72 (0.52, 0.99)	0.041
	Major	0.94 (0.54, 1.73)	0.817
	Minor	0.73 (0.53, 1.04)	0.057
Low dose	All	0.81 (0.53, 1.26)	0.334
	Major	0.61 (0.30, 1.66)	0.230
	Minor	0.95 (0.60, 1.49)	0.817
High dose	All	0.64 (0.42, 0.95)	0.032
	Major	1.27 (0.68, 2.72)	0.447
	Minor	0.57 (0.39, 0.89)	0.009
Any dose	Anastomotic leak	1.30 (0.61, 2.68)	0.481
	Cardiovascular event	0.71 (0.25, 4.13)	0.517
	Surgical-site infection	0.94 (0.58, 1.66)	0.792
	Intra-abdominal abscess	0.49 (0.19, 2.58)	0.200

NSAIDs and anastomotic ulcer after gastric by-pass?

- Multifactorial (Helicobacter Pylori, ischemia, technical issue, ...)
- NSAID cited as a potential risk factor.
- Avoidance of NSAID often recommended
- But never studied, nor demonstrated!
- Benefits of NSAIDs !



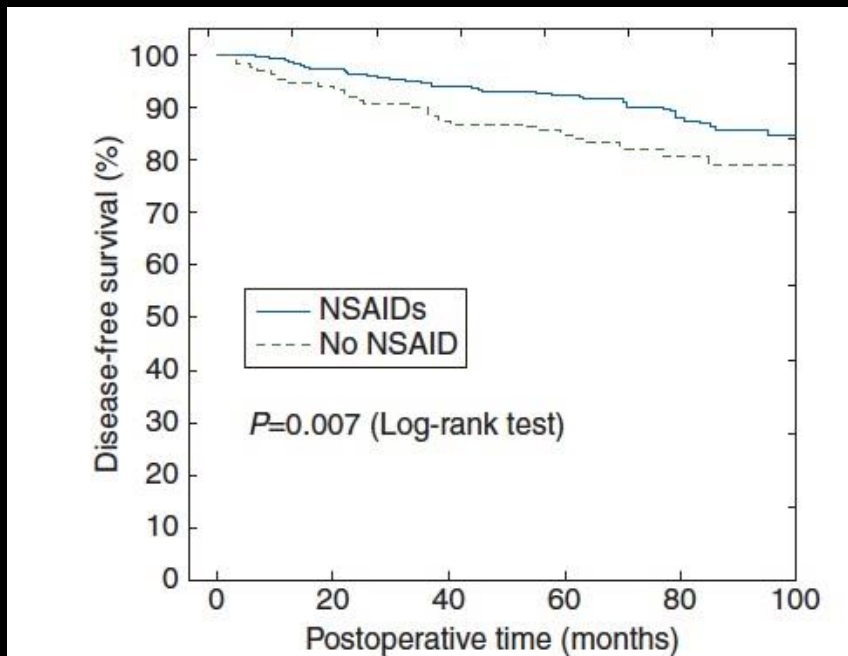
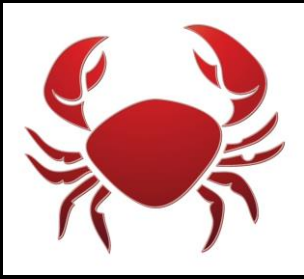
NSAIDs and bone-healing



- « Short-duration NSAID regimen is a safe and effective supplement to other modes of post-fracture pain control, without a significant increased risk of sequelae related to disrupted healing »

Dodwell ER et al., *Calcif Tissue Int* 2010; 87:193–202
Kurmis AP et al., *J Bone Joint Surg Am.* 2012;94:815-23
Su B. and O'Connor JP, *J Appl Physiol* 2013;115:892-9

NSAIDs and cancer



Forget P *et al*, *Anesth Analg*
2010, *BJA* 2014

- Reduced recurrence rate and lower mortality in breast and lung cancer patients.
- Effects more pronounced in case of high neutrophil:lymphocyte ratio. Forget P. *et al.*, *Ann Surg Oncol* 2013
- Potential mechanisms. Forget P. *et al.*, *Acta Anaesth Belg* 2013



2. Glucocorticoids

Steroids and analgesia

- Reduction in pain score at rest and at movement
- Reduction in opioid consumption
- Observed with doses of dexamethasone > 0.1 mg/kg.
Dose in obese patients?
- Benefit of pre- vs. intra-operative administration
- Magnitude of the effects: clinically significant?
- Benefits of very high doses of steroids (> 125 mg MP)!

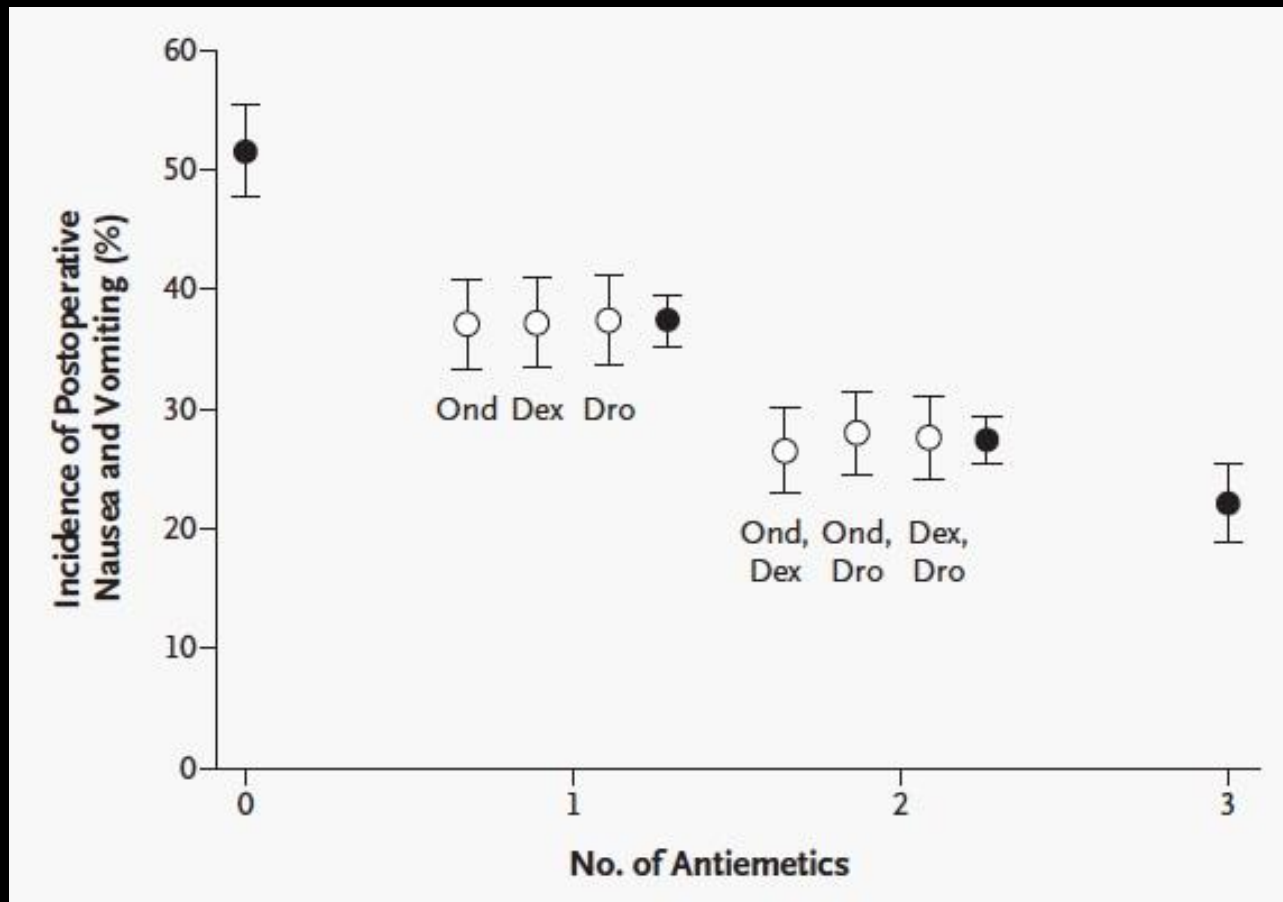
De Oliveira GS. et al., Anesthesiology 2011

Waldron NH. et al., BJA 2013

Steroids and Chronic Post Surgical Pain

- No effect of 125 mg methylprednisolone on CPSP after augmentation mammoplasty
Romundstad L. et al., Pain 2006
- No effect of doses ranging between 4-20 mg dexamethasone on post-mastectomy chronic pain
De Oliveira GS. et al, RAPM 2015

Steroids and PONV



Apfel C. et al., NEJM 2004

Steroids and PONV: dose-response

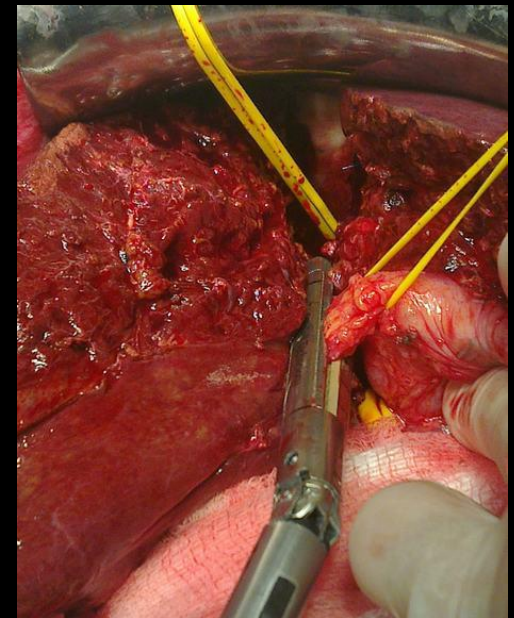
Dexamethasone to Prevent Postoperative Nausea and Vomiting: An Updated Meta-Analysis of Randomized Controlled Trials

Gildasio S. De Oliveira Jr., MD, MSCI, Lucas J. Santana Castro-Alves, MD, Shireen Ahmad, MD, Mark C. Kendall, MD, and Robert J. McCarthy, PharmD

CONCLUSIONS: Our results showed that a 4-mg to 5-mg dose of dexamethasone seems to have similar clinical effects in the reduction of PONV as the 8-mg to 10-mg dose when dexamethasone was used as a single drug or as a combination therapy. These findings support the current recommendation of the SAMBA guidelines for PONV, which favors the 4-mg to 5-mg dose regimen of systemic dexamethasone. (Anesth Analg 2013;116:58–74)

High doses GC decrease complications after major abdominal surgery

- Meta-analysis, 439 patients
- High doses GC (500 -2000 mg MP) decrease:
 - postoperative complications: OR: 0.37 [0.21-0.64]
 - LOS : -1.97 days [-3.3 to -0.61]
 - IL-6 : -55 pg/ml [82 -28]
 - postoperative fatigue
- Particularly in case of hepatectomy



Srinivasa S. et al., Ann Surg 2011

Steroids: risk-benefit ratio?



- No increased risk of surgical wound infection.
Bolac C. et al., AA 2013; Wang A. et al., Am J Surg 2013; Kurz A. et al., BJA 2015
- No association with cancer recurrence.
De Oliveira GC et al., AA 2014
- Limited effects on glycemia in non-diabetic and diabetic patients. Hans P. et al., BJA 2006; Abdelmalak BB et al., AA 2013
- No increase in bleeding after tonsillectomy in children. Shargorodski J et al., Laryngoscope 2012

Conclusions for the obese patient

■ Benefits of **NSAID**

- Reduction of opioid consumption and SE
- Anti-hyperalgesic
- Cancer recurrence?
- Not CI for bariatric surgery (anast. ulcers)
- Precautions (healing, CV)
 - Short duration (2 days)
 - Avoid COX2 selective if medical or surgical risks?

■ Benefits of **steroids**

- Prevention of PONV
- Analgesic and reduction of opioid need
- Dexamethasone 10-15 mg
- Benefit of high dose MP?
- Risk-benefit ratio
 - No risk with one dose (healing, infection)
 - Monitor glycaemia



The benefits of using NSAIDs and/or glucocorticosteroid **OUTWEIGH** potential disadvantages in most surgical patients, obese patients included !