



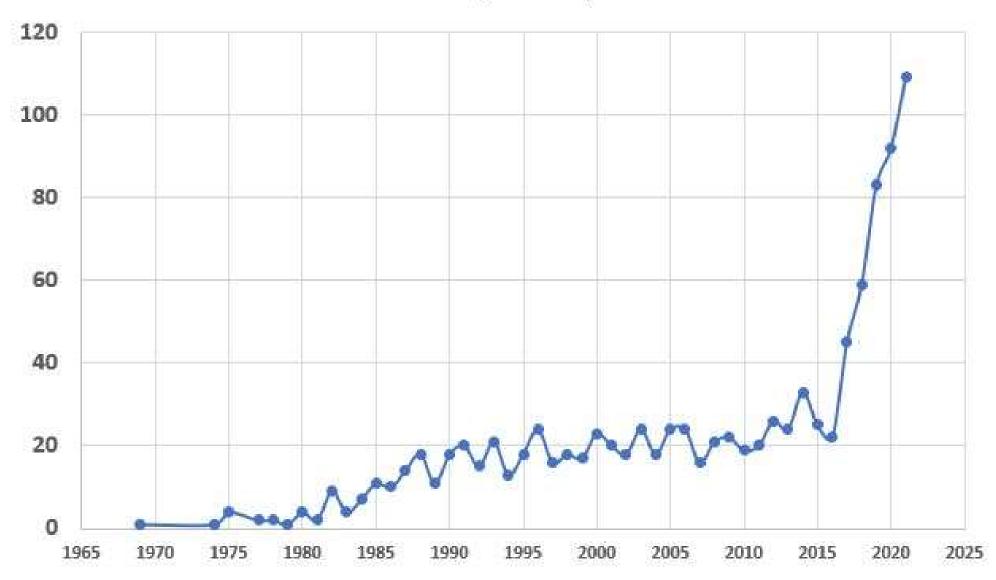
## Opioid Free Anesthesia



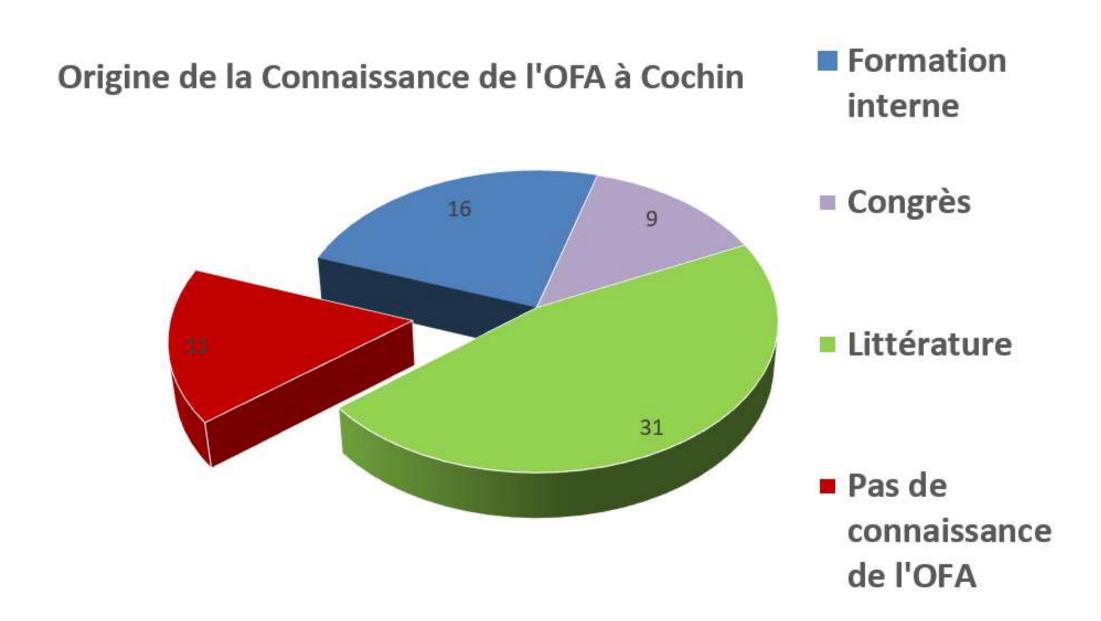
Georges Mion

Hôpital Cochin - Paris

#### OFA (pubmed)



#### Récent questionnaire OFA Cochin



Il y a 40 ans

Br. J. Anaesth. (1981), 53, 1155

### High dose fentanyl anesthesia

EFFECT OF HIGH-DOSE FENTANYL ANAESTHESIA ON THE METABOLIC AND ENDOCRINE RESPONSE TO CARDIAC SURGERY

E. S. Walsh, J. L. Paterson, J. B. A. O'Riordan and G. M. Hall

SUMMARY

The effect of high-dose fentanyl anaesthesia (75 µg kg<sup>-1</sup>) on the metabolic and endocrine responses to cardiac surgery was compared with results obtained in similar patients who had received incremental doses of papaveretum. High-dose fentanyl anaesthesia prevented the increases in blood glucose, plasma cortisol and plasma growth hormone concentrations found before cardiopulmonary bypass, but during cardiopulmonary bypass was only effective in decreasing the hyperglycaemia. The continued administration of fentanyl following operation failed to suppress the hormonal and metabolic changes so that the total urinary excretion during the first 5 days after surgery was similar in both groups of patients. High-dose fentanyl anaesthesia was associated with only transient metabolic benefits confined to the period during operation.

### 1991 Rémifentanil (OBA)

## "stress-free anesthesia"

Kehlet H. The surgical stress response: should it be prevented? Can J Surg 1991;34:565-7.

- Reduction of postoperative morbidity myocardial infarction - pulmonary infection thromboembolism
- by nociceptive blockade of global "surgical stress response"
- most effective = Regional anesthesia

# Problèmes posés par les morphiniques

- NVPO et iléus
- HIO
- Addiction (post-op ++)
- Immunité, cancer (?)
- Risques respiratoires +++

# 

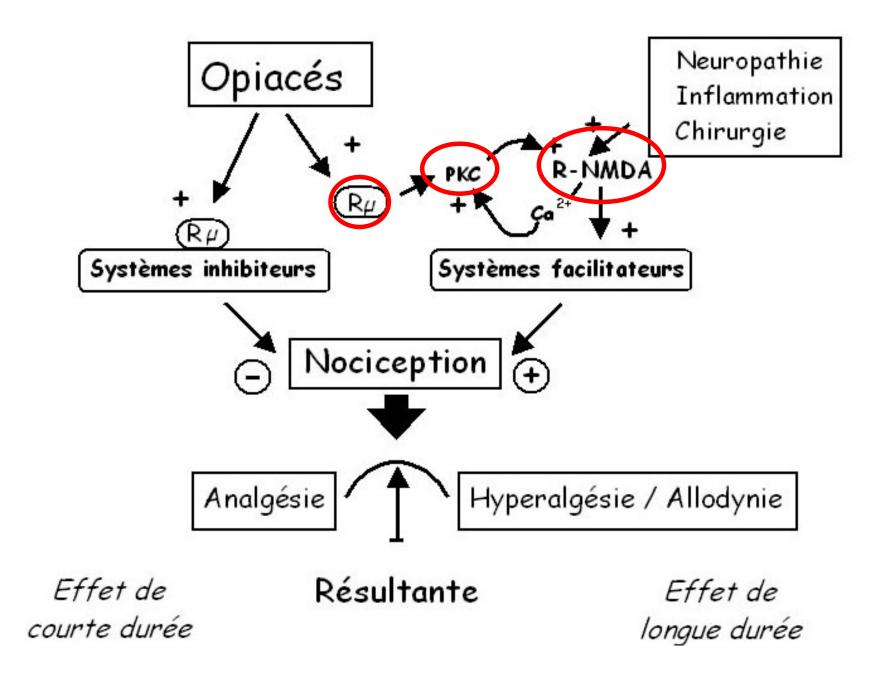
## Opioid-induced Hyperalgesia

A Qualitative Systematic Review

Martin S. Angst, M.D.,\* J. David Clark, M.D., Ph.D.†

### Hyperalgésie iatrogène (M. De Kock 2014)

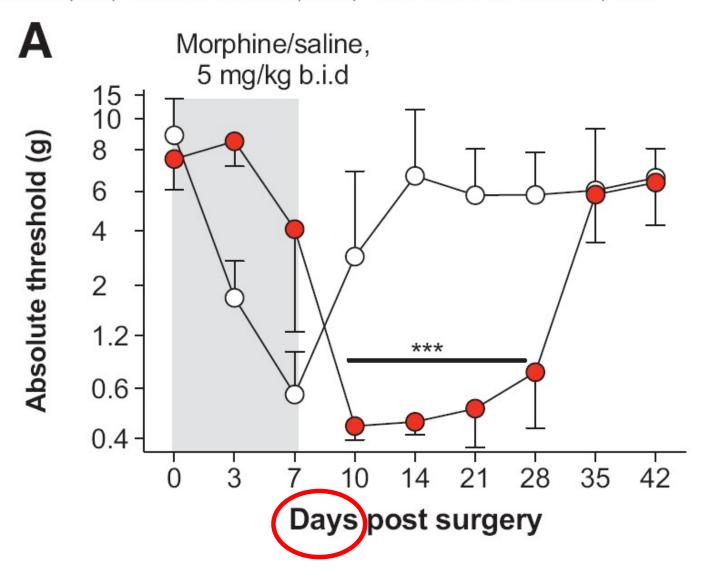
- Système NMDA-R
- Récepteurs NOP (nociceptine – 4<sup>e</sup> famille de récepteurs opiacés)
- Dynorphines (substances hyperalgésiantes)



Richebé P et al. Ann Fr Anesth Reanim 2005: 24:1349-59.

## Repeated Morphine Prolongs Postoperative Pain in Male Rats Anesth Analg 2019; 128:161-167.

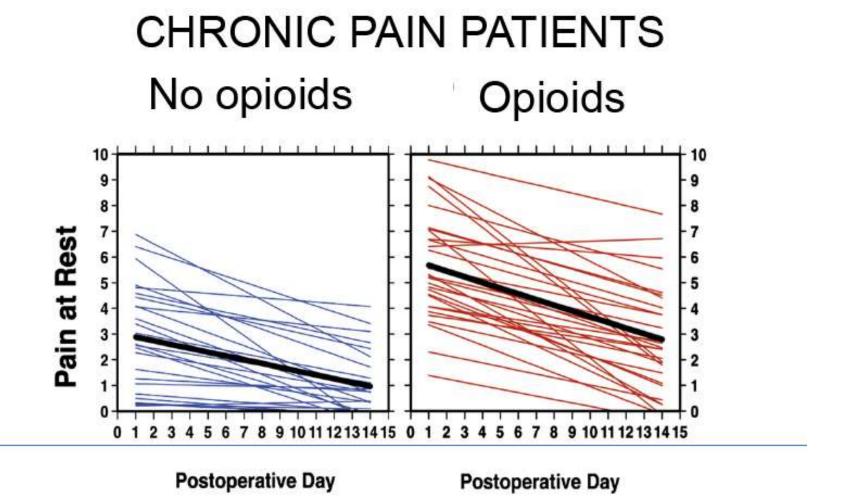
Peter M. Grace, PhD,\*†‡ Erika L. Galer, BA,\* Keith A. Strand, BA,\* Kaci Corrigan, BA,\* Debra Berkelhammer, BA,\* Steven F. Maier, PhD,\* and Linda R. Watkins, PhD\*



Postoperative Pain Trajectories in Chronic Pain Patients
Undergoing Surgery: The Effects of Chronic Opioid
Pharmacotherapy on Acute Pain

J Pain 2011; 12: 1240-6.

C. Richard Chapman, Jennifer Davis, Gary W. Donaldson, Justin Naylor, and Daniel Winchester



## Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis

D. Fletcher<sup>1,2,3\*</sup> and V. Martinez<sup>1,2,3</sup>

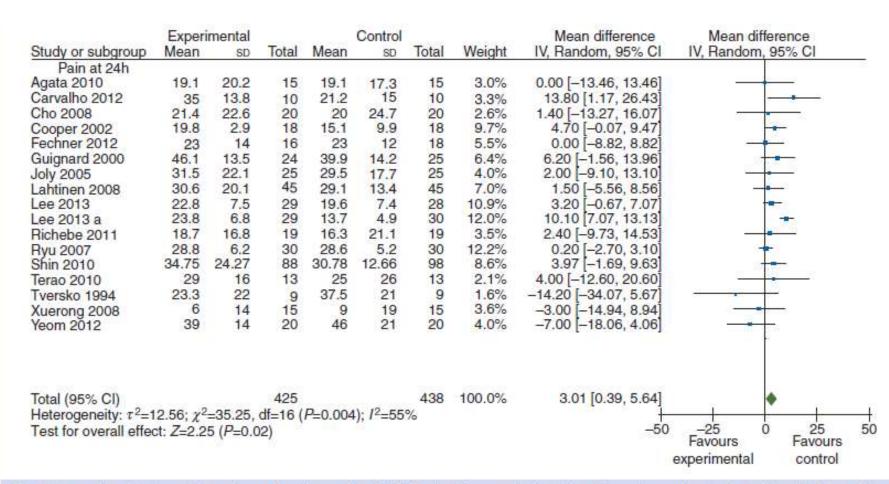


Fig 4 Forestplot of primary (A) and secondary hyperalgesia (B). Pooled data analysis of the primary hyperalgesia (pain threshold near the wound) or secondary hyperalgesia (area around the wound) in adults receiving intraoperative opioid vs control. CI, confidence interval.

## Low- versus high-dose intraoperative opioids: A systematic review with meta-analyses and trial sequential analyses

Eric Albrecht<sup>1</sup> | Sina Grape<sup>2</sup> | Jonathan Frauenknecht<sup>1</sup> | Laurent Kilchoer<sup>1</sup>

Kyle R. Kirkham<sup>3</sup>

Acta Anaesthesiol Scand. 2020;64:6–22.

#### 27 études, 1630 patients

**Results:** Twenty-seven randomised controlled trials, including 1630 patients, were identified. Pain score at rest at 24 post-operative hours was increased in the high-dose group (mean difference [95% CI]: -0.2 [-0.4, -0.1]; trial sequential analysis-adjusted CI: -0.4, -0.02; low certainty of evidence). Similarly, at 2 post-operative hours, both pain score (mean difference [95% CI]: -0.4 [-0.6, -0.2]; low certainty of evidence) and cumulative intravenous morphine equivalents consumed (mean difference [95% CI]: -1.6 mg [-2.6, -0.7]; low certainty of evidence) were significantly higher in the high-dose group. Finally, the threshold for mechanical pain was significantly lower in the high-dose group (mean difference to pressure [95% CI]: 3.8 g·mm $^{-2}$  [1.8, 5.8]; low certainty of evidence).

Morphinique dosage fort

DPO
Consommation de morphine
Zone d'hyperalgésie

plus élevées

## Immunité Cancer

#### **Immunité / Cancer**

Suppression of peritoneal macrophage phagocytosis of Candida albicans by opioids.

I Szabo, M Rojavin, J L Bussiere, T K Eisenstein, M W Adler, and T J Rogers

Journal of Pharmacology and Experimental Therapeutics November 1993, 267 (2) 703-706;

## Endogenous $\mu$ -opioid peptides modulate immune response towards malignant melanoma

Sandra Boehncke<sup>1</sup>, Katja Hardt<sup>2</sup>, Dirk Schadendorf<sup>3</sup>, Reinhard Henschler<sup>4</sup>, Wolf-Henning Boehncke<sup>2</sup> and Beatrice Duthey<sup>2</sup>

© 2010 John Wiley & Sons A/S, Experimental Dermatology, 20, 24–28

#### μ-Opioid Receptor Gene A118G Polymorphism Predicts Survival in Patients with Breast Cancer

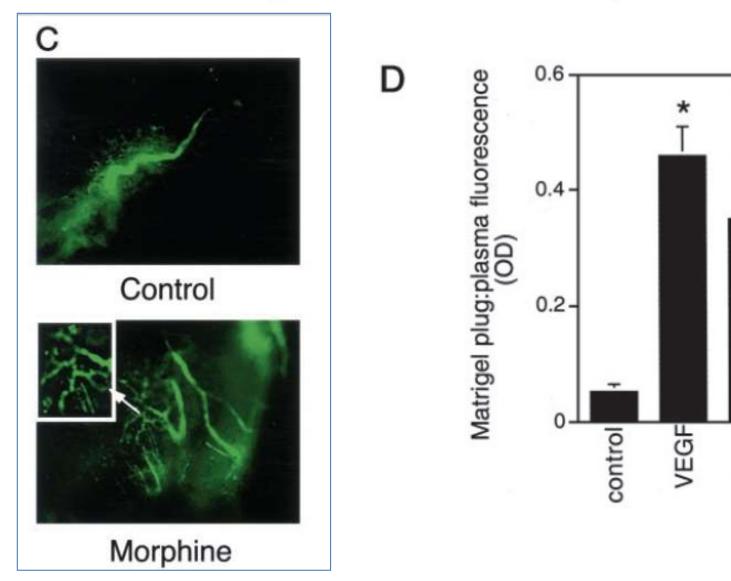
Andrey V. Bortsov, M.D., Ph.D.[Assistant Professor],
Department of Anesthesiology, University of North Carolina at Chapel Hill

#### Morphine Stimulates Angiogenesis by Activating Proangiogenic and Survivalpromoting Signaling and Promotes Breast Tumor Growth

Kalpna Gupta,<sup>2</sup> Smita Kshirsagar, Liming Chang, Robert Schwartz, Ping-Y. Law, Doug Yee, and Robert P. Hebbel

[CANCER RESEARCH 62, 4491–4498, August 1, 2002]

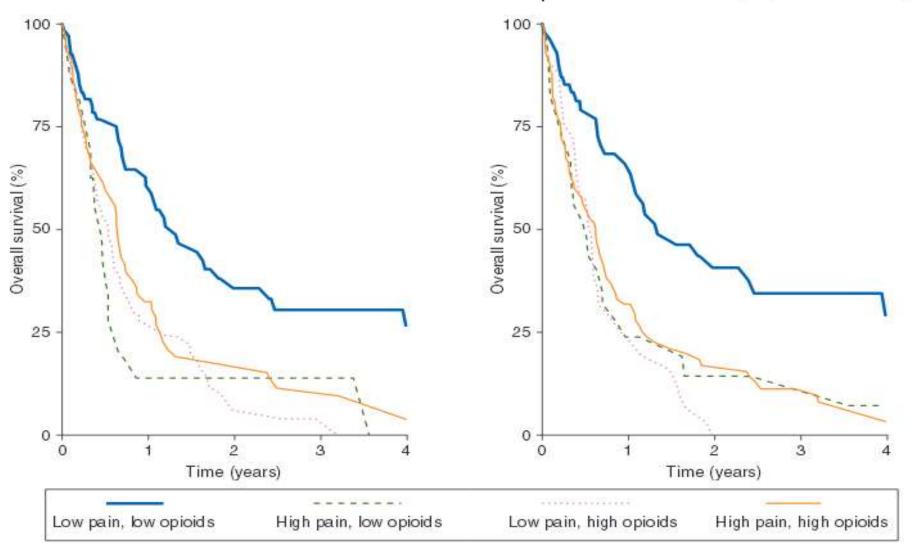
naloxone



## Association of opioid requirement and cancer pain with survival in advanced non-small cell lung cancer

D. Zylla<sup>1,2,4</sup>, M. A. Kuskowski<sup>3</sup>, K. Gupta<sup>1</sup> and P. Gupta<sup>1,2\*</sup>

British Journal of Anaesthesia 113 (S1): ii109-ii16 (2014)



## **Opioids and Cancer Mortality**

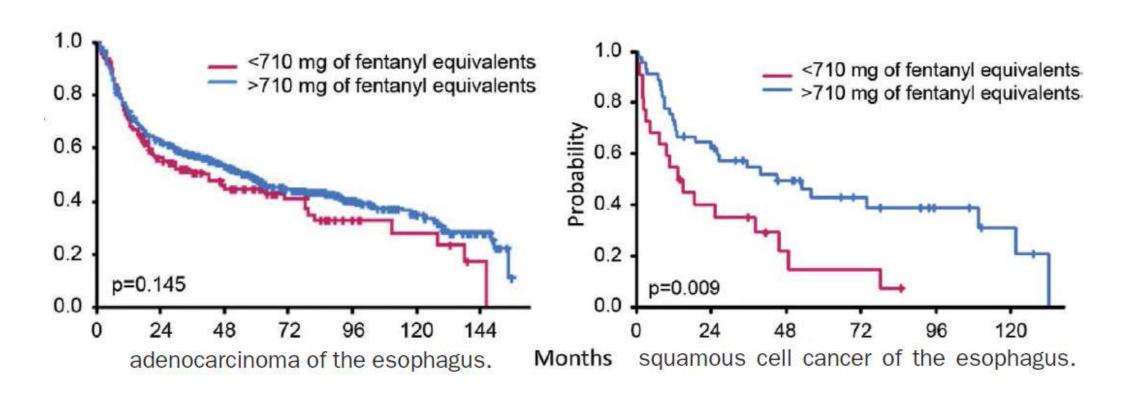
Jaya Amaram-Davila, MD<sup>1</sup> Mellar Davis, MD<sup>2</sup> Akhila Reddy, MD<sup>1,\*</sup>

> Opioids are the gold standard for the treatment of cancer-related pain. Preclinical studies have associated opioids with cancer progression and overall survival. In mice models, opioids have been shown to possess pro-tumor activity secondary to immunosuppression, migration of tumor cells, increased activity of vascular endothelial growth factor receptors, and angiogenesis leading to tumor progression. In contrast, opioids have also been associated with having antitumor activity by activation of apoptosis and phagocytosis. However, high-quality randomized controlled trials in humans that are focused on the association between opioids and survival in cancer patients are lacking, which underscores the importance of being cautious when interpreting the results of the preclinical studies. Cancer-related pain is complex and multifactorial and may worsen as the disease progresses leading to higher opioid utilization. Moreover, cancer pain by itself has been associated with poor survival. The survival in these advanced cancer patients taking opioids may be more likely to be associated with cancer progression and not the opioid use. Adequate treatment of cancer pain has the potential to improve quality of life and performance status, highlighting the importance of continuing to use opioids to manage pain efficiently. More research is clearly needed.

#### Effects of Intraoperative Opioid Use on Recurrence-Free and Overall Survival in Patients With Esophageal Adenocarcinoma and Squamous Cell Carcinoma

Kim N. Du, BS,\*† Lei Feng, MS,‡ Abigail Newhouse,†§ Jeel Mehta,†||¶ Javier Lasala, MD,†||¶ Gabriel E. Mena, MD,†||¶ Wayne L. Hofstetter, MD,# and Juan P. Cata, MD†||¶

Anesth Analg 2018; 127:210-216.

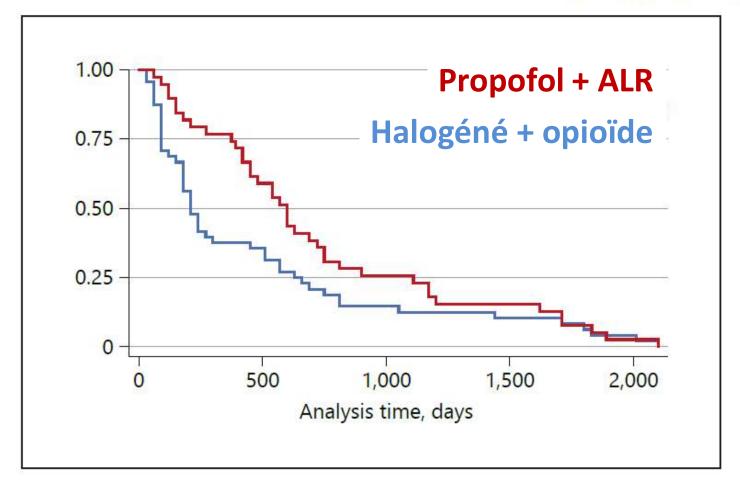


#### Anesthesia in Combination with Propofol Increases Disease-Free Survival in Bladder Cancer Patients Who Undergo Radical Tumor Cystectomy as Compared to Inhalational Anesthetics and Opiate-Based Analgesia

Jose Luis Guerrero Orriach<sup>a-c</sup> Aida Raigon Ponferrada<sup>b</sup> Alfredo Malo Manso<sup>b</sup> Bernardo Herrera Imbroda<sup>a, d</sup> Juan Jose Escalona Belmonte<sup>b</sup> Marta Ramirez Aliaga<sup>b</sup> Alicia Ramirez Fernandez<sup>b</sup> Julia Diaz Crespo<sup>b</sup> Angela M. Soriano Perez<sup>e</sup> Ana Fontaneda Heredia<sup>b</sup> Maria Emilia Dominguez Recio<sup>f</sup> Manuel Rubio Navarro<sup>b</sup> Jose Cruz Mañas<sup>b</sup>

#### Oncology

Received: October 28, 2019 Accepted: November 14, 2019 Published online: January 21, 2020

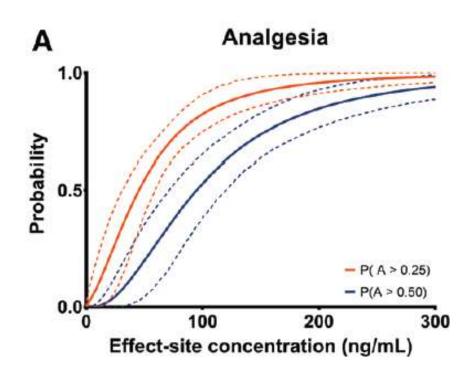


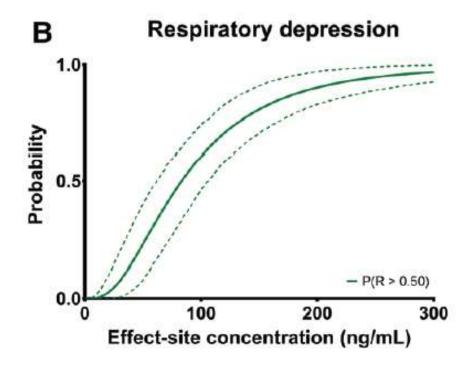
## dangers respiratoires

#### Benefit versus Severe Side Effects of Opioid Analgesia

## Novel Utility Functions of Probability of Analgesia and Respiratory Depression

Margot Roozekrans, M.D., Rutger van der Schrier, M.D., Leon Aarts, M.D., Ph.D., Elise Sarton, M.D., Ph.D., Monique van Velzen, Ph.D., Marieke Niesters, M.D., Ph.D., Albert Dahan, M.D., Ph.D., Erik Olofsen, Ph.D.





## Life-threatening critical respiratory events: a retrospective study of postoperative patients found unresponsive during analgesic therapy<sup>☆</sup>

```
Satya Krishna Ramachandran MD, FRCA (Assistant Professor)<sup>a</sup>,*
Naeem Haider MD (Assistant Professor)<sup>a</sup>,
Kelly A. Saran MS, RN (Risk Management Consultant)<sup>b</sup>,
Michael Mathis BS (Medical Student)<sup>c</sup>, Joyce Kim BSE (Medical Student)<sup>c</sup>,
Michael O'Reilly MD (Associate Professor)<sup>a</sup>
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Journal of Clinical Anesthesia (2011) 23, 207–213

Main Results: Over the 6-year period, 32 patients experienced a postoperative critical respiratory event. Twenty-six events and three deaths occurred within the first 24 hours of opioid therapy. Four of 32 patients died. Congestive heart failure, postoperative acute renal failure, obstructive sleep apnea, cardiac dysrhythmia, diabetes mellitus, coronary artery disease, and hypertension were significant associations in adult patients.

## Respiratory and haemodynamic effects of acute postoperative pain management: evidence from published data

J. N. Cashman<sup>1</sup>\* and S. J. Dolin<sup>2</sup>

British Journal of Anaesthesia 93 (2): 212–23 (2004)

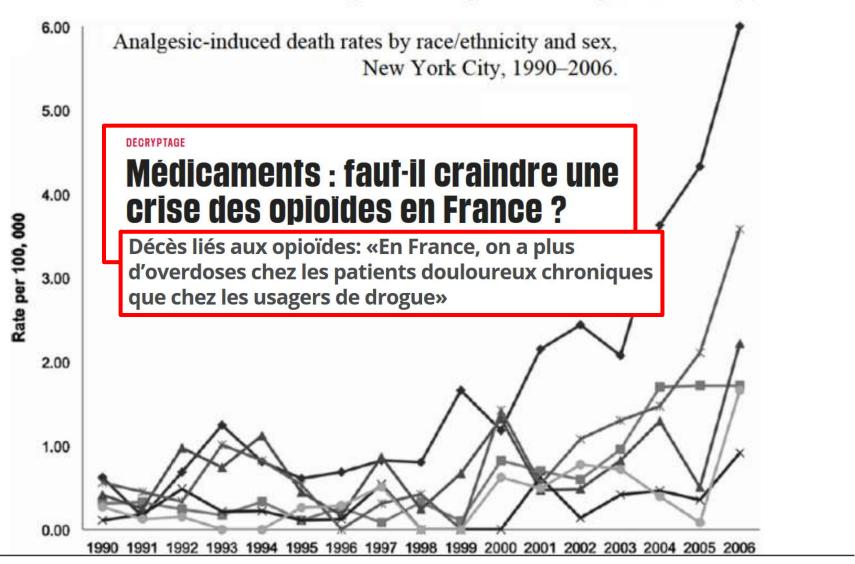
**Table 4** Reported incidence of respiratory depression as indicated by naloxone use

	Number of study groups	Total number of patients	Respiratory depression	
	Stoups	or patricing	Mean (%)	95% CI
Analgesic technique				
All	13	55 404	0.3	0.1 - 1.3%
I.M.	3	71	1.4	0.1 - 12.7%
I.VPCA	2	4691	(1.9)	1.9-2.0%
Epidural	8	50 642	0.1	0.1 – 0.2%

#### Prescription opioid mortality trends in New York City, 1990– 2006: Examining the emergence of an epidemic★

Magdalena Cerdá<sup>a,\*</sup>, Yusuf Ransome<sup>b</sup>, Katherine M. Keyes<sup>a</sup>, Karestan C. Koenen<sup>a</sup>, Melissa Tracy<sup>a</sup>, Kenneth J. Tardiff<sup>c</sup>, David Vlahov<sup>d</sup>, and Sandro Galea<sup>a</sup>

Drug Alcohol Depend. 2013 September 1; 132(0): 53-62.





### Obstructive sleep apnea, pain, and opioids: is the

riddle solved?

Volume 29 • Number 1 • February 2016

Karen K. Lam<sup>a</sup>, Samuel Kunder<sup>a</sup>, Jean Wong<sup>a</sup>, Anthony G. Doufas<sup>b</sup>, and Frances Chung<sup>a</sup>

#### **KEY POINTS**

- Opioids can exacerbate sleep-disordered breathing postoperatively and worsen hypoxemia.
- Both intermittent hypoxia and sleep fragmentation seem to cause hyperalgesia.
- Intermittent hypoxia activates systemic inflammation and upregulates reactive oxygen species and hypoxic markers.
- A certain subset of patients with OSA, characterized by decreased chemoreflex responsiveness and high arousal thresholds, may be more susceptible to OIVI.

#### Preoperatively Screened Obstructive Sleep Apnea Is Associated With Worse Postoperative Outcomes Than Previously Diagnosed Obstructive Sleep Apnea

Ana Fernandez-Bustamante, MD, PhD,\* Karsten Bartels, MD,\* Claudia Clavijo, MD,\* Benjamin K. Scott, MD,\* Rachel Kacmar, MD,\* Kenneth Bullard, BS,\* Angela F. D. Moss, MS,† William Henderson, PhD,† Elizabeth Juarez-Colunga, PhD,† and Leslie Jameson, MD\*

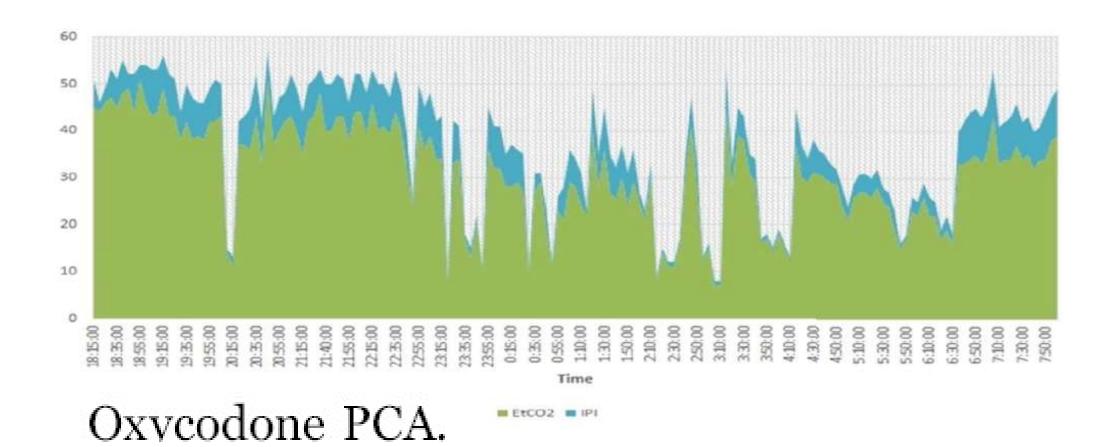
**CONCLUSIONS:** Patients classified as S-OSA have similar rates of AREs to D-OSA patients, but increased postoperative respiratory interventions, hospital use, and 30-day all-cause mortality. These worse postoperative outcomes in S-OSA patients than D-OSA patients could reflect the lack of awareness and appropriate management of this bedside S-OSA diagnosis after PACU discharge. Multidisciplinary interventions are needed for these high-risk patients. (Anesth Analg 2017;125:00–00)

[99% confidence interval, 0.75–1.09]; P = .15). S-OSA patients compared to D-OSA patients had significantly increased postoperative reintubation, mechanical ventilation, direct intensive care unit admission after surgery, hospital length of stay, and 30-day all-cause mortality.

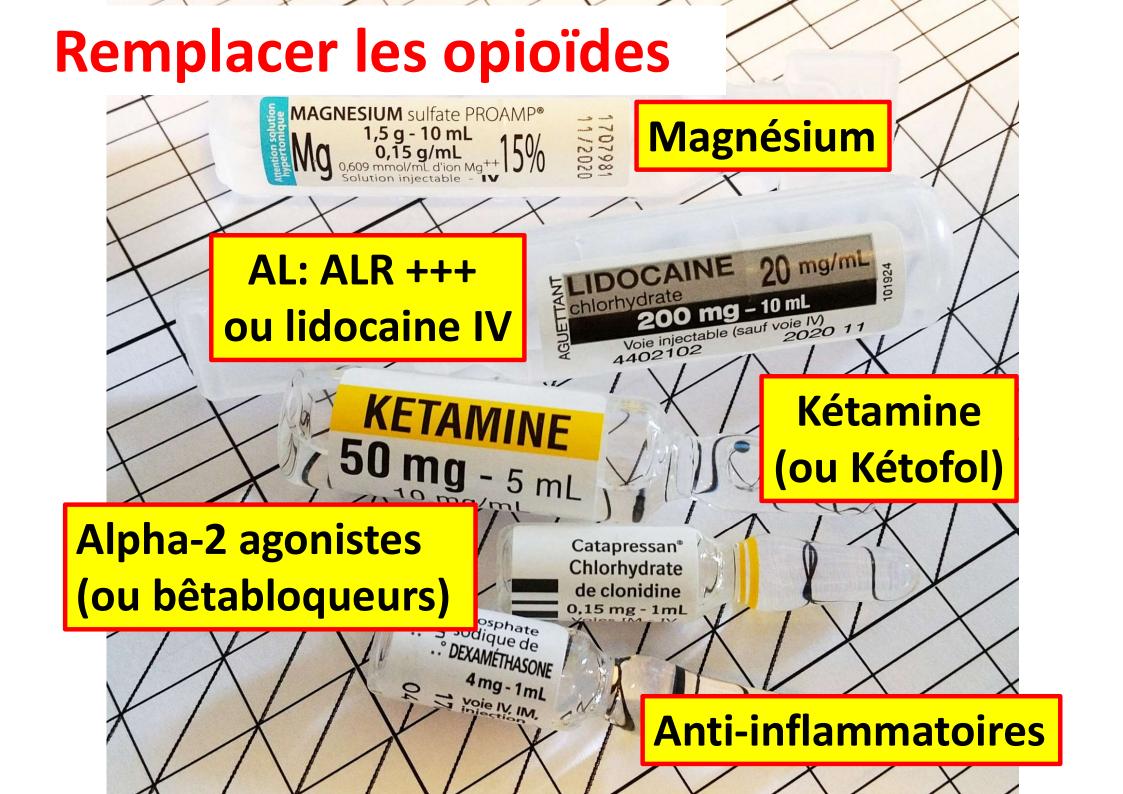
Post operative capnostream monitoring in patients with obstructive sleep apnoea symptoms − Case series<sup>★</sup>

Vasanth Rao Kadam<sup>a,\*</sup>, Mazyar Danesh<sup>b</sup>

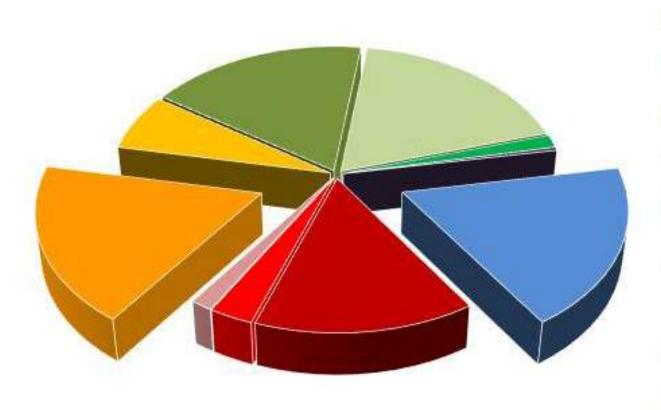
Sleep Science 9 (2016) 142–146



The four parameters EtCo<sub>2</sub>, Spo<sub>2</sub>, respiratory rate (RR) and Pulse Rate (PR) are integrated to give one number called Integrated Pulmonary Index (IPI). IPI has been used as a single parameter for



#### Choix des molécules de l'OFA à Cochin



- Lidocaïne
- Béta-bloquants
- AINS
- Aucune
- Clonidine
- Kétamine
- Paracétamol
- Dexmedetomidine
- Magnésium
- Gabapentine





## Alpha 2-agonistes

- Analgésie : récepteurs spécifiques
- Sédation +++
- Diminuent du tiers à la moitié
  - les besoins en morphiniques
  - les besoins en hypnotiques

## 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

Grégoire Blaudszun, M.D.,\* Christopher Lysakowski, M.D.,† Nadia Elia, M.D., M.Sc.,‡ Martin R. Tramèr, M.D., D.Phil.§

In conclusion, in patients undergoing surgery with general anesthesia, there is evidence that perioperative systemic administration of  $\alpha$ 2 agonists decreases postoperative opioid consumption, pain intensity, and nausea. There is no evi-

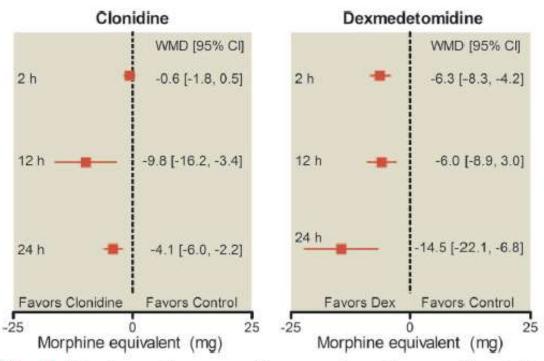


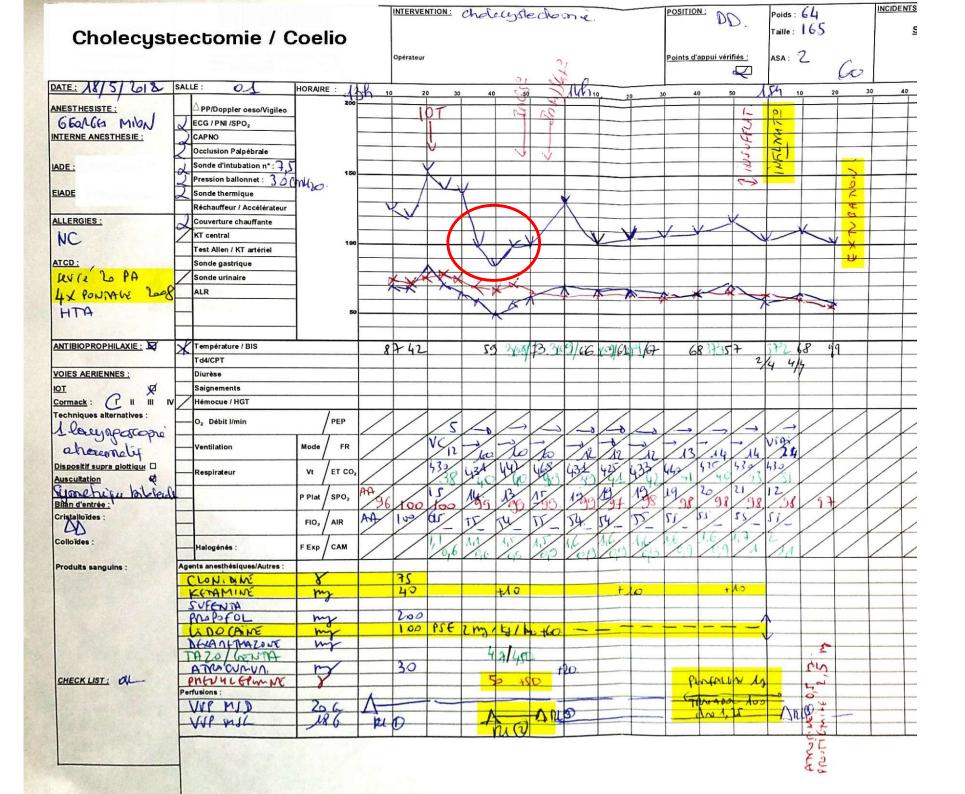
Fig. 2. Postoperative morphine-sparing. Doses of opioids

## Clonidine



• 0,5 à 2  $\mu$ g/kg

• T1/2 $\alpha$  : 20 min



## Dexmédétomidine





(Dexdor)

AMM: sédation en réanimation

Délai d'action 15 min Pic 1h Demi-vie 2 h (Elimination hépatique)

0.3 à 0.5 µg/kg en 10 min PSE 0.1 à 0.3 µg/kg/h

### **ANESTHESIOLOGY**

Balanced Opioid-free
Anesthesia with
Dexmedetomidine versus
Balanced Anesthesia
with Remifentanil for
Major or Intermediate
Noncardiac Surgery

Plus de 300 patients

The Postoperative and Opioid-free Anesthesia (POFA) Randomized Clinical Trial

(Anesthesiology 2021; 134:541-51)

Helene Beloeil, M.D., Ph.D., Matthias Garot, M.D.,

**Results:** The study was stopped prematurely because of five cases of severe bradycardia in the dexmedetomidine group. The primary composite outcome

# Alpha 2-agonistes

- Effets secondaires :
  - Bradycardie
  - Hypotension
  - Sédation



CI: troubles conductifs +++

# Kétamine

- blocage des récepteurs NMDA
- $t_{1/2}\alpha = 10 \text{ min}$
- $t_{1/2} \beta = 1-3 h$



# Propriétés analgésiques

- Effets analgésiques
  - Inhibition NMDA-R et canaux HCN1
  - Inhibition récepteurs muscariniques (SAC)
  - anticalcique
  - activation systèmes monoaminergiques descendants
  - effet anesthésique local (canaux sodiques)
  - action μ non significative (naloxone sans effet)
- Effets anti-proinflammatoires (NfkB)
- Effets antidépresseurs (action rapide)

# 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\*

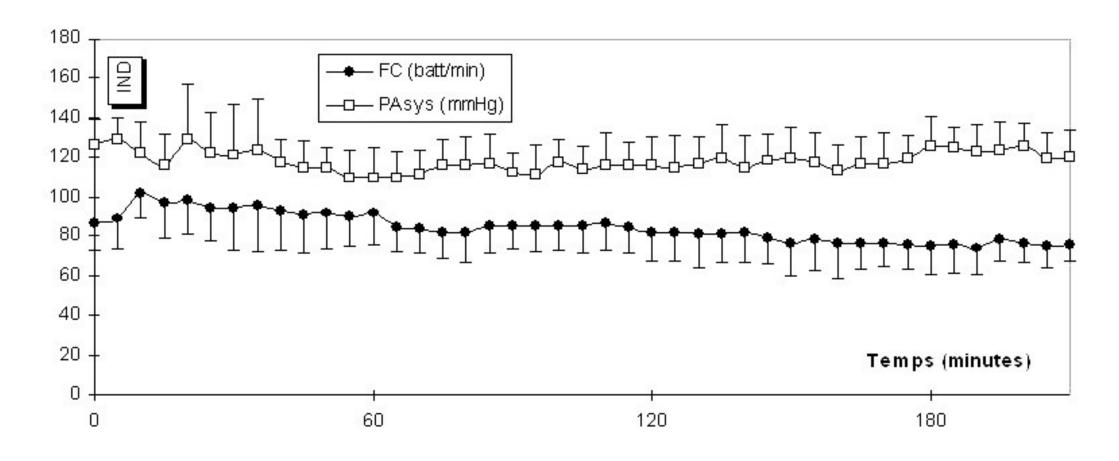
Pain Medicine 2015; 16: 383-403

### 2482 patients

The mean reduction of opioid consumption when using low-dose IV infusion ketamine (infusion rate less than 1.2 mg/kg/h) is 40%. Ketamine also reduces pain scores

Une PERFUSION de kétamine Réduit de 40% la consommation d'opioïdes

# Il y a 25 ans : Kétofol

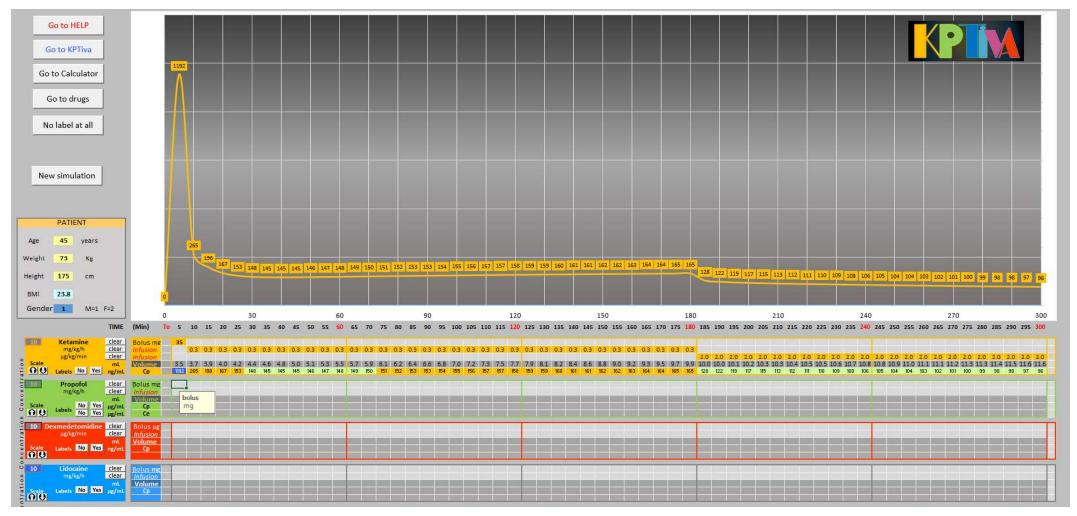


Mion G. Kétamine 1st Ed

## Kétamine

- Induction 0.5 1 mg/kg
- Entretien 0,25 mg/kg/h
- Stop ou diminution avant extubation
- 24-48 h Post-op (2-1 μg/kg/min)?





georgesmion.com

## Lidocaine IV



- $T_{1/2} \alpha = 5-8 \text{ min}$
- $T_{1/2} \beta = 90 \text{ min}$
- Extraction hépatique Cyt. P450

#### Local Anesthetics and the Inflammatory Response

A New Therapeutic Indication?

Anesthesiology 2000; 93:858-75

Markus W. Hollmann, M.D,\* and Marcel E. Durieux, M.D., Ph.D.†

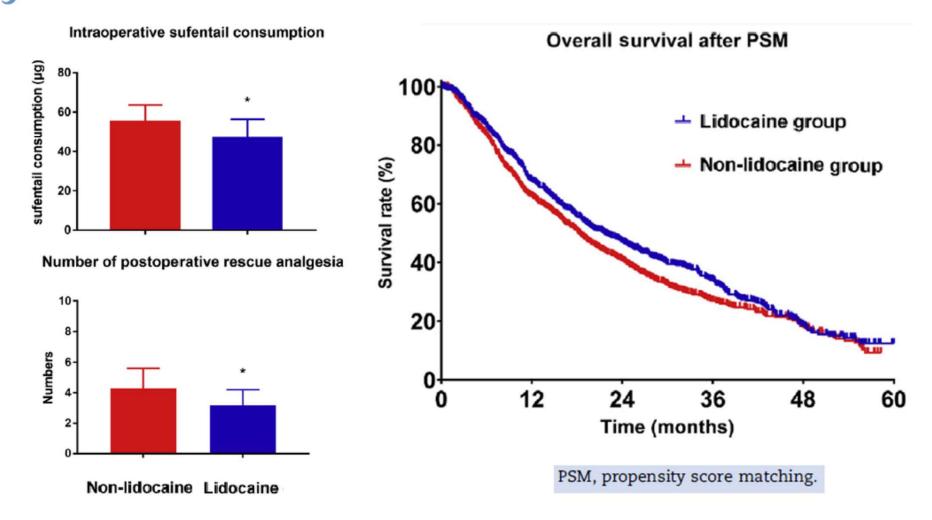
### **Effets anti nociceptifs**

- Blocage des canaux sodiques et des courants potassiques
- Effet anti-pro-inflammatoire +++
   Récepteurs membranaires
   couplés à des protéine G
- Anti-hyperalgésique
   Anti NMDA, atténuation du wind-up spinal

Association between intraoperative intravenous lidocaine infusion and survival in patients undergoing pancreatectomy for pancreatic cancer: a retrospective study

Hao Zhang<sup>1,2,3,†</sup>, Li Yang<sup>2,3,†</sup>, Xuqin Zhu<sup>2,3,†</sup>, Minmin Zhu<sup>2,3</sup>, Zhirong Sun<sup>2,3</sup>, Juan P. Cata<sup>4,5,\*\*</sup>, Wankun Chen<sup>1,2,3,\*\*\*</sup> and Changhong Miao<sup>1,2,3,\*</sup>

#### BJA Br J Anaesth 2020 Aug; 125: 141-148.



#### Perioperative Use of Intravenous Lidocaine

Marc Beaussier<sup>1</sup> · Alain Delbos<sup>2</sup> · Axel Maurice-Szamburski<sup>3</sup> · Claude Ecoffey<sup>4</sup> · Luc Mercadal<sup>5</sup>

Drugs (2018) 78:1229-1246

Concentrations usuelles: 2-4 µg/mL

Convulsions: 15 µg/mL

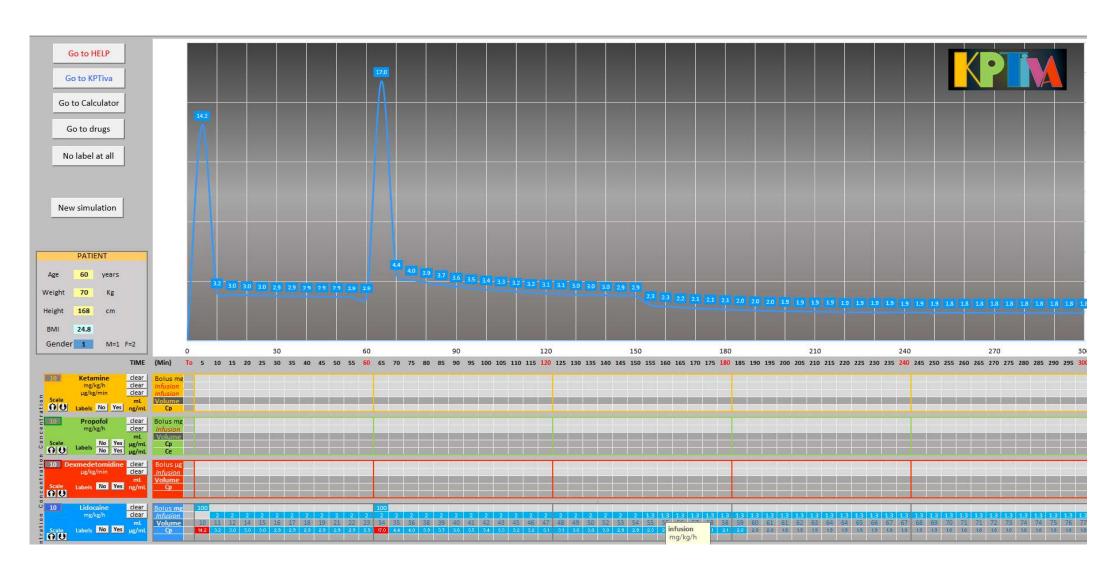
Cardiotoxicité: 20 µg/mL

## Lidocaine IV



- Induction 1,5 mg/Kg
- Entretien: 2 mg/kg
- Extra Bolus 1 mg/kg (par h)
- Post-op ? (1,3 mg/kg)

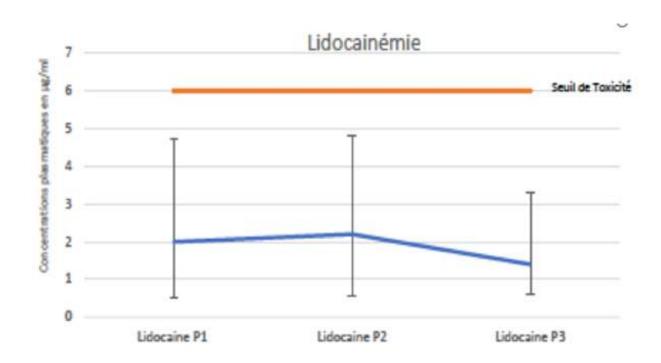






Étude pharmacocinétique et pharmacodynamique de la lidocaïne intra-veineuse associée à la ropivacaïne utilisée par voie péridurale dans les chirurgies abdominales majeures.

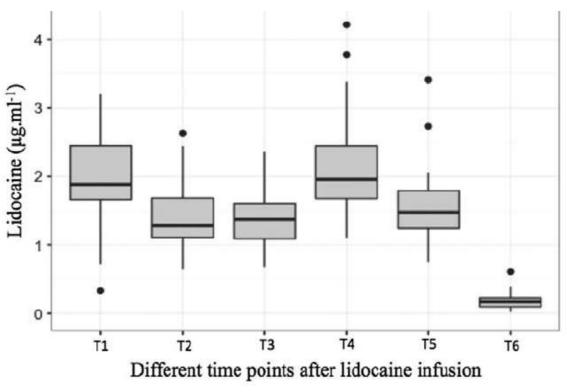
## bolus lidocaïne 1,5 mg/kg débit continu 1,5 mg/kg/h.



1ère lidocaïnémie 30 minutes après le bolus= 2 [1,5-2,7]  $\mu$ g/ml 2ème à l'arrêt de la perfusion = 2,2 [1,65-2,6]  $\mu$ g/ml 3ème 2 heures après = 1,4 [0,8-1,9]  $\mu$ g/ml.

# Serum Concentrations of Lidocaine During Bariatric Surgery

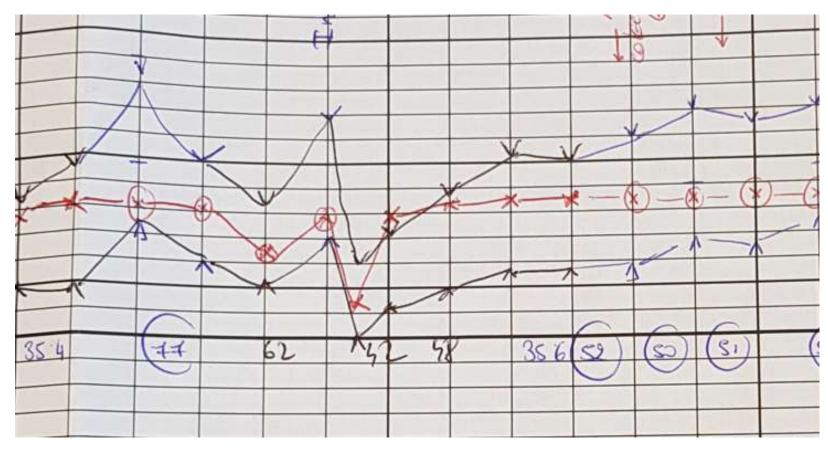
Jean-François Carabalona, MD,\* Benjamin Delwarde, MD,\*† Antoine Duclos, MD, PhD,‡§ Mary-Charlotte Le Goff, MD,\* Mustapha Moulsma, PharmD, PhD,|| Antony Citterio-Quentin, PharmD, PhD,¶ Yves Bouffard, MD,\* and Thomas Rimmelé, MD, PhD\*†



**Figure.** Lidocaine serum concentration—time profile. T1, T2, and T3 correspond respectively to 10, 20, and 30 min after the beginning of lidocaine infusion; T4 represents the end of the 2 mg·kg<sup>-1</sup>·hour<sup>-1</sup> lidocaine infusion; T5 is the end of the 1 mg·kg<sup>-1</sup>·hour<sup>-1</sup> lidocaine infusion; T6 is drawn at 8:00 AM, the day after the end of lidocaine infusion. Data are presented as box plots. The box represents the

Anesth Analg 2020;130:e5-e8

#### Collapsus lors d'un bolus IV de 1,5 mg/kg lidocaïne



Patiente de 68 ans, neuropathie périphérique, OFA (PSE lido + kétamine) pour colectomie

Tachycardie à l'incision, bolus de lidocaïne, collapsus avec bradycardie brutale. Situation maitrisée par atropine + noradrénaline

Arrêt de la perfusion de lidocaïne



Cochrane Database of Systematic Reviews 2015, Issue 7. Art. No.: CD009642.

### 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

Cochrane Database of Systematic Reviews 2018, Issue 6. Art. No.: CD009642.

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

Weibel S, Jelting Y, Pace NL, Helf A, Eberhart LHJ, Hahnenkamp K, Hollmann MW, Poepping DM, Schnabel A, Kranke P

#### 68 trials (4525 randomized participants)

#### Quality of the evidence

We rated the quality of evidence for most outcomes as very low. This was because of inconsistent findings across studies and the fact that the evidence came from small studies that were of moderate design quality or a limited number of studies. The quality of the evidence for minimal or no effect on pain at 24 and 48 hours was moderate quality. The studies involved a variety of surgical procedures. The dose of lidocaine used, and how long it was delivered for after the end of surgery, also varied between studies.

## Lidocaine IV

PO: Gérer les risques de toxicité

- Formation
- Voie dédiée, valve anti-retour
- attention aux associations lido iv + ALR

# Mélange LIDOKET



							pour 80 Kg
	mg	N	dose	mL	mg/mL	0,1 mL/kg/h	8 mL/h
Amp lido	200	4	800	40	16	1,6 mg/kg/h	128 mg/h
Amp ket	50	2	100	10		0,2 mg/Kg/h	





### **Association lido-ket?**

- Très peu d'études publiées
- Additif ou synergique ?
- Symptômes psychomimétiques plus fréquents (diminuer les doses ?)
- Intérêt sur le long terme ?

#### Original research



### Physicochemical stability of an admixture of lidocaine and ketamine in polypropylene syringe used in opioid-free anaesthesia FREE

Benoît Beiler<sup>1</sup>, Damien Barraud<sup>2</sup>, Jean Vigneron<sup>3</sup>, Béatrice Demoré<sup>3, 4</sup>

Author affiliations

Eur J Hosp Pharm 2020;27(e1):e79-e83.

#### Abstract

Objectives Opioid-free anaesthesia is a treatment strategy of pain management based on the use of drugs such as lidocaine, ketamine and dexmedetomidine that do not interact significantly with opioid receptors. In particular, these drugs are used by anaesthesiologists to ensure adequate levels of analgesia during surgical procedures for burn patients such as daily wound dressings and graft surgeries. Furthermore, for hypothermia prevention and wound-healing purposes, ambient temperature must be kept high for these patients, usually between 27°C and 30°C. To facilitate the use of this technique, clinicians want to mix lidocaine and ketamine in the same syringe. No stability data is available to determine the feasibility of this admixture and at this temperature. The objective was to study the physicochemical stability of lidocaine 20 mg/mL with ketamine 2.5 mg/mL diluted with 0.9% sodium chloride (0.9% NaCl) stored at 28°C in polypropylene syringe for 48 hours.

**Methods** Physical stability was evaluated by visual examination and by measuring turbidity with a spectrophotometer. Chemical stability was determined after preparation and after 6, 24 and 48 hours of conservation with a high performance liquid chromatography and pH measurements. The method was validated according to International Conference on Harmonisation Q2(R1) guidelines.

**Results** Both lidocaine (99.98%±1.44%) and ketamine (100.70%±0.95%) retained more than 95% of their initial concentration after 48 hours storage. pH measurements remained stable over the course of the study (less than 0.21 point of variation). No signs of physical instability were observed after visual and subvisual inspections.

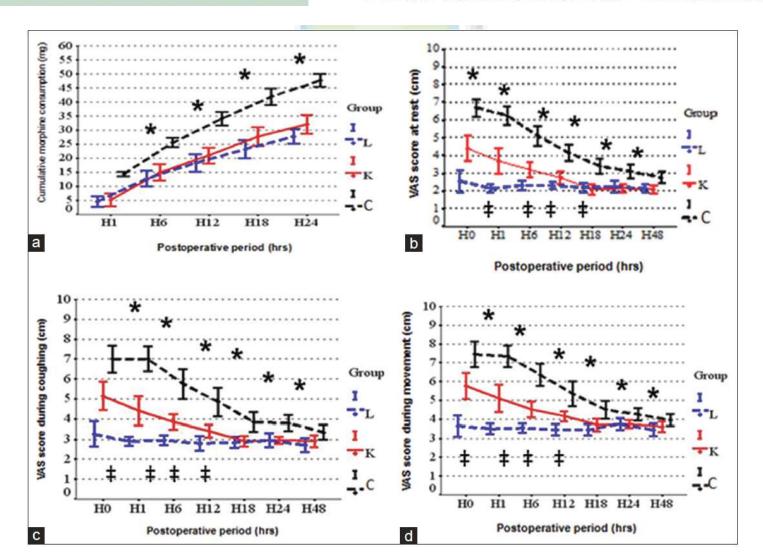
Conclusions The physicochemical stability of lidocaine 20 mg/mL and ketamine 2.5 mg/mL diluted with 0.9% NaCl in a polypropylene syringe stored at 28°C protected from light was demonstrated for 48 hours. This infusion technique is therefore feasible from a pharmaceutical point of view in burn-unit settings.

A comparison between intravenous lidocaine and ketamine on acute and chronic pain after open nephrectomy: A prospective, double-blind, randomized, placebo-controlled study

ALI JENDOUBI, IMED BEN NACEUR, ABDERRAZAK BOUZOUITA, MEHDI TRIFA<sup>1</sup>, SALMA GHEDIRA, MOHAMED CHEBIL, MOHAMED HOUISSA

Faculty of Medicine of Tunis,

2017 Saudi Journal of Anesthesia



Minimum infusion rate and hemodynamic effects of propofol, propofol-lidocaine and propofol-lidocaine-ketamine in dogs Veterinary Anaesthesia and Analgesia, 2012, 39, 160–173

Rodrigo Mannarino, Stelio PL Luna, Eduardo R Monteiro, Suzane L Beier & Vanessa B Castro

Administration of CRIs of lidocaine (PL) or lidocaine in combination with ketamine (PLK) decreased the MIR of propofol by  $18 \pm 7\%$  and  $37 \pm 18\%$ ,

# Effects of intravenous lidocaine, ketamine, and the combination on the minimum alveolar concentration of sevoflurane in dogs

Jeffrey Wilson\* DVM, Thomas J Doherty† MSc MVB Diplomate ACVA, Christine M Egger\* DVM MVSc Diplomate ACVA, Andrew Fidler\* BS, Sherry Cox‡ PhD & Barton Rohrbach‡ VMD, MPH Diplomate ACVPM (Epidemiology)

#### Veterinary Anaesthesia and Analgesia, 2008, **35**, 289–296

Treatment	MAC <sub>B</sub>	MAC <sub>T</sub>	Change (%)*	Time MAC <sub>B</sub> †	Time MAC <sub>T</sub> ‡
L 50	$2.0 \pm 0.2^{a}$	1.6 ± 0.1	-22.6 ± 3.6 <sup>a</sup>	162.8 ± 12.8 <sup>a</sup>	153.8 ± 17.7 <sup>a</sup>
L 100	$1.8 \pm 0.2^{a}$	$1.3 \pm 0.1$	$-29.0 \pm 3.5^{a, b}$	$162.5 \pm 12.8^{a}$	$160.2 \pm 17.7^{a}$
L 200	$1.8 \pm 0.2^{a}$	1.1 ± 0.1	$-39.6 \pm 3.5^{b}$	$152.3 \pm 12.8^{a}$	$187.8 \pm 17.7^{a}$
K 50	$1.9 \pm 0.2^{a}$	1.1 ± 0.1	$-40.0 \pm 3.5^{b}$	$173.3 \pm 12.8^{a}$	$185.7 \pm 17.7^{a}$
K 100	$1.7 \pm 0.2^{a}$	$0.9 \pm 0.1$	$-44.7 \pm 3.5^{b}$	$186.2 \pm 12.8^{a}$	$187.3 \pm 17.7^{a}$
K + L	$2.0 \pm 0.2^{a}$	$0.7 \pm 0.1$	$-62.8 \pm 3.5^{\circ}$	$169.7 \pm 12.8^{a}$	198.2 ± 17.7 <sup>a</sup>

For all treatment groups the difference between baseline MAC (MAC<sub>B</sub>) and post-treatment MAC (MAC<sub>T</sub>) was statistically significant (p < 0.05). MAC data are expressed as least-squares mean  $\pm$  SEM. MAC<sub>B</sub> = baseline MAC, MAC<sub>T</sub> = post-treatment MAC. \*Percentage change from baseline MAC = [(MAC<sub>T</sub> - MAC<sub>B</sub>)/MAC<sub>B</sub>] × 100. †Time in minutes (least squares mean  $\pm$  SEM) from induction to complete MAC<sub>B</sub> determination in duplicate. ‡Time in minutes (least squares mean  $\pm$  SEM) from start of CRI to complete MAC<sub>T</sub> determination in duplicate. <sup>a, b, c</sup> Values in the same column with the same letter are not significantly different (p > 0.05).

# MgSO4 IV



- Analgésique (NMDAR)
- Vasodilatateur
- Potentialise les curares
- Élimination urinaire

30-50 mg/kg en 15 min (1-2 amp) puis perfusion 15 mg/kg/h

## Anti-inflammatoires

Dexaméthasone

 $100 \mu g/kg$ 

AINS

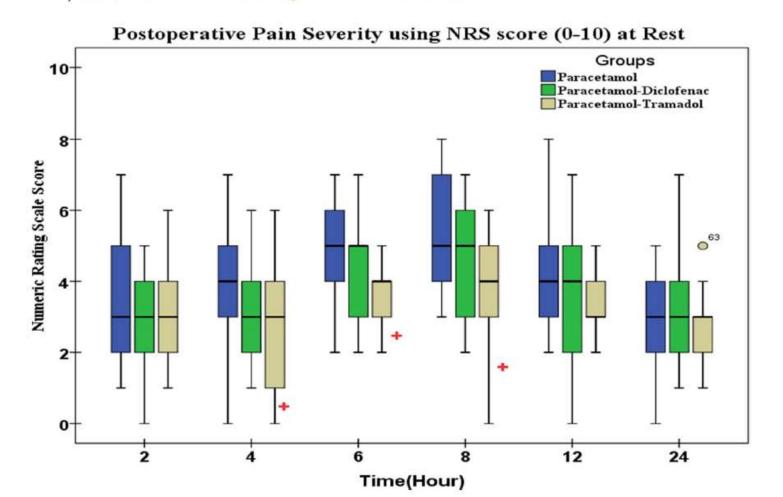
respecter les CI +++



Comparison of preemptive paracetamol, paracetamol-diclofenac & paracetamol-tramadol combination on postoperative pain after elective abdominal surgery under general anesthesia, Ethiopia: a randomized control trial study, 2018

BMC Anesthesiology (2020) 20:191

Zemedu Aweke<sup>1</sup>, Fetene Seyoum<sup>1</sup>, Tewoderos Shitemaw<sup>2\*</sup> and Derartu Neme Doba<sup>1</sup>



# Cas cliniques patients à risque respiratoire

 Gaszynski et al. Dexmed for awake intubation and OFA in a superobese patient with suspected difficult intubation. Drug Design, Development and Therapy 2014:8 909–912.

 Gaszynski. OFA in patient with Steinert syndrome (myotonic dystrophy) Case report. Medicine 2016;95:37(e4885).

# moins de douleurs, de NVPO et de temps passé en SSPI

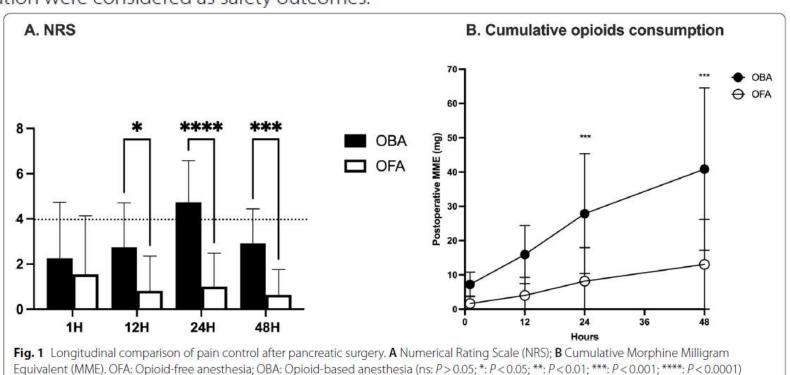
- Ziemann-Gimmel et al. OFA reduces postoperative nausea and vomiting in bariatric surgery
   BJA 2014; 112: 906–11.
- Bakana et al. OFA with propofol, dexmed and lido for laparoscopic cholecystectomy: a prospective RCT. Rev Bras Anestesiol 2015;65:191-199.
- Tripathy et al. OFA for breast cancer surgery:
   An observational study. J Anaesthesiol Clin
   Pharmacol 2018; 34: 35–40.

# Opioid-free versus opioid-based anesthesia in pancreatic surgery Hublet et al. BMC Anesthesiology

(2022) 22:9

Stéphane Hublet<sup>1</sup>, Marianne Galland<sup>1</sup>, Julie Navez<sup>2</sup>, Patrizia Loi<sup>2</sup>, Jean Closset<sup>2</sup>, Patrice Forget<sup>3</sup> and Pierre Lafère<sup>1\*</sup>

**Methods:** Perioperative data from 77 consecutive patients who underwent pancreatic resection were included and retrospectively reviewed. Patients received either an OBA with intraoperative remifentanil (n = 42) or an OFA (n = 35). OFA included a combination of continuous infusions of dexmedetomidine, lidocaine, and esketamine. In OBA, patients also received a single bolus of intrathecal morphine. All patients received intraoperative propofol, sevoflurane, dexamethasone, diclofenac, neuromuscular blockade. Postoperative pain management was achieved by continuous wound infiltration and patient-controlled morphine. The primary outcome was postoperative pain (Numerical Rating Scale, NRS). Opioid consumption within 48 h after extubation, length of stay, adverse events within 90 days, and 30-day mortality were included as secondary outcomes. Episodes of bradycardia and hypotension requiring rescue medication were considered as safety outcomes.



#### Impact of Opioid-Free Anesthesia after videoassisted thoracic surgery: a propensity score study

Jean Selim <sup>1</sup>, Xavier Jarlier <sup>2</sup>, Thomas Clavier <sup>3</sup>, Fairuz Boujibar <sup>4</sup>, Marie-Mélody Dusseaux <sup>2</sup>, Juliette Thill <sup>2</sup>, Céline Borderelle <sup>2</sup>, Vanessa Ple <sup>2</sup>, Jean-Marc Baste <sup>4</sup>, Emmanuel Besnier <sup>5</sup>, Zoubir Djerada <sup>6</sup>, Vincent Compere <sup>2</sup>

#### Ann Thorac Surg. 2021 Oct 15;S0003-4975(21)01723-9.

**Methods:** The main objective of this retrospective study with propensity score analysis (PSA) was to compare the cumulative postoperative morphine consumption at 48 hours between a group receiving dexmedetomidine, lidocaine, ketamine (OFA group), and a group receiving remifentanil plus morphine (opioid anesthesia-group (OA)). Postoperative pain at 24 and 48 hours and respiratory and hemodynamics complications were also assessed.

**Results:** 81 patients were included: 48 in the OFA group and 33 in the OA group. The cumulative postoperative morphine consumption at 48 hours was lower in the OFA group than in the OA group (28.50 [0-62.25] mg vs. 55 [34-79.50] mg, P=0.002, with PSA; OFA: -27.67 [-46;-11.50] mg, P=0.002). The postoperative pain score was significantly lower in the OFA group compared to the OA group at 24 hours (2 [0-4] vs. 3 [2-5], P=0.064, with PSA; OFA: -1.40 [-2.47;-0.33], P=0.0088) and 48 hours (0 [0-3] vs. 2.5 [0-5], P=0.034, with PSA; OFA:-1.87 [-3.45;-0.28], P=0.021). There were no differences between groups concerning respiratory or hemodynamic complications.

**Conclusions:** Our results suggest that OFA after VATS or RATS is safe and is associated with less postoperative morphine cumulative consumption and pain at 48 hours.

#### Feasibility and postoperative opioid sparing effect of an opioid-free anaesthesia in adult cardiac surgery: a retrospective study

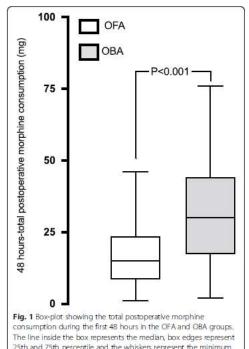


Clément Aguerreche<sup>1</sup>, Gaspard Cadier<sup>1</sup>, Antoine Beurton<sup>1,2</sup>, Julien Imbault<sup>1</sup>, Sébastien Leuillet<sup>3</sup>, Alain Remy<sup>1</sup>, Cédrick Zaouter<sup>4</sup> and Alexandre Ouattara<sup>1,2\*</sup>

Aguerreche et al. BMC Anesthesiology

(2021) 21:166

Methods: We conducted a single-centre and retrospective study including 80 patients above 18 years old who underwent on-pump cardiac surgery between November 2018 and February 2020. Patients were divided into two groups: OFA (lidocaine, ketamine, dexmedetomidine, MgSO4) or opioid-based anaesthesia (remifentanil and antihyperalgesic medications such as ketamine and/or MgSO4 and/or lidocaine at the discretion of the anesthesiologist). The primary endpoint was the total amount of opioid consumed in its equivalent of intravenous



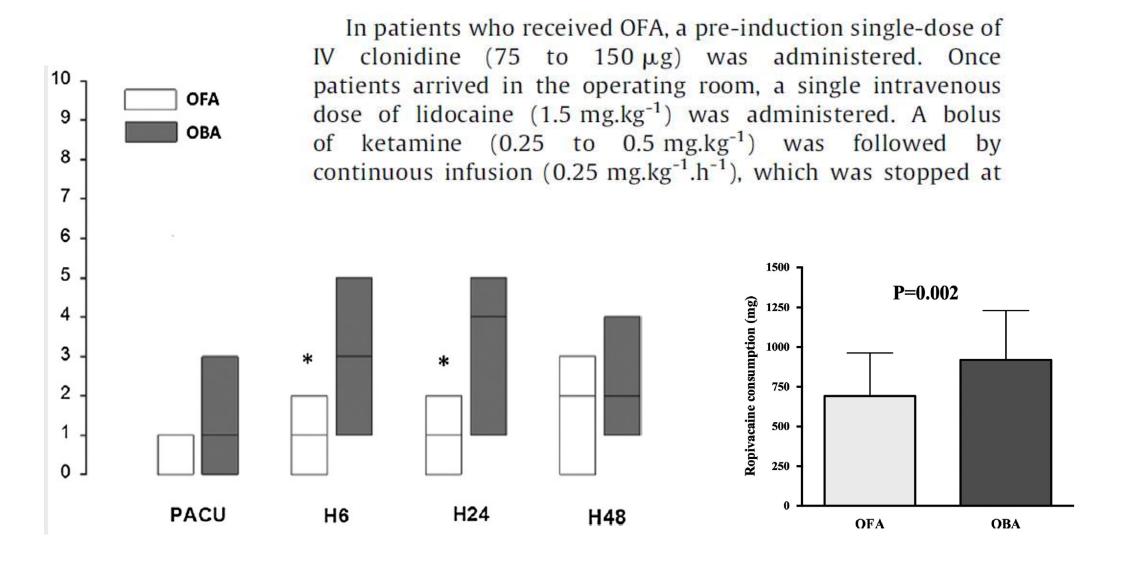
MORPHINE PO

25th and 75th percentile and the whiskers represent the minimum and maximum values

Effect of opioid-free anaesthesia on postoperative epidural ropivacaine requirement after thoracic surgery: A retrospective unmatched case-control study

Anaesth Crit Care Pain Med xxx (2018) xxx-xxx

Maeva Bello <sup>a,b</sup>, Sébastien Oger <sup>a</sup>, Sandrine Bedon-Carte <sup>c</sup>, Chloée Vielstadte <sup>a</sup>, Francesco Leo <sup>d</sup>, Cédrick Zaouter <sup>e</sup>, Alexandre Ouattara <sup>b,e,\*</sup>

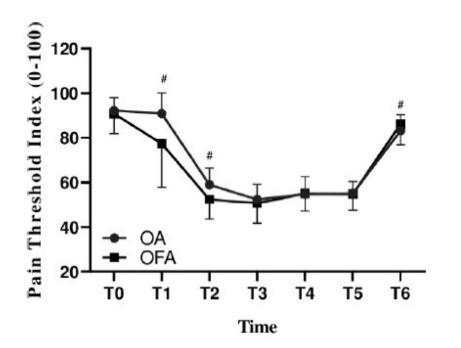


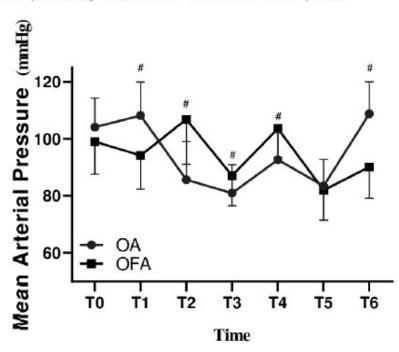
Opioid-free anesthesia compared to opioid anesthesia for lung cancer patients undergoing video-assisted thoracoscopic surgery: A randomized controlled study

Guangquan An<sup>1©</sup>, Yiwen Zhang<sup>2©</sup>, Nuoya Chen<sup>2¤a</sup>, Jianfeng Fu<sup>2</sup>, Bingsha Zhao<sup>2¤b</sup>, Xuelian Zhao<sup>6</sup>\*

#### Methods

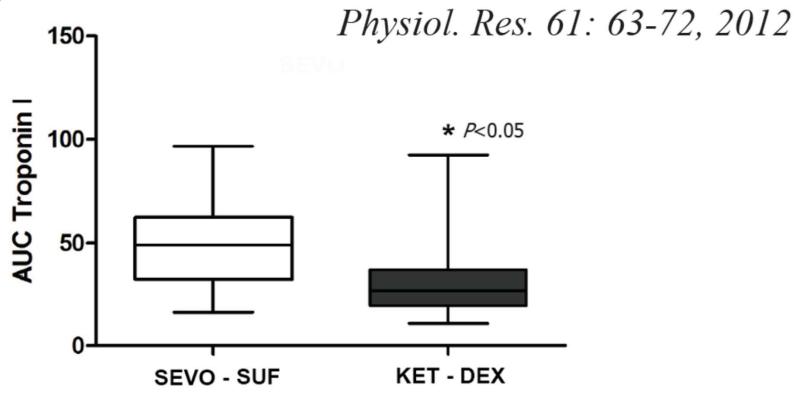
Patients (ASA I-II, 18–65 years old, BMI <30 kg m<sup>-2</sup>) scheduled to undergo video-assisted thoracoscopic surgery under general anesthesia were randomly allocated into two groups to receive opioid-free anesthesia (group OFA) with dexmedetomidine, sevoflurane plus thoracic paravertebral blockade or opioid-based anesthesia (group OA) with remifentanil, sevoflurane, and thoracic paravertebral blockade. The primary outcome variable was pain





# Comparison of the Effects of Ketamine-Dexmedetomidine and Sevoflurane-Sufentanil Anesthesia on Cardiac Biomarkers After Cardiac Surgery: An Observational Study

H. ŘÍHA<sup>1,2</sup>, T. KOTULÁK<sup>1</sup>, A. BŘEZINA<sup>1</sup>, L. HESS<sup>3</sup>, P. KRAMÁŘ<sup>1</sup>, O. SZÁRSZOI<sup>2,4</sup>, I. NETUKA<sup>2,4</sup>, J. PIRK<sup>2,4</sup>



**Fig. 3.** Area under the curve (AUC) of troponin I values on the morning of the first day after cardiac surgery emloying ketamine-dexmedetomidine (KET-DEX) or sevoflurane-sufentanil (SEVO) anesthesia.

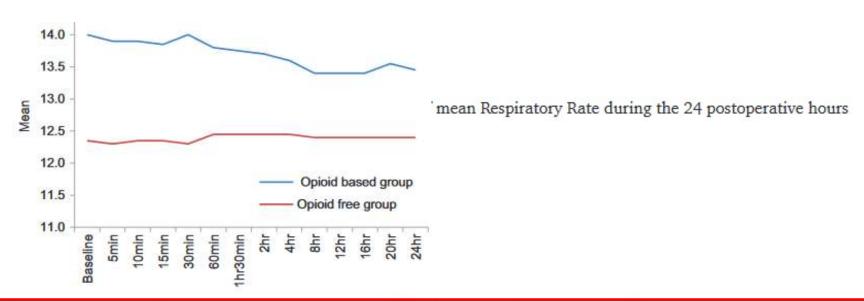
### Comparison of opioid-based and opioid-free TIVA for laparoscopic urological procedures in obese patients

Shaman Bhardwaj, Kamakshi Garg<sup>1</sup>, Sumeet Devgan<sup>2</sup>

Journal of Anaesthesiology Clinical Pharmacology | Volume 35 | Issue 4 | October-December 2019

prospective, randomized, blinded controlled study,

Incidence of respiratory depression, defined as fall in saturation, was more in opioid-based group. Postoperative analysis requirement (225  $\pm$  48.4 vs 63.6  $\pm$  68.5 mg of tramadol with *P* value of <0.001) and PACU discharge times (18.1  $\pm$  5.4 vs 11.7  $\pm$  4.3 hours with *P* value of <0.001) were significantly less in the opioid-free group.



respiratory depression, defined as fall in saturation, was more in opioid-based group.





Review

### Opioid-Free Anesthesia Benefit-Risk Balance: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Arthur Salomé <sup>1</sup>, Hakim Harkouk <sup>1,2</sup>, Dominique Fletcher <sup>1,2</sup> and Valeria Martinez <sup>1,2,\*</sup>

J. Clin. Med. 2021, 10, 2069

Abstract: Opioid-free anesthesia (OFA) is used in surgery to avoid opioid-related side effects. However, uncertainty exists in the balance between OFA benefits and risks. We searched for randomized controlled trials (RCTs) comparing OFA to opioid-based anesthesia (OBA) in five international databases. The co-primary outcomes were postoperative acute pain and morphine consumption at 2, 24, and 48 h. The secondary outcomes were the incidence of postoperative chronic pain, hemodynamic tolerance, severe adverse effects, opioid-related adverse effects, and specific adverse effects related to substitution drugs. Overall, 33 RCTs including 2209 participants were assessed. At 2 h, the OFA groups had lower pain scores at rest MD (0.75 (-1.18; -0.32)), which did not definitively reach MCID. Less morphine was required in the OFA groups at 2 and 24 h, but with very small reductions 1.61 mg (-2.69; -0.53) and -1.73 mg (p < 0.05), respectively, both not reaching MCID. The reduction in PONV in the OFA group in the PACU presented an RR of 0.46 (0.38, 0.56) and an RR of 0.34 (0.21; 0.56), respectively. Less sedation and shivering were observed in the OFA groups with an SMD of -0.81 (-1.05; -0.58) and an RR of 0.48 (0.33; 0.70), respectively. Quantitative analysis did not reveal differences between the hemodynamic outcomes, although severe side effects have been identified in the literature. No clinically significant benefits were observed with OFA in terms of pain and opioid use after surgery. A clear benefit of OFA use was observed with respect to a reduction in PONV However, more data on the safe use of OFAs should be collected and caution should be taken in the development of OFA.

## Analgesic impact of intra-operative opioids vs. opioid-free anaesthesia: a systematic review and meta-analysis

J. Frauenknecht, K. R. Kirkham, A. Jacot-Guillarmod and E. Albrecht

Anaesthesia 2019, 74, 651-662

Opioids are administered peri-operatively for postoperative analgesia, and intra-operatively to control the sympathetic response to surgical stimuli, frequently as a surrogate for presumed pain. However, opioid use during surgery is a matter of dispute in contemporary practice and carries the risk of side-effects such as postoperative nausea and vomiting. This meta-analysis investigated whether opioid-inclusive, compared with opioid-free anaesthesia, would reduce postoperative pain, without increasing the rate of postoperative nausea and vomiting. The electronic databases Medline and PubMed were searched until June 2018. We included trials investigating pain outcomes and comparing any type of intra-operative opioid administration with placebo injection or no intra-operative opioid. Most meta-analyses were performed using a random effects model. We rated the quality of evidence for each outcome. The primary outcome was pain score at rest (analogue scale, 0–10) at two postoperative hours. Our secondary outcomes included the rate of postoperative nausea and vomiting within the first 24 postoperative hours and length of stay in the recovery area. Twentythree randomised controlled trials, including 1304 patients, were identified. Pain scores at rest at two postoperative hours were equivalent in the opioid-inclusive and opioid-free groups with a mean difference (95%CI) of 0.2 (-0.2 to 0.5),  $I^2 = 83\%$ , p = 0.38 and a high quality of evidence. Similarly, there was high-quality evidence that the rate of postoperative nausea and vomiting was reduced in the opioid-free group, with a risk ratio (95%CI) of 0.77 (0.61–0.97),  $I^2 = 16\%$ , p = 0.03 and high-quality evidence for a similar length of stay in the recovery area, the mean difference (95%CI) being 0.6 (-8.2 to 9.3), min,  $I^2 = 60\%$ , p = 0.90. As there is strong evidence that opioid-inclusive anaesthesia does not reduce postoperative pain, but is associated with more postoperative nausea and vomiting, when compared with opioid-free anaesthesia, we suggest that anaesthetists should reconsider their intra-operative opioid choices on a case-by-case basis.

Total opioid-free general anaesthesia can improve postoperative outcomes after surgery, without evidence of adverse effects on patient safety and pain management: A systematic review and meta-analysis

Acta Anaesthesiol Scand. 2022;66:170–185.

Alexander Olausson<sup>1</sup> | Carl Johan Svensson<sup>2,3</sup> | Paulin Andréll<sup>3,4</sup> | Pether Jildenstål<sup>1,5,6,7</sup> | Sven-Egron Thörn<sup>2,3</sup> | Axel Wolf<sup>1,2,8</sup> |

Results: The study comprised 1934 patients from 26 RCTs. Common interventions included laparoscopic gynaecological surgery, upper gastrointestinal surgery, and breast surgery. There is firm evidence that opioid-free anaesthesia significantly reduced adverse postoperative events (OR 0.32, 95% CI 0.22 to 0.46,  $I^2 = 56\%$ , p < 0.00001), mainly driven by decreased nausea (OR 0.27, (0.17 to 0.42), p < 0.00001) and vomiting (OR 0.22 (0.11 to 0.41), p < 0.00001). Postoperative opioid consumption was significantly lower in the opioid-free group (-6.00 mg (-8.52 to -3.48), p < 0.00001). There was no significant difference in length of post-anaesthesia care unit stay and overall postoperative pain between groups.

Conclusions: Opioid-free anaesthesia can improve postoperative outcomes in several surgical settings without evidence of adverse effects on patient safety and pain management. There is a need for more evidence-based non-opioid anaesthetic protocols for different types of surgery as well as postoperative phases.

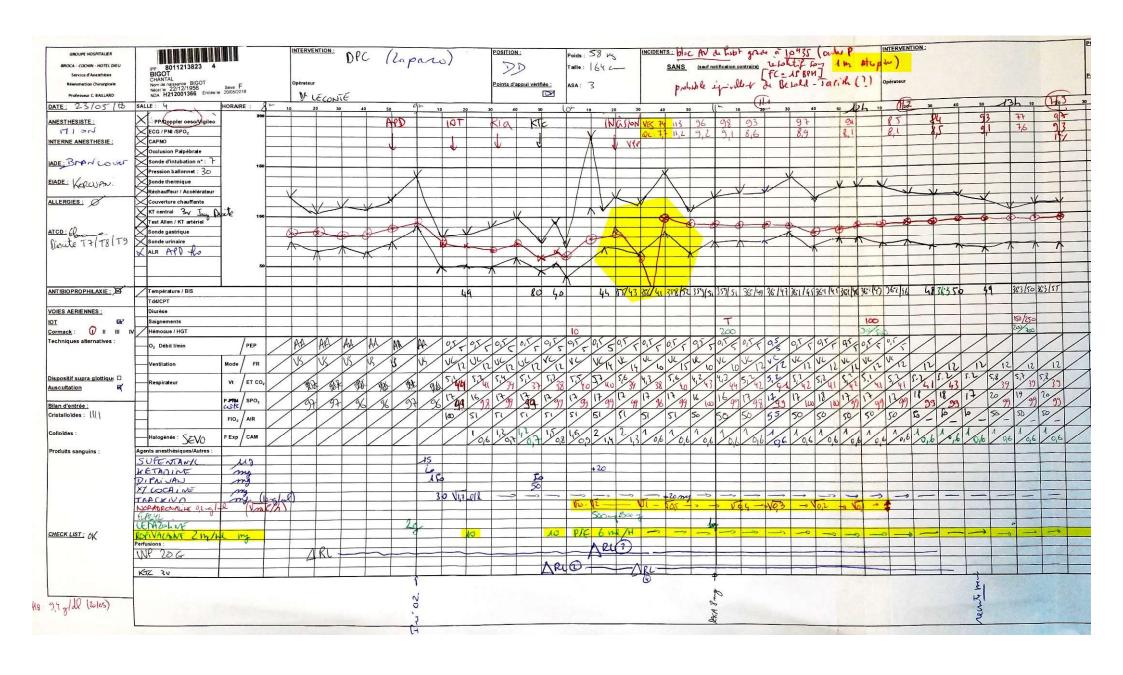
### Contre-indications

### Alpha2A:

**Trouble conductif = CI Absolue** 

- Relatives (hypotension)
  - ATCD cérébraux vasculaires
  - Coronaropathie mal équilibrée
  - Patients âgés sous bêta-bloqueurs
  - Hypovolémie

### DPC / APD tho - Trouble conductif



### Perioperative Use of Intravenous Lidocaine

Marc Beaussier 10 · Alain Delbos 2 · Axel Maurice-Szamburski 3 · Claude Ecoffey 4 · Luc Mercadal 5

Drugs (2018) 78:1229-1246

### Réduction du débit hépatique

- Insuffisance cardiaque
- Cirrhose sévère
- Insuffisance rénale grave



### Chez l'obèse?

- Bolus sur le poids réel
- Entretien sur le poids idéal

### Difficultés pratiques

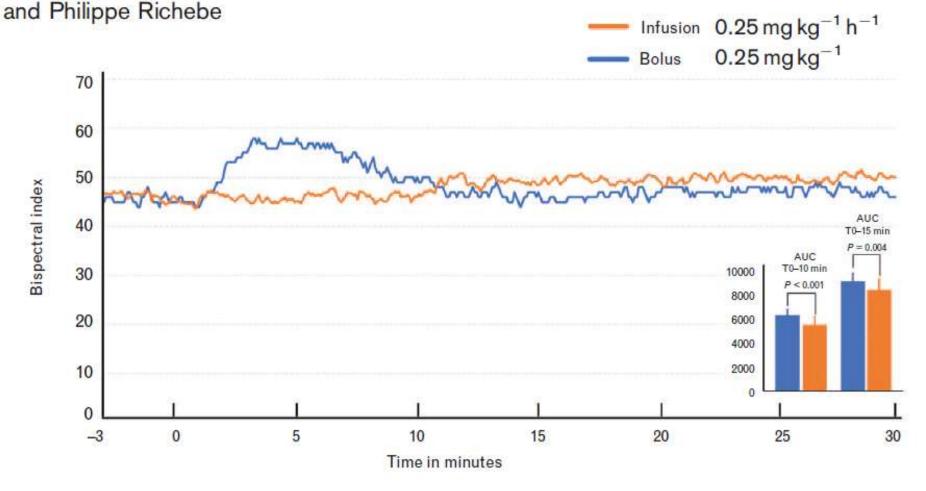
- Demi-vie de distribution de la clonidine
  - Injecter dès la pose de la VVP (ECG!)
  - Clonidine en PM (PO) ?
- Hypotension
  - La diminution des halogénés pose un pb de narcose
  - « Clé de l'OFA = baby NORADRENALINE »
- Reprise d'une VS en l'absence de curare
  - Intérêt de l'aide inspiratoire



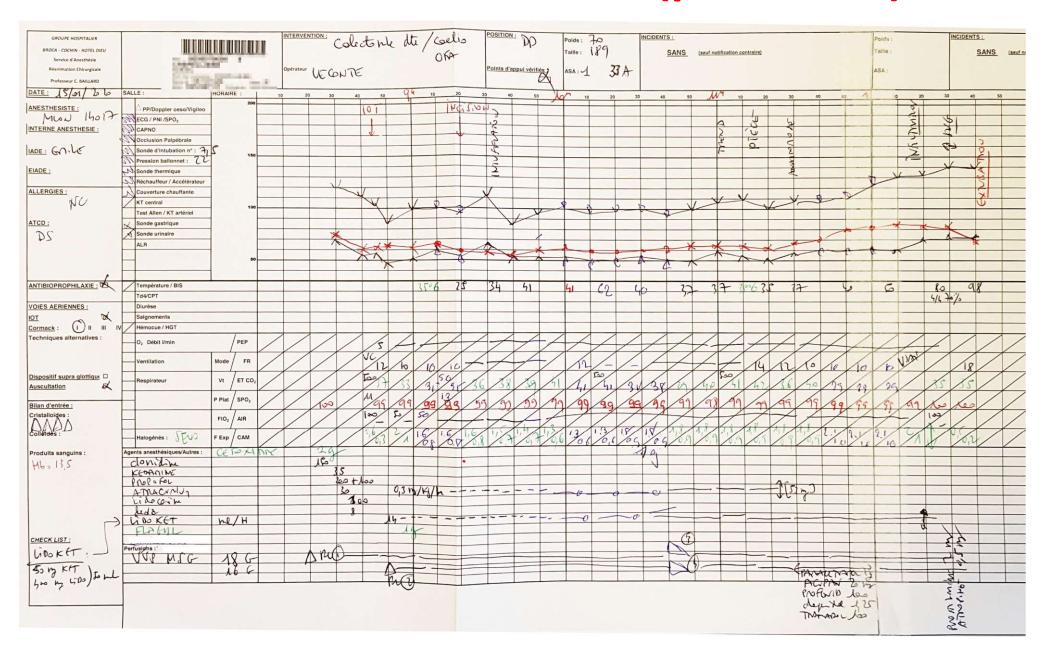
## The impact of bolus versus continuous infusion of intravenous ketamine on bispectral index variations and desflurane administration during major surgery

The KETABIS study

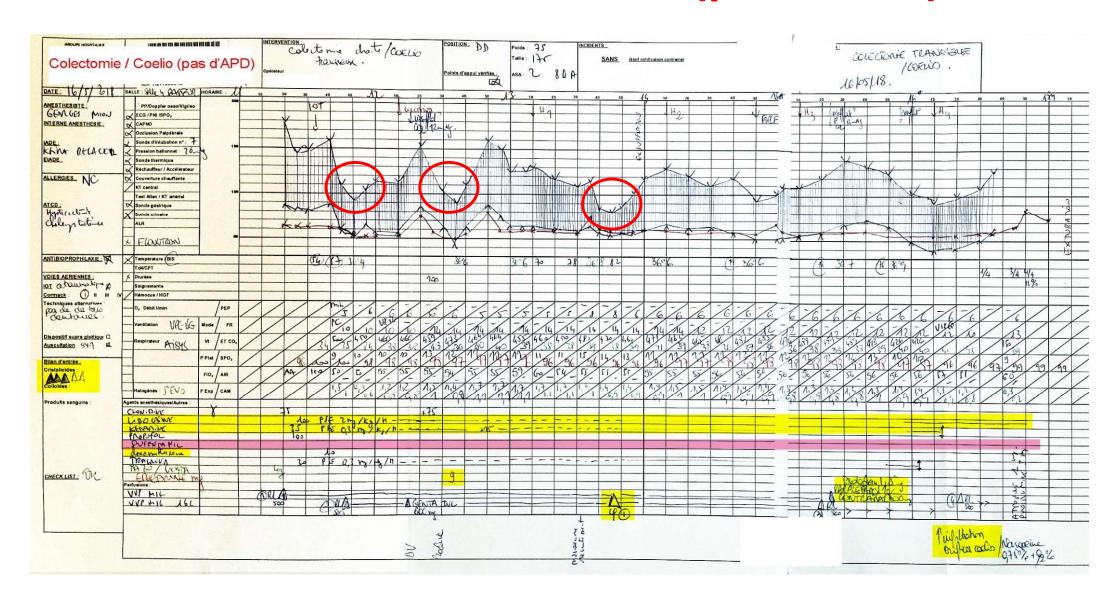
Lucie Carrara, Mathieu Nault, Louis Morisson, Nadia Godin, Moulay Idrissi, Annik Fortier, Marie Claude Guertin, Véronique Brulotte, Louis-Philippe Fortier, Olivier Verdonck



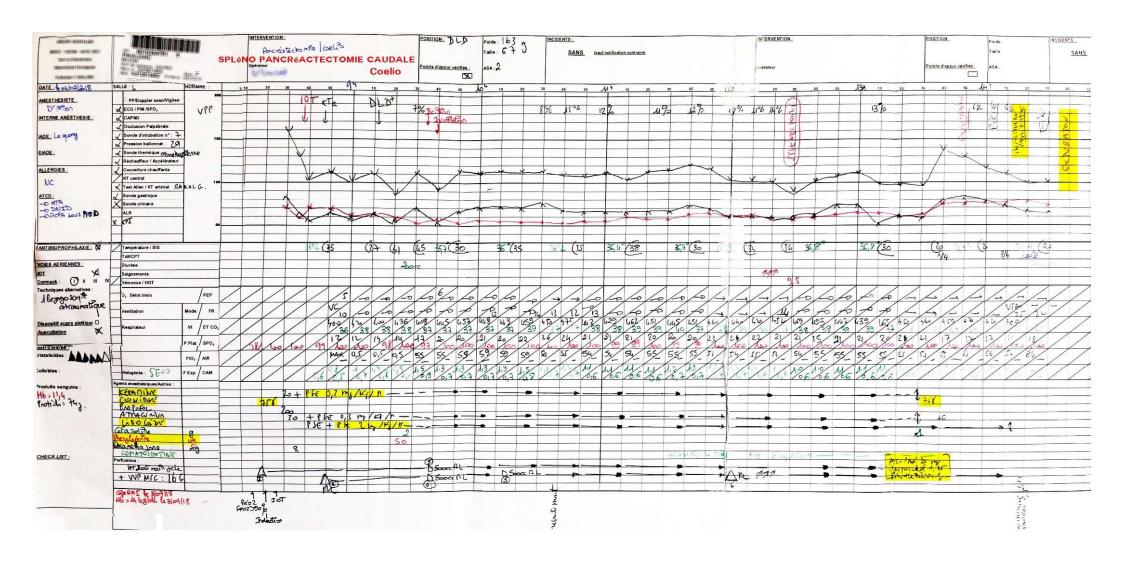
### Colectomie / coelio (pas d'APD)



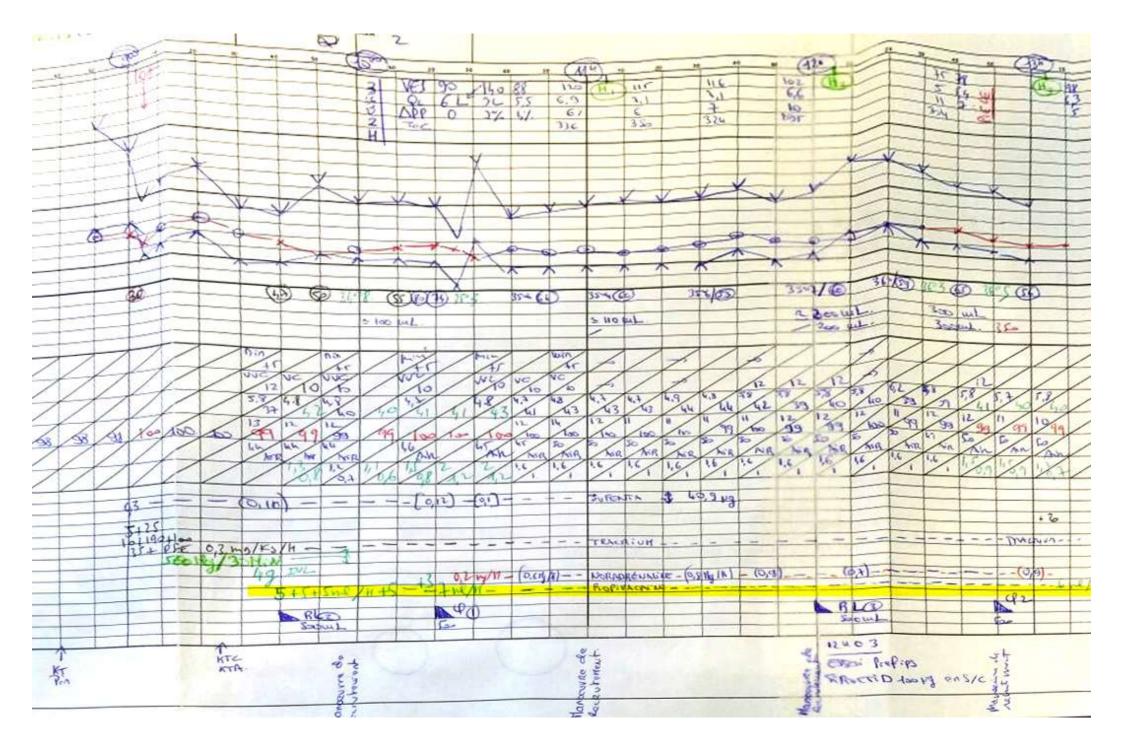
### Colectomie / coelio (pas d'APD)

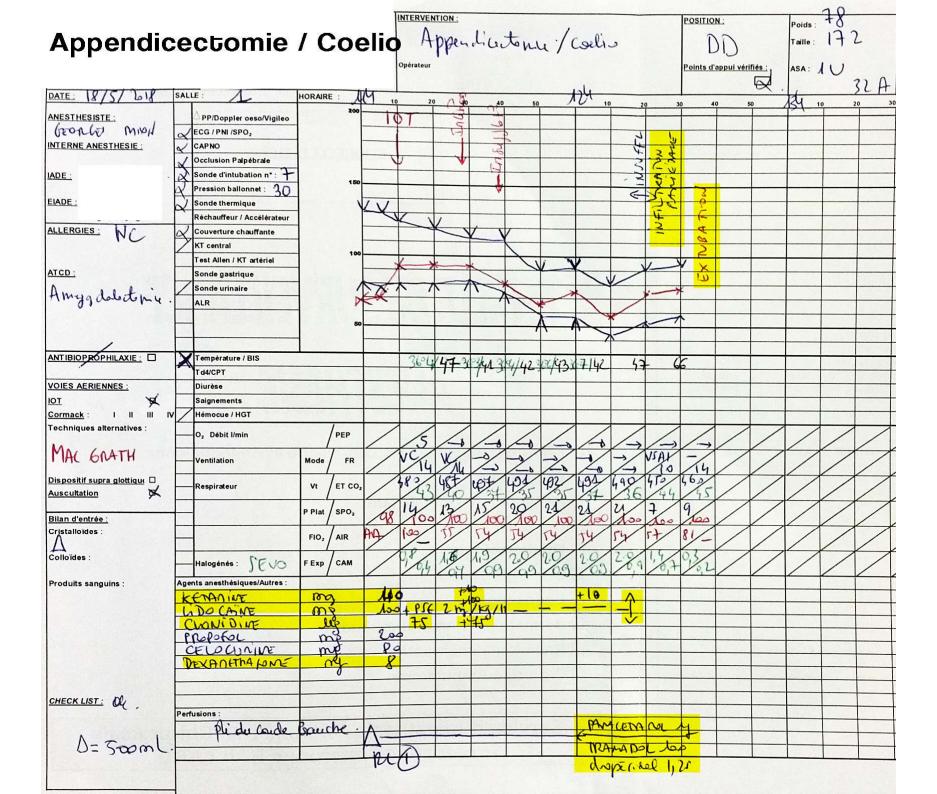


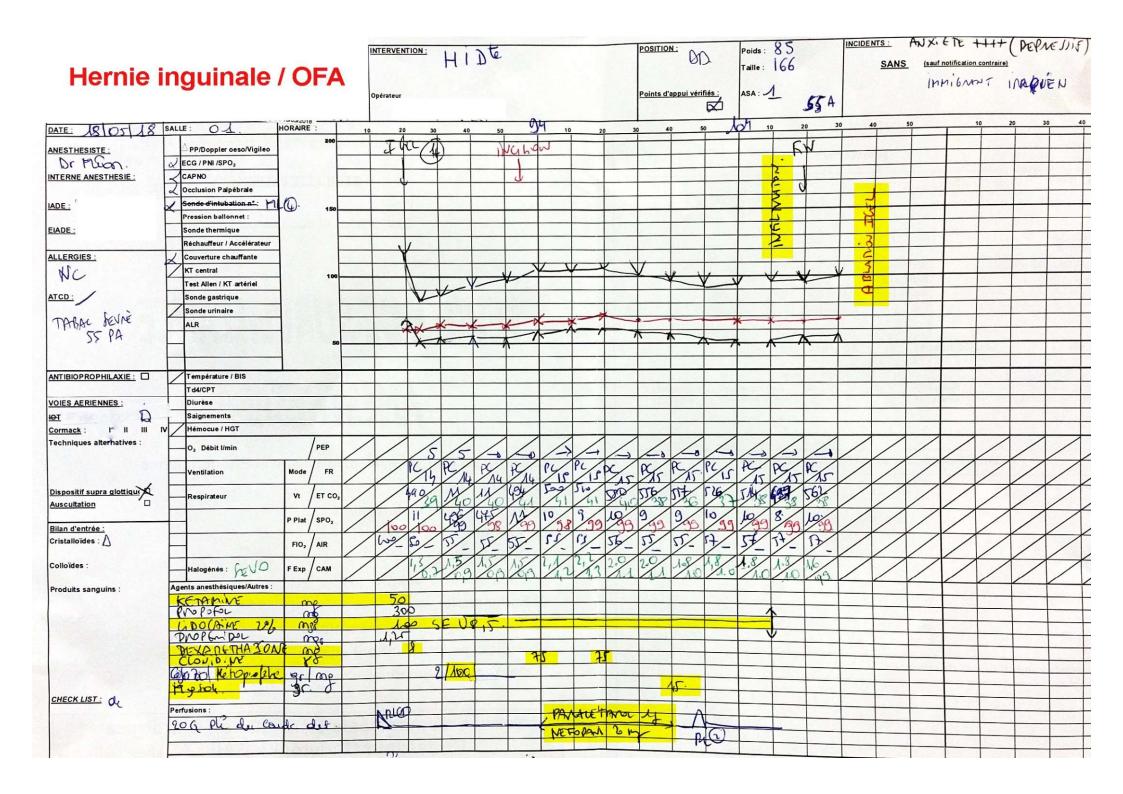
### DPC / coelio (pas d'APD)



### **DPC / APD Tho**

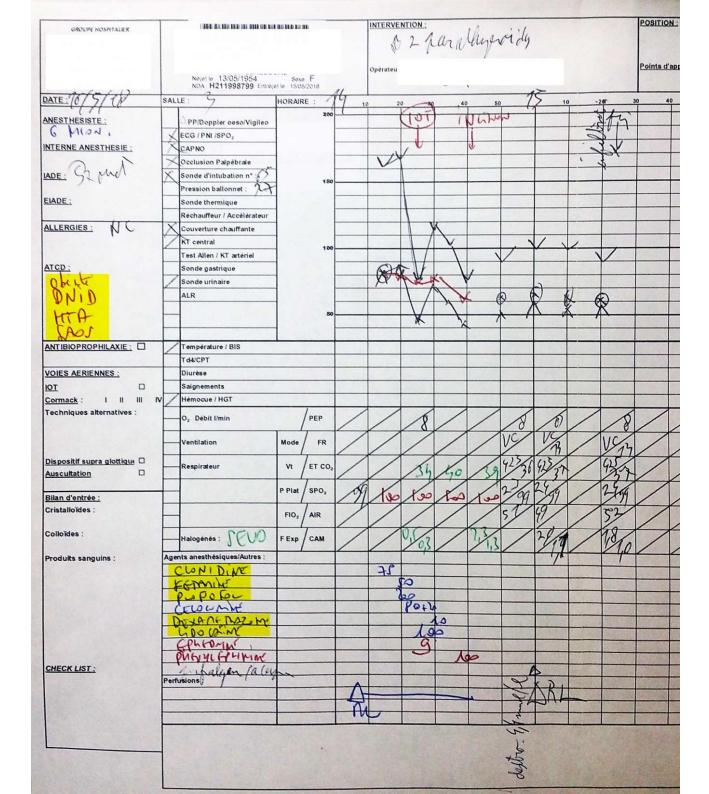




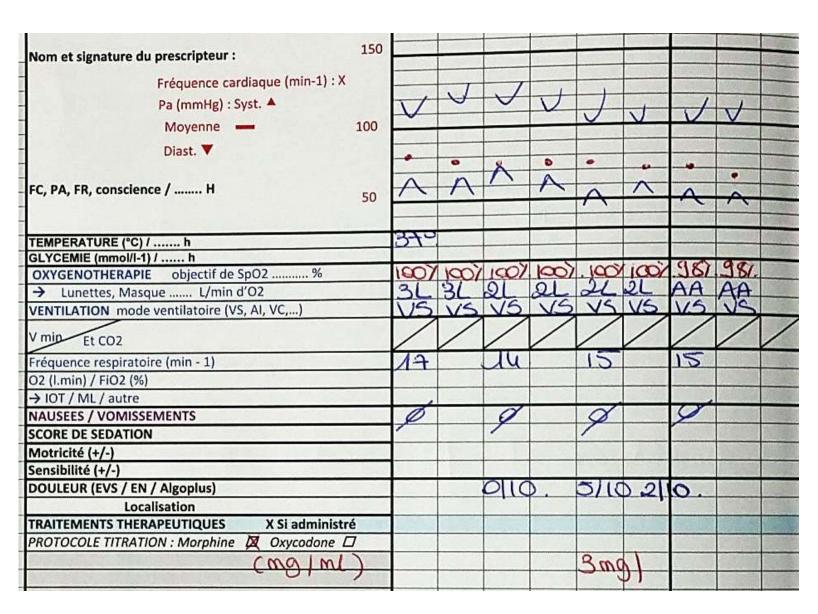


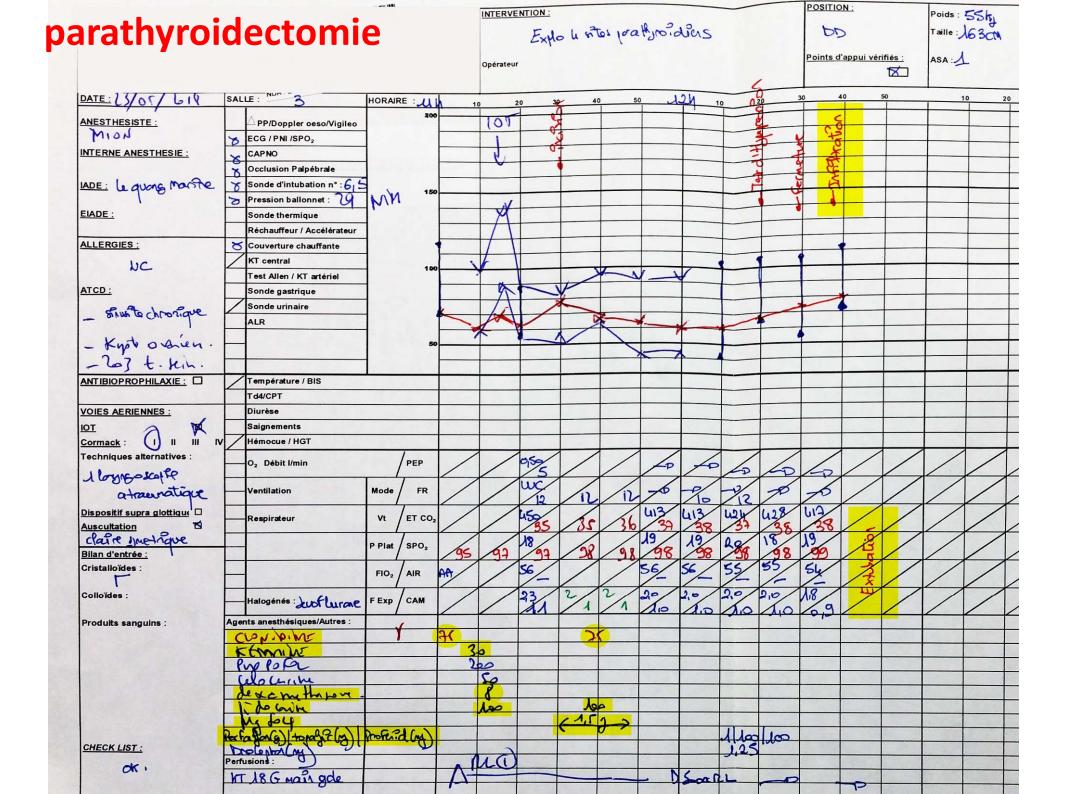
### Obésité Morbide

SAOS appareillé

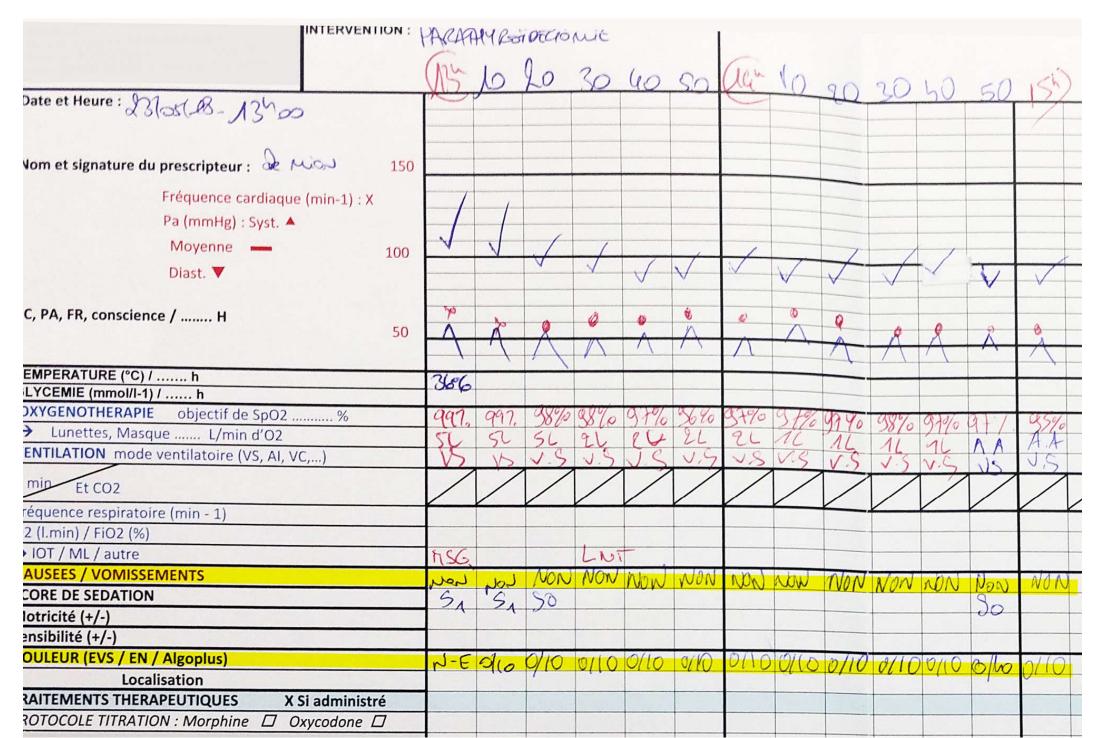


## Diminution de la consommation de morphine en PO

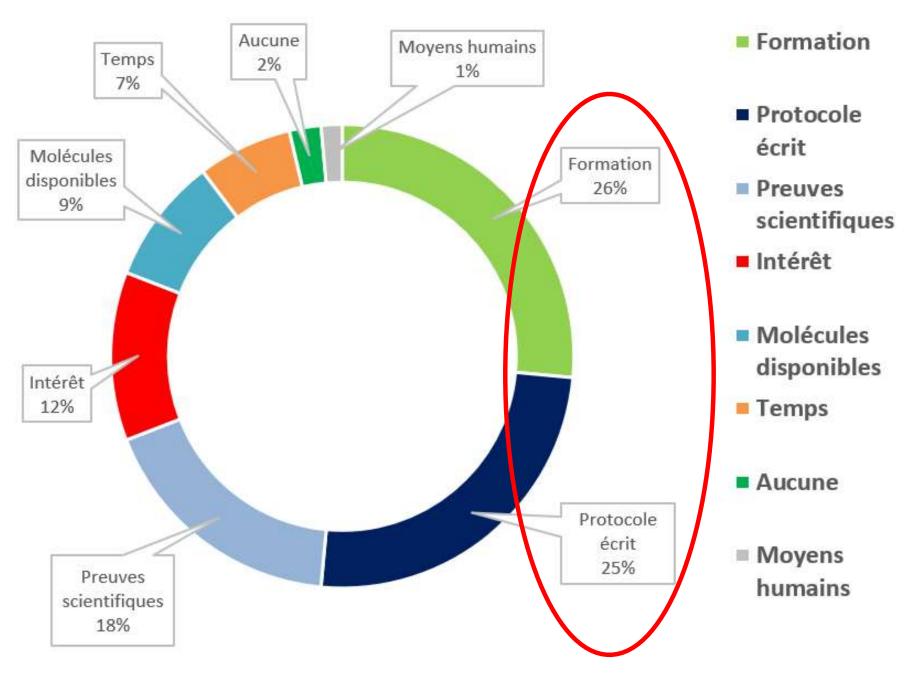


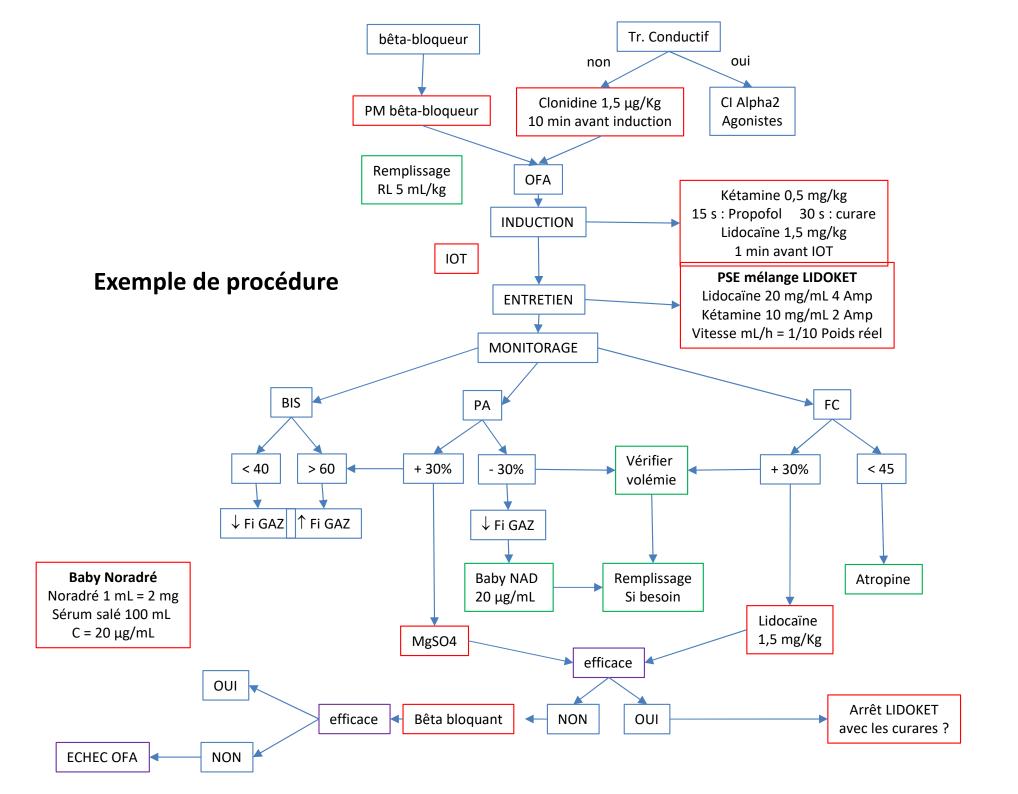


### Parathyroidectomie (SSPI)



#### Quelles limites à l'OFA à Cochin?





# Conclusion OBA, OSA ou OFA?

- Faisable, maturité de la spécialité pour questionner le dogme de l'OBA
- peu d'EBM
- Indications claires (SAOS, addiction aux opioïdes...)
- Contre-indications moins claires
- Donc prudence et protocolisation de mise
- Nécessité de grandes études prospectives et de big data

