# ERASing opioid monotherapy by EmbRASing multimodal analgesia in cardiovascular surgery

J. Erin (Allender) Ledford, PharmD, BCPS- AQ Cardiology, BCCCP
Cardiology Critical Care Clinical Specialist
Director- PGY2 Critical Care Residency
WakeMed Health & Hospitals, Raleigh, NC
eledford@wakemed.org

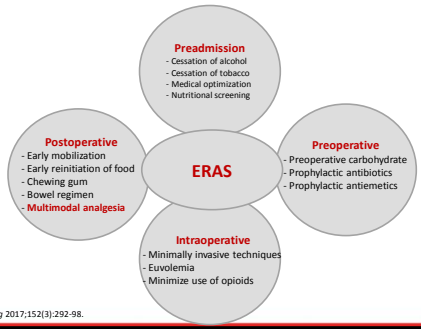
## Disclosures

- No financial disclosures or conflicts of interest

## Objectives

- Discuss literature regarding the use of multimodal pain therapy in critically ill patients

## Enhanced Recovery After Surgery



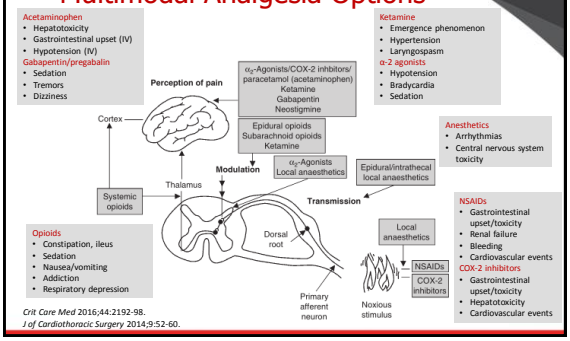

*JAMA Surg* 2017;152(3):292-98.

## Multimodal Analgesia

- Types of pain
  - Nociceptive
    - Visceral
    - Somatic
  - Neuropathic
- Effects of pain:
  - Protein catabolism
  - Hyperglycemia
  - Hypertension
  - Tachycardia
  - Immunosuppression
  - Respiratory insufficiency
  - Myocardial ischemia

*Methodist Debakey Cardiovasc J* 2018;14:77-88.
*Eur J Cardiothorac Surg* 2007;32:527-31.

## Multimodal Analgesia Options




*Crit Care Med* 2016;44:2192-98.
*J of Cardiothoracic Surgery* 2014;9:52-60.

## Guideline Recommendations for Multimodal Analgesia: ICU Patients

| Medication | Recommendation | Grade of Recommendation |
|---|---|---|
| acetaminophen | Use as adjunct | Conditional recommendation, very low quality of evidence |
| ketamine | Use low-dose (0.5 mg/kg IV push then 1-2 mcg/kg/min infusion) as adjunct | Conditional recommendation, very low quality of evidence |
| gabapentin/pregabalin/ carbamazepine | Use if neuropathic pain present | Strong recommendation, moderate quality of evidence |
| lidocaine | Do not routinely use as adjunct | Conditional recommendation, low quality of evidence |
| Cyclooxygenase (COX)-1-selective NSAID | Do not routinely use as adjunct | Conditional recommendation, low quality of evidence |

*Crit Care Med* 2018;46(9):e825-73.

## Multimodal Analgesia: Acetaminophen After Cardiac Surgery

| Trial | Treatment groups | Results |
|---|---|---|
| Cattabriga (2007) | • APAP 1 gram IV q6h X 3 days (n= 56)<br>• Matching PBO IV q6h X 3 days (n= 57)<br>*Background analgesia and sedation:* preoperative meperidine; intraoperative propofol, remifentanil, desflurane; postoperative tramadol infusion X 24 hours, morphine IV bolus for breakthrough pain | • Primary endpoint: IV APAP-treated patients had significant reductions in postoperative pain at 12, 18 and 24 hours (1 vs 2 on VAS) but not at any other time points<br>• Use of morphine was lower in IV APAP group (48 mg vs 97 mg over 3 days, NS)<br>• Limitations: small study, no other route of administration studied, opioid infusion used, hemodynamics not assessed |
| Pettersson (2005) | • APAP 1 gram IV q6h until 0900 on POD1 (n=39)<br>• APAP 1 gram PO q6h until 0900 on POD1 (n=38)<br>*Background analgesia and sedation:* preoperative morphine or ketobemidone; intraoperative propofol, fentanyl, sevoflurane; postoperative ketobemidone infusion | • Primary endpoint: IV APAP-treated patients used significantly less opioid (17.4 mg vs 22.1 mg)<br>• No differences in postoperative nausea, vomiting or VAS<br>• Limitations: small study, short duration, postoperative opioid infusion used, hemodynamics not assessed, no PBO arm |

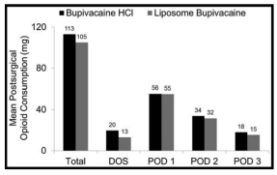
PBO = placebo; VAS = visual analog scale; NS = not significant; POD = postoperative day

*Eur J Cardiothorac Surg* 2007;32:527-31.
*J Cardiothorac and Vasc Anesth* 2005;19(3):306-09.

## Multimodal Analgesia: Bupivacaine After Cardiac Surgery

| Trial | Treatment groups | Results |
|---|---|---|
| Balky (2015) | • Bupivacaine (n= 30)<br>• Liposomal bupivacaine (n= 30)<br>*Background analgesia and sedation:* opioids and ketorolac | • No significant difference in hospital LOS (3.9 vs 4.6 days in liposomal group)<br>• No significant difference in VAS or morphine equivalents used (71 mg vs 75 mg in liposomal group)<br>• Limitations: small study, single center, non-randomized study design, no PBO arm |

LOS = length of stay




*Innovations* 2015;10:416-19.

## Multimodal Analgesia: Pregabalin After Cardiac Surgery

| Trial | Treatment groups | Results |
|---|---|---|
| Pesonen (2011) | • Pregabalin 150 mg PO X 1 (1 hour prior to surgery) then 75 mg PO bid X 5 days (n= 29)<br>• Matching PBO (n= 31)<br>*Background analgesia and sedation:* intraoperative propofol, fentanyl, sevoflurane; postoperative propofol, paracetamol 1 gram IV tid, oxycodone for breakthrough pain | • Primary endpoint: pregabalin-treated patients used significantly more oxycodone prior to extubation (10.8 vs 8.6 mg) but used less after (9 mg vs 16 mg)<br>• Time to extubation significantly longer in pregabalin group (10.6 hours vs 8.3 hours)<br>• Limitations: small study, primary endpoint changed during study, not intention-to-treat |
| Joshi (2013) | • Pregabalin 150 mg PO X 1 (2 hours prior to anesthesia induction) then 75 mg PO bid X 2 days (n= 20)<br>• Matching PBO (n= 20)<br>*Background analgesia and sedation:* intraoperative propofol, fentanyl, midazolam, isoflurane; postoperative propofol X 2 hours, paracetamol 1 gram IV q6h, tramadol and diclofenac IV for breakthrough pain | • Primary endpoint: pregabalin-treated patients had lower VAS scores at rest and during deep breathing throughout the first 48 postoperative hours<br>• Tramadol consumption lower in pregabalin group (67.8 mg vs 167.1 mg, $p < 0.001$)<br>• Peak inspiratory flow rates significantly higher in pregabalin group<br>• Limitations: small study |

*Br J Anaesth* 2001;106:873-81.
*Ann Card Anaesth* 2013;16:180-85.

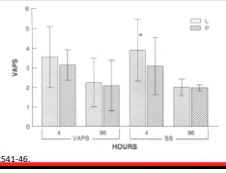
## Multimodal Analgesia: Gabapentin After Cardiac Surgery

| Trial | Treatment groups | Results |
|---|---|---|
| Menda (2010) | • Gabapentin 600 mg PO X 1 two hours before surgery (n= 30)<br>• Matching PBO (n= 30)<br>*Background analgesia and sedation:* Preoperative midazolam; intraoperative midazolam, fentanyl, propofol; postoperative morphine PCA X 24 hours, propofol | • Primary endpoint: total morphine consumption significantly lower in gabapentin group (6.7 vs 15.5 mg) for first 24 hours<br>• Gabapentin-treated patients had significantly lower pain scores but longer durations of mechanical ventilation (6.6 vs 1.2 hours) and more oversedation events at 2, 6 and 12 hours<br>• Limitations: single center and surgeon, only male patients included, small |
| Rapchuk (2010) | • Gabapentin 1200 mg PO X 1 (2 hours prior to surgery) then 600 mg PO bid X 2 days (n= 27)<br>• Matching PBO (n= 27)<br>*Background analgesia and sedation:* intraoperative propofol, fentanyl, midazolam, thiopentone, sevoflurane, isoflurane; postoperative fentanyl PCA, paracetamol 1 gram qid | • Primary endpoint: no significant differences in fentanyl PCA usage in first 48 postoperative hours (1355 mcg in gabapentin group vs 1562 mcg)<br>• No differences in sleep scores, anti-emetic or adjunct analgesia use, VAS scores or side effects<br>• Limitations: small study |

PCA = patient-controlled analgesia
*J Cardiothorac Vasc Anesth* 2010;24:808-13.
*Anaesth Intensive Care* 2010;38:445-51.

## Multimodal Analgesia: Lidocaine After Cardiac Surgery

| Trial | Treatment groups | Results |
|---|---|---|
| Insler (1995) | • Lidocaine 1.5 mg/kg IV over 10 minutes then 30 mcg/kg/min infusion up to 48 hours (n=440)<br>• Matching PBO (n= 45)<br>*Background analgesia and sedation:* preoperative morphine; intraoperative fentanyl, midazolam, enflurane; postoperative fentanyl, midazolam | • Primary endpoint: no significant differences in visual analog pain scores (VAPS)<br>• No differences in time to extubation, postoperative fentanyl dose, length of stay<br>• Limitations: small study, underpowered to detect differences in VAPS |

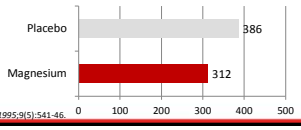



*J Cardiothorac Vasc Anesth 1995*;9(5):541-46.

## Multimodal Analgesia: Magnesium After Cardiac Surgery

| Trial | Treatment groups | Results |
|---|---|---|
| Ferasatkish (2008) | • Magnesium 0.032 mmol/kg/hr, starting in operating room (n=109)<br>• Matching PBO (n= 109)<br><br>*Background analgesia and sedation:* preoperative morphine and diazepam; intraoperative sufentanil, midazolam, isoflurane; postoperative fentanyl, propofol | • Primary endpoint: duration of postoperative mechanical ventilation significantly shorter in magnesium group<br>• Magnesium-treated patients had significantly lower pain scores and used less IV morphine in first 24 postoperative hours (13.6 vs 20.1 mg)<br>• 2 patients in magnesium group experienced severe bradycardia, hypotension<br>• Limitations: single center |

**Duration of mechanical ventilation (minutes)**

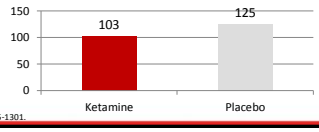



*J Cardiothorac Vasc Anesth 1995*;9(5):541-46.

## Multimodal Analgesia: Ketamine After Cardiac Surgery

| Trial | Treatment groups | Results |
|---|---|---|
| Lahtinen (2004) | • S (+)-ketamine 75 mcg/kg bolus then 1.25 mcg/kg/min infusion X 48 hours (n=44)<br>• Matching PBO (n= 46)<br><br>*Background analgesia and sedation:* intraoperative and postoperative propofol, oxycodone PCA started after extubation | • Primary endpoint: ketamine-treated patients used less oxycodone (p = 0.023)<br>• VAS scores at rest and during a deep breath, duration of mechanical ventilation and cognitive function were similar<br>• 8% of patients in ketamine group had psychotomimetic disturbances<br>• Limitations: use of S (+)-ketamine and PCA, single center |

**Oxycodone use (mg)**




*Anesth Analg 2004*;99:1295-1301.

## Summary

- Acetaminophen and GABA analogs are opioid-sparing and reduce pain scores
- Adverse effects may preclude widespread adoption of magnesium and ketamine infusions
- The utility of bupivacaine and lidocaine is unclear

## WakeMed ERAS Cardiac Protocol

**Preoperative**
- 22 gram carbohydrate drink
- Gabapentin 300 mg PO X 1
- APAP 1000 mg PO X 1

**Intraoperative**
- Insulin infusion
- Anti-emetics

**Postoperative**
- Gabapentin 300 mg PO bid X 4 days then 300 mg PO daily X 2 days*
- APAP 1000 mg PO q6h X 5 days
- Dexmedetomidine or propofol infusion
- Bowel regimen

*Dose reduced to 100 mg if ≥ 70 YO

*J Thorac Cardiovasc Surg* 2019;157:1881-88.

## WakeMed ERAS Cardiac Study: Patient Population

Cardiac Surgery patients

Pre-ERAS (n = 489)

Post-ERAS (n = 443)

*J Thorac Cardiovasc Surg* 2019;157:1881-88.

## WakeMed ERAS Cardiac Study: Baseline demographics

| Characteristics | Pre-ERAS (n = 489) | Post-ERAS (n = 443) |
|---|---|---|
| Mean age, years | 65 | 65 |
| Female, % | 31 | 31 |
| Body mass index | 29 | 29 |
| Diabetes mellitus, % | 57 | 58 |
| Surgery type | | |
| Isolated CABG | 62 | 61 |
| Mitral/tricuspid valve surgery | 15 | 14 |
| Aortic valve surgery | 16 | 18 |
| Other | 7 | 7 |

*J Thorac Cardiovasc Surg* 2019;157:1881-88.

## WakeMed ERAS Cardiac Study: Results

| Outcomes | Pre-ERAS (n = 489) | Post-ERAS (n = 443) | p value |
|---|---|---|---|
| Mean IV morphine equivalents used, mg | 29 | 21 | < 0.01 |
| Hospital LOS, days | 7 | 6 | < 0.01 |
| ICU LOS, hours | 43 | 28 | < 0.01 |
| Postoperative ventilator time, hours | 5.2 | 5.3 | 0.53 |
| Reintubation rate, % | 5.3 | 4.1 | 0.44 |
| GI complications, % | 6.8 | 3.6 | 0.04 |

GI = gastrointestinal

*J Thorac Cardiovasc Surg* 2019;157:1881-88.

## Summary

- Multimodal analgesia is opioid-sparing and improves outcomes in cardiac surgery patients
- The impact of multimodal analgesia for the general ICU patient population is unknown
  - Organ function
  - Adverse effect profile
  - Medical history