Postoperative Delirium

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Objectives

- Explore risk factors and advice for preoperative screening
- Provide some recommendations for perioperative care
- Identify novel techniques currently under investigation

Why Do I Care?

Why Should We Care?

- Aging population
  - Statistics Canada Estimates by 2036, 23-25% of population will be ≥ 65 yo
  - Estimated 1/3 of people ≥ 65 will receive anesthetic in any year
- New onset delirium increases length of stay by average of 8 days
  - This prolongation was not seen in patients with admitting diagnoses of delirium
- Medical and Surgical patients showed increased RR 1.95 of mortality , OR 2.41 institutionalization

McCusker J, Cole MG, Dendukuri N, Belzile E. **Does delirium increase hospital stay?** Journal of American Geriatrics Society. 2003; 51: 1539-46.

Witlox J, Eurelings LS, de Jonghe JF et al. **Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis.** JAMA 2010; 304: 443-51.

What is Delirium

- DSM V Characterizes it based on 5 criteria
  I. Disturbance in attention and awareness
  II. Fluctuant, developing over short time period
  III. Disturbance in cognition
  IV. Disturbances are not explained by pre-existing diagnosis
  V. Evidence of medical problem, medication side effect, or substance intoxication/withdrawal

- May be hyperactive or hypoactive
  - Mix of both

Pathophysiology

- Inflammation and stress
  - Leads to release of inflammatory mediators including interlukin-1, TNFα, interferon
  - Increases permeability of blood-brain barrier
  - Leads to altered neurotransmission, drug trapping
- Cholinergic and dopaminergic activity implicated
  - Anticholinergics can precipitate delirium, cholinesterase inhibitors can treat
  - Antipsychotic agents working via dopamine may provide benefit

- **Extremely** Multifactorial

Pathophysiology

- The INTUIT Study: Investigating Neuroinflammation Underlying Postoperative Cognitive Dysfunction
- Ongoing observational prospective cohort
- Evaluating monocyte chemoattractant protein 1 in CSF pre and postoperatively up to 1 yr
- Assess for delirium postop day 1-5, cognitive function up to 1 yr

Berger M, Oyeyemi D, Olurinde MO et al. **The INTUIT Study: Investigating Neuroinflammation Underlying Postoperative Cognitive Dysfunction.** Journal of American Geriatrics Society. 2019.

Risk Factors

Patient

- AGE
- ♂
- Dehydration/malnutrition
- Depression
- Dementia
- Polypharmacy
- Metabolic derangements
- Disease states
  - Hypoxia
  - Febrile
  - Anemia
  - Shock

Procedure

- Type of OR
  - Hip Fracture, vascular, cardiothoracic
- Emergent vs Urgent vs Elective
- Duration of OR (?)
- Physical restraints
- Urinary Catheters

Inouye SK. **Delirium in older persons.** NEJM 2006; 354: 1157-65.

Ouimet S, Kavanagh BP, Gottfried SB, Skrobik Y. **Incidence, risk factors and consequences of ICU delirium.** Intensive Care Med 2007; 33: 66-73.

Prediction Tools

- 0= 1-2% risk of delirium
- 1-2= 8-19%
- ≥3 = 45-55%

Table 1 A clinical prediction rule for delirium after elective non-cardiac surgery[18]

Variable	Criteria	Points
Cognitive impairment	TICS score < 30	1
Age ≥ 70	Yes	1
Physical impairment	SAS Class IV (unable to perform 3 METs)	1
Laboratory abnormality	Sodium < 130 or > 150 $mmol \cdot L^{-1}$	1
	Potassium < 3.0 or > 6.0 $mmol \cdot L^{-1}$	
	Glucose < 3.3 or > 16.7 $mmol \cdot L^{-1}$	
Aortic aneurysm surgery	Yes	2
Non-cardiac thoracic surgery	Yes	1

TICS = telephone interview for cognitive status (a score < 30 indicates minimal cognitive impairment);[49] SAS = specific activity scale;[50] METs = metabolic equivalents (Class IV is equivalent to exercise tolerance ≤ 2 METS); 0 points = 1-2% incidence of delirium; 1-2 points = 8-19% incidence of delirium; ≥ 3 points = 45-55% incidence of delirium

- Marcantonio ER, Goldman L, Mangione CM, et al. **A clinical prediction rule for delirium after elective noncardiac surgery.** JAMA 1994; 271: 134-9.

Prediction Tools

1. Rapidity of onset of the insult
2. Severity of the insult
3. Preoperative health status

Noimark D. **Predicting the onset of delirium in the post-operative patient.** Age Ageing 2009; 38: 368-73.

Table 2 Patient-specific predictors of delirium[20]

Predictor	Criteria for increased risk
Age	Increasing age
ASA physical status	ASA ≥ III
Sex	Male
Cognitive impairment	Dementia
	MMSE < 24
	Poor executive function
	Attention deficits
Depression	Presence of preoperative depression
Smoking	Preoperative smoking
Comorbidity	Presence of multiple comorbidities
	Risk factors for vascular disease
Medications	Three or more medications
	Anticholinergic effect
Alcohol	Alcohol use
Functional status	Inability to perform activities of daily living
Visual or hearing	Visual or hearing impairment
Laboratory abnormalities	Anemia (inconsistent)
	Hypoalbuminemia
	Electrolyte abnormalities (inconsistent)
	Renal insufficiency

ASA = American Society of Anesthesiologists; MMSE = Mini-Mental Status Examination

How do we diagnose? When?

- POD 1-3 highest occurrence
- Do we recognize and diagnose delirium?

- Limited utility for anesthesiologist
  - Lack of follow-up
  - Role for connectcare?

Confusion Assessment Method

1. Acute onset and fluctuating
2. Inattention
3. Disorganized thinking
4. Altered LOC

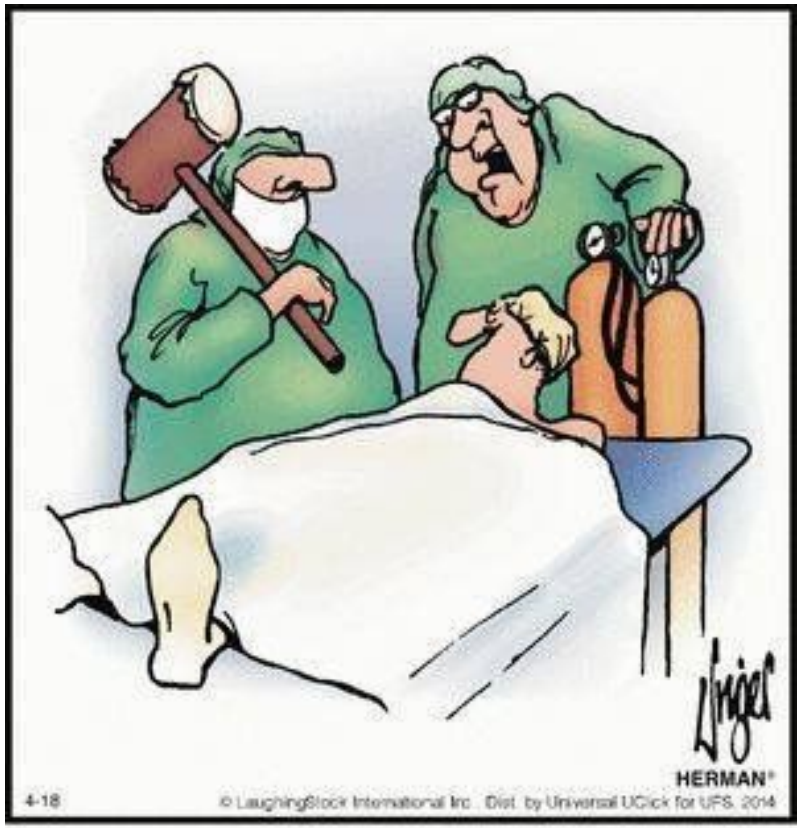
Delirium = Must have 1 and 2, and then one of 3 or 4.

Has been adapted for ventilated patients in ICU

Note: MMSE noted to be least accurate in large systematic review for predicting delirium

Wong CL, Holroyd-Leduc J, Simel DL, Straus SE. **Does this patient have delirium?: value of bedside instruments.** JAMA 2010; 304: 779-86.

So I've identified my patient at risk, now what?



"I'm your anesthetist and he's my backup man."

Preoperatively

- **Consult geriatrician?**
- RCT for 126 patients admitted for hip fracture
  - Recommended ≥ 24 hr preop
  - Instituted protocol for preventive supportive measures including rehydration, restoration of electrolytes, med reconciliation, analgesia strategy, and plan for early mobilization postop
  - Delirium in 32% pts with early geriatric consult vs 50% in control group
  - Obvious limitation meeting patients *immediately* preop
    - Role for PAC?

Marcantonio ER, Flacker JM, Wright RJ, Resnick NM. **Reducing delirium after hip fracture: a randomized trial.** J Am Geriatr Soc 2001; 49: 516-22.

Early Geriatric Consultation

- RCT comparing patients randomized to geriatric unit postop vs conventional orthopedic unit post hip fracture repair
- Incidence reduced 20%
- Duration reduced by 5 days

Lundstrom M, Olofsson B, Stenvall M, et al**. Postoperative delirium in old patients with femoral neck fracture: a randomized intervention study.** Aging Clin Exp Res 2007; 19: 178-86.

Geriatric Consultation

Bottom line

- Unlikely feasible to get geriatrics involved preop
- Determine what they do to optimize, do it ourselves?
- Modify the modifiable RFs

Ounce of prevention = Pound of cure

Haldol

- RCT comparing prophylactic Haldol 72 hours preop vs placebo
  - Haldol 0.5mg PO TID 72 hours both pre and post op
  - No difference in incidence of delirium, both 6.4 days mean reduction in duration of delirium, and subsequently 5.5 days mean reduction in hospital stay
  - Both groups had preop geriatric consultation

Kalisvaart KJ, de Jonghe JF, Bogaards MJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. Journal of the American Geriatrics Society 2005; 53: 1658-66.

Haldol

- Randomized prospective study with 201 patients ≥75yo going for major abdominal or orthopedic surgery
- Postop Day: 0-5 received Haldol 5mg IV via slow infusion
- Incidence of severe delirium was 18.2% in haldol group compared to 32% in control
- No difference in duration of delirium
- No adverse events at high dose of 5mg

Fukata S, Kawabata Y, Fujisjiro K, et al. Haloperidol prophylaxis for preventing aggravation of postoperative delirium in elderly patients: a randomized, open-label prospective trial. Surg Today 2017 Jul; 47 (7): 815-826

Haldol

- Efficacy of low dose (0.5mg) IV haldol in RCT for 135 patients post major thoracic surgery (noncardiac)
- Found no efficacy for incidence nor duration of POD
- May be dose dependent

Khan BA, Perkins AJ, Campbell NL, et al. Preventing Postoperative Delirium After Major Noncardiac Thoracic Surgery- A Randomized Clinical Trial. Journal of American Geriatrics Society. 2018. Dec;66 (12): 2289-2297.

Haldol

- Useful for patients at risk, and appears to be safe even at high doses.
- Unclear ideal dose
  - Relationship for prophylaxis of POD *appears* to be dose-dependant

Haldol

Prophylactic Antipsychotic Use for Postoperative Delirium: A Systematic Review and Meta-Analysis

Tomoya Hirota, MD, and Taro Kishi, MD, PhD

Table 1. Study, Patient, and Treatment Characteristics of Included Randomized Controlled Trials

Study	N	Study Design	Population	Intervention	Diagnostic Criteria	Outcome Measures[a]	Comments
Hakim et al,[18] 2012 (Egypt)	101	DBPCT parallel	Age ≥ 65 y, male: 68.3% On-pump cardiac surgery NYHA class III or IV: 62.4% MMSE score ≥ 25 ICU setting All patients had subsyndromal delirium prior to randomization	RIS: n = 51, 0.5 mg bid until incidence of delirium PLA: n = 50	ICDSC ≥ 3 every 8 h *DSM-IV-TR*	**Incidence of delirium: RIS > PLA** Duration of delirium: RIS = PLA Severity of delirium: RIS = PLA (highest score on the ICDSC) Length of ICU stay: RIS = PLA Length of hospital stay: RIS = PLA	Switched to standard treatment (RIS up to 4 mg/d and HAL as needed)
Kalisvaart et al,[14] 2005 (Netherlands)	430	DBPCT parallel	Mean age = 79.1 y, male: 20.2% Orthopedic (hip) surgery APACHE II mean score = 13.4 MMSE mean score = 24.7 Non-ICU setting	HAL: n = 212, 0.5 mg tid until postoperative day 3 PLA: n = 218	*DSM-IV-TR* CAM	**Incidence of delirium: HAL = PLA** Duration of delirium: HAL > PLA Severity of delirium: HAL > PLA (maximum DRS-R-98 score) Length of hospital stay: HAL > PLA	Switched to standard treatment (HAL and/or lorazepam) when delirium was diagnosed
Kaneko et al,[22] 1999 (Japan)	80	Nonblind parallel	Mean age = 72.8 y, male: 64.1% Gastrointestinal surgery Cognitive impairment: 7.7% Non-ICU setting	HAL: n = 40, 5 mg IV until postoperative day 5 PLA (normal saline): n = 40	*DSM-III-R*	**Incidence of delirium: HAL > PLA**	Switched to standard treatment (HAL and/or lorazepam) when delirium was diagnosed
Larsen et al,[16] 2010 (United States)	495	DBPCT parallel	Mean age = 73.7 y, male: 45.7% Orthopedic surgery (knee and hip joint replacement) ASA class ≥ 3: 42.0% No dementia Non-ICU setting	OLA: n = 243, 5 mg twice perioperative administration PLA: n = 252	*DSM-III-R* MMSE DRS-R-98 CAM	**Incidence of delirium: OLA > PLA** Time to onset of delirium: OLA > PLA Duration of delirium: OLA < PLA Severity of delirium: OLA < PLA (maximum DRS-R-98 score) Length of hospital stay: OLA = PLA	Continued blind treatment and additional standard treatment (nonpharmacologic and/or HAL/OLA as needed) when delirium was diagnosed
Prakanrattana and Prapaitrakool,[15] 2007 (Thailand)	126	DBPCT parallel	Mean age = 61.0 y, male: 58.7% On-pump cardiac surgery NYHA class III or IV: 33.3% ICU setting	RIS: n = 63, 1 mg when regained consciousness from surgery PLA: n = 63	CAM-ICU	**Incidence of delirium: RIS > PLA** Length of ICU stay: RIS > PLA Length of hospital stay: RIS = PLA	
Wang et al,[17] 2012 (China)	457	DBPCT parallel	Mean age = 74.2 y, male: 63.0% Noncardiac surgery ASA class ≥ 3: 38.7% ICU setting	HAL: n = 229, 0.5 mg IV within 1 h after enrollment, followed by 0.1 mg/h for 12 h PLA: n = 228	Richmond Agitation Sedation Scale CAM-ICU	**Incidence of delirium: HAL > PLA** Time to onset of delirium: HAL = PLA Length of ICU stay: HAL > PLA Length of hospital stay: HAL = PLA	Continued blind treatment and additional standard treatment (nonpharmacologic and/or IV HAL 0.5–1.0 mg every 20 min) when delirium was diagnosed

[a]In Outcome Measures column, boldface indicates primary outcome measure of each study, ">" indicates superiority of experimental drug to placebo, and "=" indicates no significant difference between 2 groups.
Abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation II, ASA = American Society of Anesthesiology, CAM = Confusion Assessment Method, DBPCT = double-blind, placebo-controlled trial, DRS-R-98 = Delirium Rating Scale-Revised-98, HAL = haloperidol, ICDSD = Intensive Care Delirium Screening Checklist, ICU = intensive care unit, IV = intravenous, MMSE = Mini-Mental State Examination, NYHA = New York Heart Association, OLA = olanzapine, PLA = placebo, RASS = Richmond Agitation Sedation Scale, RIS = risperidone.

Atypical Antipsychotics

- Olanzapine has FDA black box warning for sudden death (stroke) in patients with dementia
- Multiple small studies investigating Risperidone, limited benefit
- Risperidone may be better tolerated than Olanzapine due to less anticholinergic and antihistaminic effects
- Dosing?

- **No role for atypical antipsychotics in these patients**

Anticholinesterase Inhibitors - Donepezil

No difference in postoperative delirium in multiple studies evaluating donepezil

- **No role for donepezil**

Sampson EL, Raven PR, Ndhlovu PN et al. **A randomized, double-blind, placebo-controlled trial of donepezil hydrochloride (Aricept) for reducing the incidence of postoperative delirium after elective total hip replacement.** International Journal of Geriatric Psychiatry. 2007;22(4):343-349

Marcantonio ER, Palihnich K, Appleton P, Davis RB. **Pilot randomized trial of donepezil hydrochloride for delirium after hip fracture.** Journal of American Geriatrics Society. 2011;59(2):282-288

Does Opioid Choice Matter?

- Systematic review (2006) of 3 RCTs and 3 Observational Studies suggests no difference
  - Avoid Meperidine because of its anticholinergic properties

Fong, H, Sands, L, Leung J. **The Role of Postoperative Analgesia in Delirium and Cognitive Decline in Elderly Patients: A Systematic Review.** Anesthesia & Analgesia 2006; 102(4):1255-1266.

Does Opioid Choice Matter?

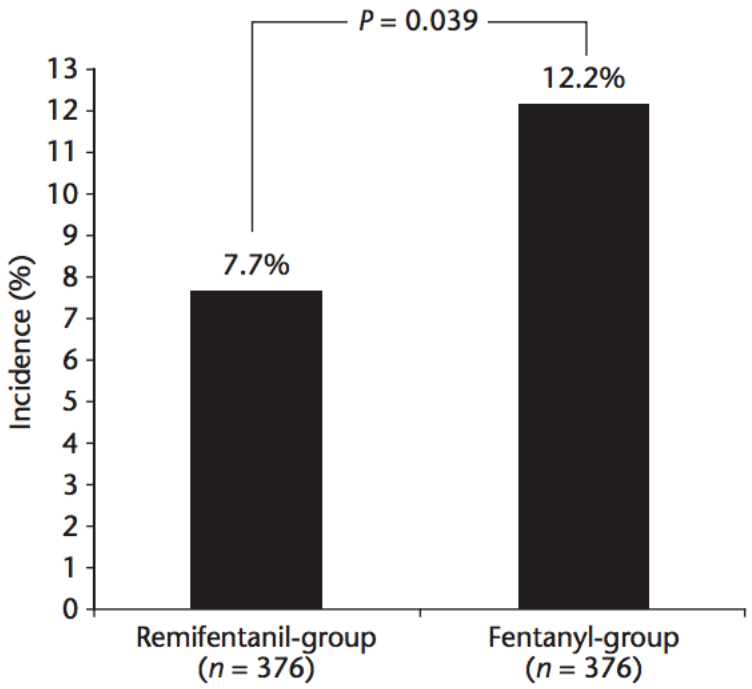


FIGURE 1: Incidence of delirium episodes in the recovery room in patients who received either remifentanil or fentanyl intraoperative opioid anaesthesia during elective surgery

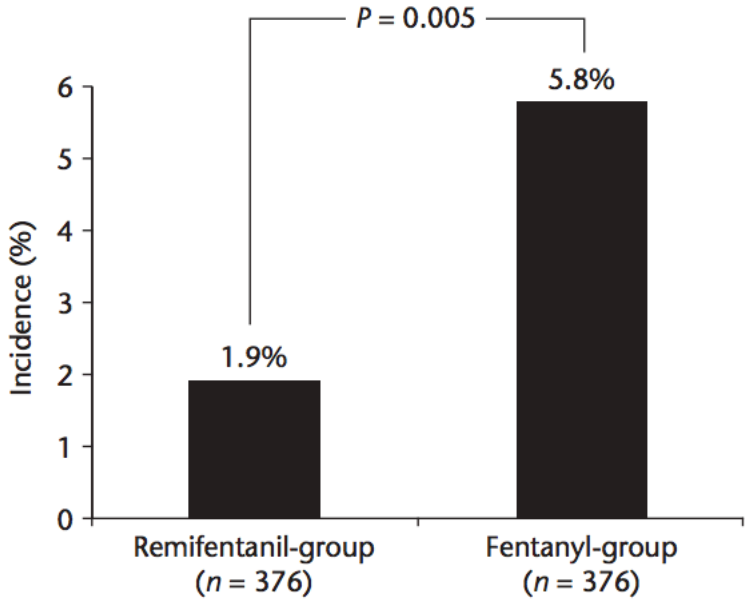


FIGURE 2: Incidence of delirium episodes on the first post-operative day in patients who received either remifentanil or fentanyl intraoperative opioid anaesthesia during elective surgery

Observational Study

Radtke FM, Franck M, Lorenz M et al. **Remifentanil Reduces the Incidence of Post-Operative Delirium.** Journal of International Medical Research. 2010; 38(4) 1225-1232.

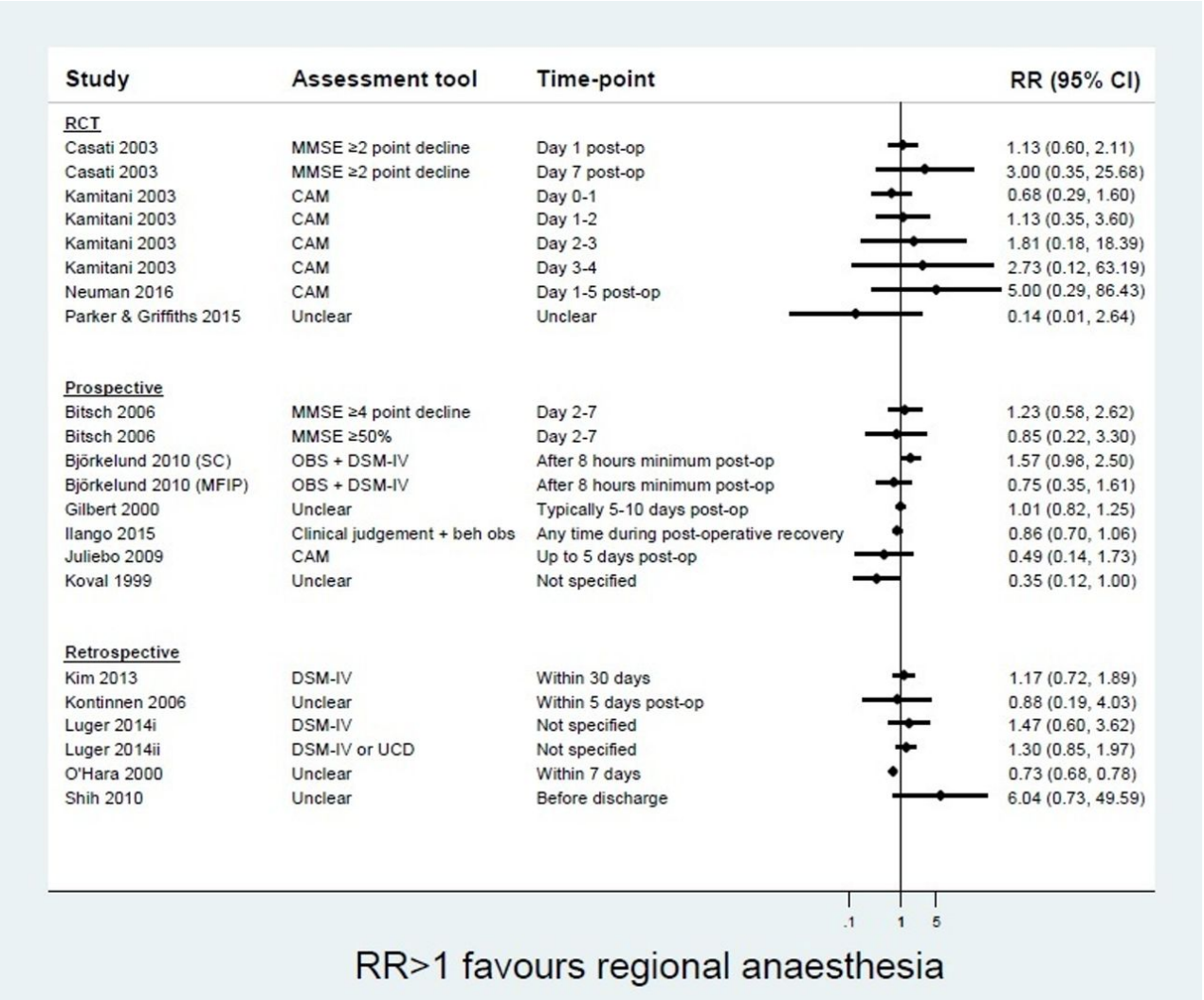
Does Opioid Choice Matter?

- Limited evidence to suggest a difference
- Potentially harm with using Remifentanil in at risk patients

- **No!**

GA vs Regional

- Large systematic review of 104 studies in elderly (≥60 yo) patients for hip fracture repair
- No difference in primary outcome of postoperative delirium
- Very Limited evidence to suggest any mortality benefit, shortened length of stay, reduction in adverse events, or earlier mobilization



Patel V, Champaneria R, Dretzke J, *et al*
Effect of regional versus general anaesthesia on postoperative delirium in elderly patients undergoing surgery for hip fracture: a systematic review
BMJ Open 2018;**8:**e020757.

Gabapentin

- Very small, poorly powered trial of 21 patients going for spine surgery suggested a dramatic statistically significant reduction in POD
- Leung et al (2017) conducted double-blinded RCT with 697 patients, stratified for surgery type, anesthetic technique, and preoperative risk via CAM
  - NO difference in incidence or duration of POD
  - Slight reduction in postop opioid requirements
- **No role for gabapentin to prevent POD**

Leung JM, Sands LP, Chen N et al. **Perioperative Gabapentin Does Not Reduce Postoperative Delirium in Older Surgical Patients: A Randomized Clinical Trial.** Anesthesiology. 2017;127(4): 633-644

Ketamine

- Avidan et al (2017) found in large multicenter DB-RCT no benefit to subanesthetic dose of ketamine intraop
  - may have found to be harmful via postop dissociative experiences, nightmares etc
- Hovaguimian et al (2018) meta analysis also revealed no benefit, low quality evidence

- **Avoid ketamine if possible**

Avidan MS, Maybrier HR, Abdallah AB et al. **Intraoperative ketamine for prevention of postoperative delirium or pain after major surgery in older adults: an international, multicentre, double-blind, randomised clinical trial.** Lancet. 2017;390(10091):267-275

Hovaguimian F, Tschopp C, Beck-Schimmer B, Puhan M. **Intraoperative ketamine administration to prevent delirium or postoperative cognitive dysfunction: A systematic review and meta-analysis.** Acta Anesthesiology Scandinavica. 2018;62(9):1182-1193

Dexamethasone

- If primarily due to inflammation, preventing inflammatory processes should prevent postoperative delirium?
- Evidence of delirium reduction in patients undergoing CABG
- Very few studies on Dex for postoperative delirium

- **Dexamethasone likely useful in these patients**

Mardani D, Bigdelian H. **Predictors and clinical outcomes of postoperative delirium after administration of dexamethasone in patients undergoing coronary artery bypass surgery.** International Journal of Preventative Medicine. 2012;3(6):420-427

TIVA vs Inhalational

- Radtke et al (2010) found no statistical difference in incidence of delirium in PACU or on ward postoperative day 1 in 1002 patients
  - Limitation= observational cohort study
- Miller et al (2018) comprehensive systematic review of 28 RCTs including 4507 patients undergoing noncardiac surgery
  - Found no significant difference in rates of POD or POCD
- Tanaka et al (2017) DB-RCT of 100 obese patients going for elective TKR with femoral catheter in situ
  - no difference between Desfluorane vs Propofol maintenance in terms of POD, POCD
- **NO Difference between TIVA vs Inhalational Anesthetic**

Fluids

- Fasting Duration significant for incidence of delirium in observational study

	Recovery room ($n=910$)			Ward ($n=862$)		
Characteristic	Delirium ($n=100$)	No delirium ($n=810$)	P	Delirium ($n=38$)	No delirium ($n=824$)	P
Age (years)	55.8 ± 16.2	50.1 ± 17.0	0.003	56.4 ± 15.2	50.5 ± 16.9	0.003
Sex						
Female	45 (45.0%)	380 (46.9%)	0.751	15 (39.5%)	388 (47.1%)	0.408
ASA PS			0.019			0.019
1 and 2	66 (66.0%)	623 (76.9%)		22 (57.9%)	625 (75.8%)	
3 and 4	34 (34.0%)	187 (23.1%)		16 (42.1%)	199 (24.2%)	
Preoperative fasting (fluids) (h)			<0.001			<0.001
2–6	11 (11.0%)	209 (25.8%)		1 (2.6%)	201 (24.4%)	
>6	89 (89.0%)	601 (74.2%)		37 (97.4%)	623 (75.6%)	
Preoperative fasting (solids) (h)			0.426			0.210
6–12	36 (10.0%)	325 (90.0%)		11 (3.3%)	322 (96.7%)	
>12	64 (11.7%)	485 (88.3%)		27 (5.1%)	502 (94.6%)	
Anaesthetic			0.525			0.134
Inhalative	56 (56.0%)	423 (52.2%)		25 (65.8%)	433 (52.5%)	
Intravenous	44 (44.0%)	387 (47.8%)		13 (34.2%)	391 (47.5%)	
Opioid			0.011			0.004
Fentanyl	65 (65.0%)	413 (51.0%)		29 (76.3%)	426 (51.7%)	
Remifentanil	35 (35.0%)	397 (49.0%)		9 (23.7%)	398 (48.3%)	
Fentanyl dosage ($\mu g\,kg^{-1}\,h^{-1}$)	4.0 ± 3.0	3.9 ± 2.8	0.90	3.5 ± 1.7	4.0 ± 2.9	0.24
Duration of surgery (min)	93.2 ± 63.0	77.5 ± 57.8	0.004	98.0 ± 67.6	78.1 ± 58.5	0.024
Site			<0.001			<0.001
Intraabdominal and intrathoracic	28 (19.2%)	118 (80.8%)		13 (9.6%)	122 (90.4%)	
Other	72 (9.4%)	692 (90.6%)		25 (3.4%)	702 (96.6%)	

Data were expressed as mean ± SD, except for categorical data as number and percentage; P values are with respect to χ^2 test or Mann–Whitney U test. ASA PS, American Society of Anaesthesiologists physical status.

Radtke F, Franck M, MacGuill M et al. **Duration of fluid fasting and choice of analgesic are modifiable factors for early postoperative delirium.** European Journal of Anaesthesiology 2010;27:411–416

Fluids

- Dehydration known modifiable risk factor for POD,
- Consider fasting time

- **Euvolemia, preop rehydration**
- **Electrolyte correction**

EEG Monitoring

Intraoperative Electroencephalogram Suppression Predicts Postoperative Delirium

Bradley A. Fritz, MD,* Philip L. Kalarickal, MD,* Hannah R. Maybrier, BS,* Maxwell R. Muench, BS,* Doug Dearth, MD,* Yulong Chen, BA,* Krisztina E. Escallier, MD,* Arbi Ben Abdallah, PhD,* Nan Lin, PhD,† and Michael S. Avidan, MBBCh*

- Observational cohort study (2016) of 727 patients receiving GA with planned ICU disposition, Age ≥18 yo
- Duration of EEG Suppression recorded
- CAM assessment for delirium twice daily for postop day 1-5
- Follow-up at 30 days for QoL, functionality, cognitive abilities assessed using validated scoring systems
- POD in 26% of patients

Table 2. Predictors of Postoperative Delirium in a Multiple Logistic Regression (n = 619)

	Non-transformed model		Transformed model[a]	
Variable	**Odds ratio (99% CI)**	***P***	**Odds ratio (99% CI)**	***P***
Age (per year)	1.01 (0.98–1.03)	0.37	1.00 (0.98–1.03)	0.69
Male sex	0.92 (0.69–1.23)	0.46	0.89 (0.67–1.19)	0.31
ASA physical status >3	0.81 (0.60–1.11)	0.08	0.80 (0.58–1.08)	0.06
Age-adjusted Charlson index (per unit)	1.10 (0.93–1.30)	0.15	1.09 (0.92–1.30)	0.18
Sensory impairment	1.04 (0.63–1.70)	0.83	1.03 (0.62–1.74)	0.85
Alcohol use >5 drinks per week	1.02 (0.62–1.66)	0.93	1.02 (0.62–1.68)	0.91
Surgery type				
Noncardiac	Reference		Reference	
Coronary artery bypass grafting	1.12 (0.62–1.66)	0.57	1.26 (0.76–2.11)	0.24
Open cardiac	0.95 (0.60–1.51)	0.77	1.03 (0.65–1.62)	0.89
Length of surgery (per minute)	1.00 (1.00–1.00)	0.65	1.00 (1.00–1.00)	0.61
Intraoperative ketamine use	0.70 (0.38–1.29)	0.13	0.71 (0.39–1.30)	0.15
Intraoperative opioid dose (per 1 morphine equivalent/kg increase)	1.08 (0.71–1.64)	0.65	1.05 (0.69–1.61)	0.76
Blood transfusion (dichotomous)[a]	—	—	1.82 (0.83–4.00)	0.05
Blood transfusion (per unit)[a]	1.29 (1.14–1.46)	<0.0001	1.77 (1.07–2.94)[a]	0.004
Mean end-tidal anesthetic concentration (per 0.1 MAC unit)	0.66 (0.50–0.87)	0.0001	0.66 (0.50–0.88)	0.0002
Duration of electroencephalogram suppression (in minutes)[a]	1.05 (1.003–1.103)[b]	0.0065	1.22 (1.06–1.40)	0.0002

Factors that predict POD:

- Duration of Burst Suppression
- EtMAC
- Blood Transfusion

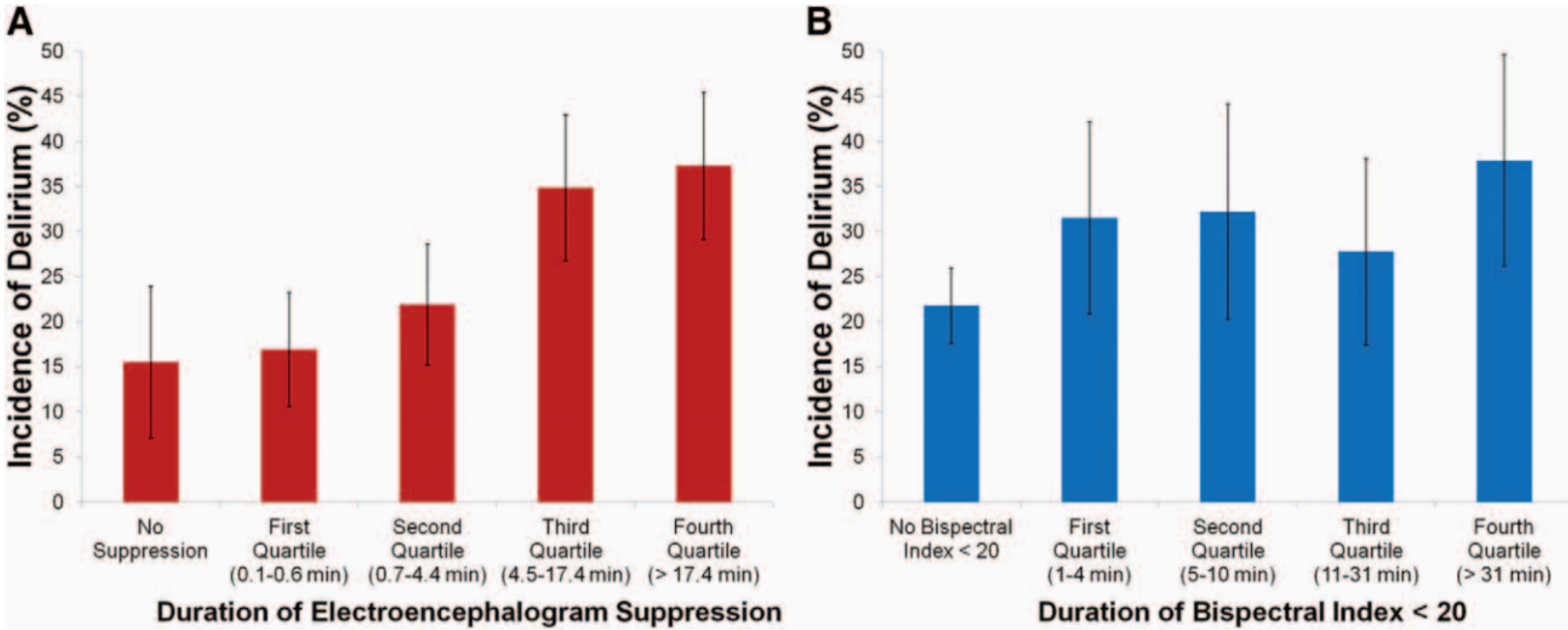


Figure 2. This descriptive figure depicts the univariable relationships between these 2 electroencephalogram parameters and incident delirium. There is no control for covariates in this descriptive figure. A, Incidence of delirium among patients who experienced no electroencephalogram suppression (n = 71) and among patients who experienced electroencephalogram suppression (n = 548) divided into quartiles based on duration of electroencephalogram suppression. B, Incidence of delirium among patients who never experienced bispectral index <20 (n = 362) and among patients who experienced bispectral index <20 (n = 257) divided into quartiles based on duration of bispectral index <20. Error bars represent 95% confidence intervals around the incidence of delirium in each group.

EEG Monitoring

- Prolonged burst suppression predicted postoperative delirium in Day 1-5 in ICU
- Higher EtMAC corresponded to higher burst suppression ratios
- Prolonged burst suppression found to have no effect on QoL or cognitive impairment, but significant impact on functional independence at 30 days

- Limitation: Observational

EEG Monitoring

- Single-center RCT of 1232 patients undergoing major surgery with GA
- EEG-Guided group
  - POD 26% (vs 23% for Usual Care Group)
  - Significantly lower EtMAC (0.69 vs 0.8)
  - Reduced duration of burst suppression (median 7 mins vs 13 mins)
  - More undesirable movement (22.3% vs 15.4%)
  - No difference in MAP, PONV, serious adverse events
  - Lower 30 day mortality (0.65% vs 3.07%)
  - No awareness

Wildes TS, Mickle AM, Abdallah AB, et al. **Effect of Electroencephalography-Guided Anesthetic Administration on Postoperative Delirium Among Older Adults Undergoing Major Surgery**The ENGAGES Randomized Clinical Trial**.** AMA. 2019;321(5):473-483

EEG Monitoring

Bottom Line

- **Unclear**

Does MAP Matter?

- No correlation between lower map values (≤90% preoperative values) and incidence of POD in elderly patients with GA for noncardiac surgery
- RCT Pilot Trial, 101 patients

Langer T, Santini A, Zadek F et al. I**ntraoperative hypotension is not associated with postoperative cognitive dysfunction in elderly patients undergoing general anesthesia for surgery: results of a randomized controlled pilot trial.** Journal of Clinical Anesthesiology. 2019;52:111-118.

MAP > 55mmHg

- Ongoing Multicenter DB-RCT of 322 patients randomized to MAP targets 60-70mmHg vs 80-90mmHg to assess for POD from Day 1-7
- Willingham et al (2014) found 3x higher risk of 90 day postop all cause mortality associated with combo of burst suppression + MAP < 55mmHg

At present, unclear but stands to reason keep these patients tightly within 20% of preoperative values

Hu A, Qiu Y, Zhang P, et al. **Comparison of the effect of high versus low mean arterial pressure levels on clinical outcomes and complications in elderly patients during non-cardiothoracic surgery under general anesthesia: study protocol for a randomized controlled trial.** Trials. 2017;18(1);554.

Willingham M, Abdallah AB, Gradwohl S, et al. **Association between intraoperative electroencephalographic suppression and postoperative mortality.** BJA. 2014;113(6);1001-1008.

Dexmedetomidine

- Could prevent inflammatory ramp up
- Has analgesic and sedative effects
- Opioid-sparing
- Resembles natural sleep patterns

- “Magic Bullet” for Postoperative Delirium
  -Anne Donovan in CJA Jan 2019

Dexmedetomidine

- Evidence is inconsistent
- RCT of 143 pts undergoing thoracic surgery running Sevo with Dexmedetomidine vs Sevo alone
- Dexmed ($0.5 \mu g \bullet kg^{-1} \bullet hr^{-1}$) started at induction, terminated at OR end-time
- Assessed for rates of emergence agitation, postoperative delirium to Postop Day 3.
- RRR 0.62 in emergence agitation, no difference for POD
- Reduction in serum catecholamines
- Increase in cytokines

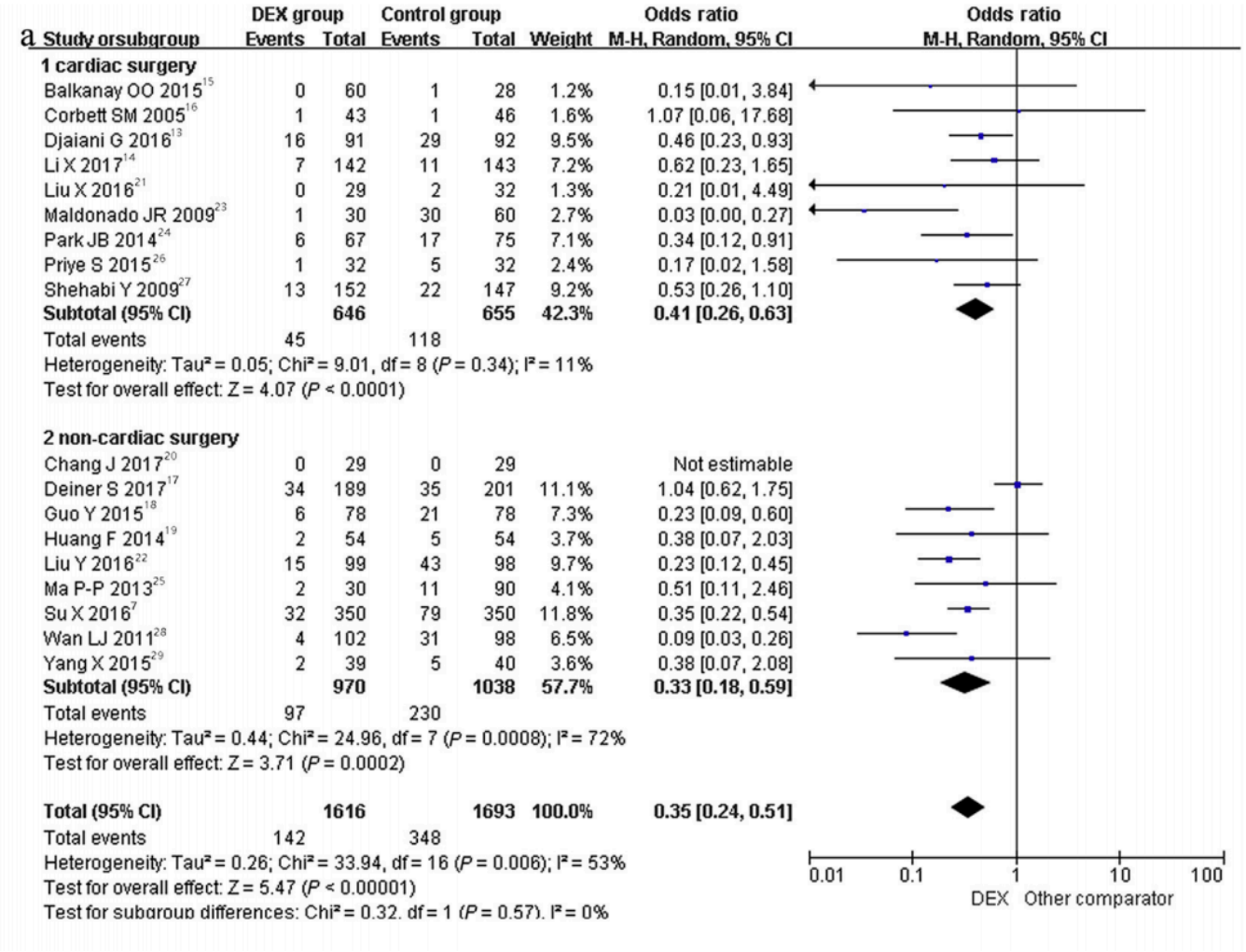
Kim JA, Ahn HJ, Yang M et al. **Intraoperative use of dexmedetomidine for the prevention of emergence agitation and postoperative delirium in thoracic surgery: a randomized-controlled trial.** CJA. 2019.

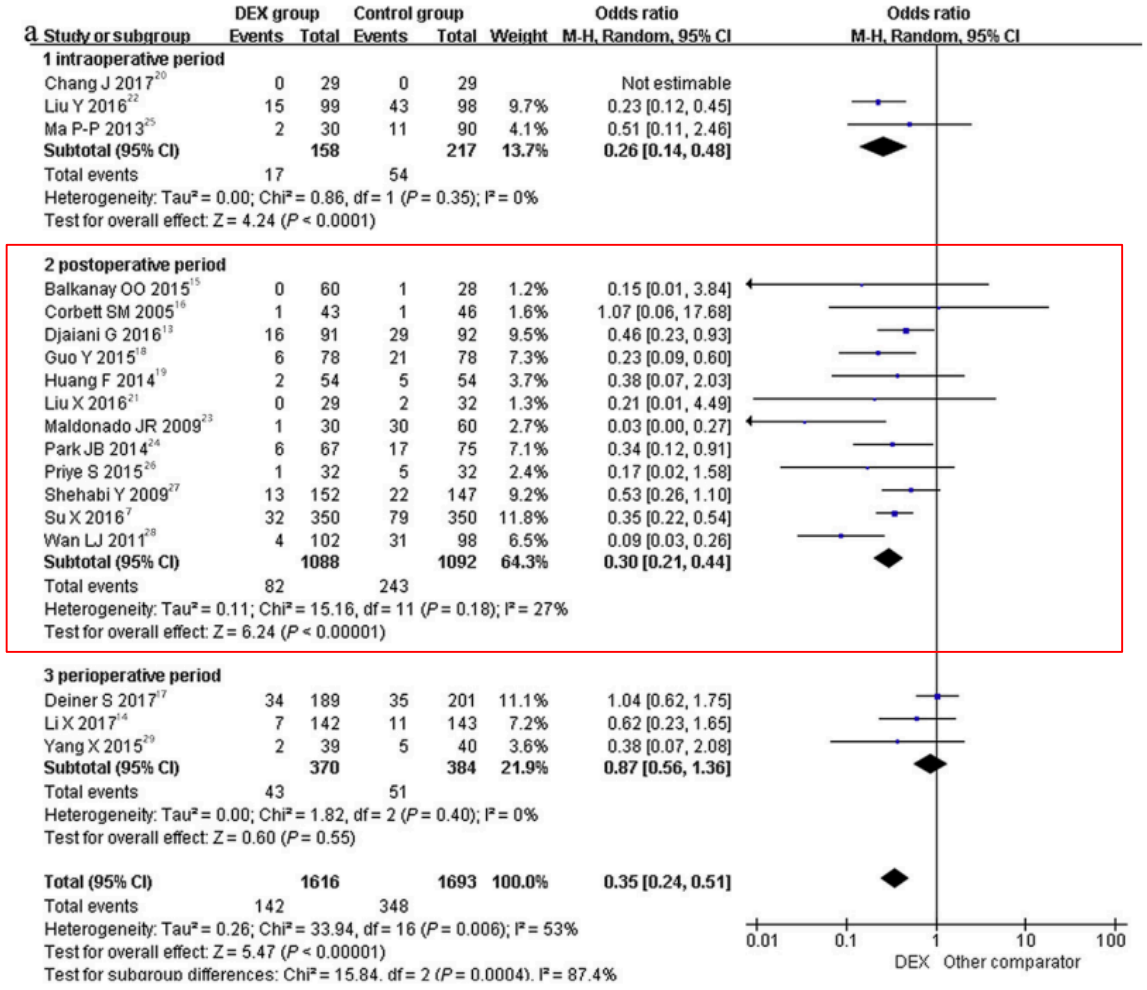
Dexmedetomidine

- Systematic review of 18 studies including 3309 patients, 9 cardiac (8 on pump) and 9 noncardiac surgeries
- Found firm evidence of reduction in POD in all patient populations
- Insufficient evidence for length of stay, mortality benefit
- Dosage and timing unclear
- Tailor to type of procedure and postop disposition plan

Duan X, Coburn M, Rossaint R et al. **Efficacy of perioperative dexmedetomidine on postoperative delirium: systematic review and meta-analysis with trial sequential analysis of randomised controlled trials.** BJA. 2018;121(2):384-397

Dexmedetomidine





Dexmedetomidine

- When stratified for POD as primary outcome (9 studies) may be evidence to suggest
  - ± loading dose of 0.5 $\mu g \bullet kg^{-1} \bullet hr^{-1}$
  - maintenance infusion at 0.2 $\mu g \bullet kg^{-1} \bullet hr^{-1}$ may be optimal
  - But still unclear on timing/duraton

- Further evidence needed to elucidate optimal dosing tailored to procedure

Novel Strategies – Paracetamol?

DEXACET RCT (2019)

- 120 patients ≥60yo undergoing on-pump CABG, or CABG + Valve Replacement
- Randomized to one of 4 groups
  - Dexmed + Paracetamol
  - Dexmed + Placebo
  - Propofol + Paracetamol
  - Propofol + Placebo
- Sedation started at chest closure, paracetamol given q6h x 48hrs

Subramaniam B, Shankar P, Shaefi S et al. **Effect of Intravenous Acetaminophen vs Placebo Combined With Propofol or Dexmedetomidine on Postoperative Delirium Among Older Patients Following Cardiac Surgery: The DEXACET Randomized Clinical Trial.** JAMA. 2019(321(7):686-696

Novel Strategies – Paracetamol?

- Paracetamol group
  - Lower incidence of POD
  - Reduced opioid requirements
  - Shorter ICU length of stay
- Dexmedetomdine group
  - No difference in terms of incidence of POD or ICU length of stay
  - Reduced opioid requirements

Novel Strategies

CSF Beta-amyloid 1–42 Concentration Predicts Delirium Following Elective Arthroplasty Surgery in an Observational Cohort Study

Emma L. Cunningham, PhD, Bernadette McGuinness, PhD,* Daniel F. McAuley, MD,† Jamie Toombs, MSc,‡ Tim Mawhinney, BSc,§ Seamus O'Brien, PhD,§ David Beverland, MD,§ Jonathan M. Schott, MD,¶ Michael P. Lunn, PhD,¶ Henrik Zetterberg, PhD,‡||** and Anthony P. Passmore, MD**

- 282 patients going for elective primary hip/knee replacement under spinal anesthesia
- Anesthesiologist aspirates 5mL of CSF
  - sent for analysis of beta-amyloid, and tau proteins
- Independent association of CSF Beta-amyloid and tau proteins levels to be predicitve of POD
- May be due to subclinical Alzheimer Dementia
- Potentially useful for follow up, early intervention?

Recommendations

- Identify patients at risk!
- Consult geriatrician or treat as geriatrician would
  - Adequate preop hydration, correction of electrolyte imbalance where possible
  - May be ideal role for PAC
- Consider haldol, dexamethasone
- May use BIS/Sedline, titrate inhalational to avoid burst suppression
- Prudent to keep MAP > 55mmHg
- Potential utility of dexmedetomodine

Recommendations

- We are perioperative physicians
- Include in anesthetic considerations for the at risk patient

Acknolwedgements

- Dr Clinton Torok-Both
- Dr Michael Vargo

Additonal References

Chaput AJ, Bryson GL. **Postoperative delirium: risk factors and management: Continuing Professional Development.** CJA. 2012; 59:304–320