Who are we enrolling into postoperative delirium intervention studies and what interventions are we testing?

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Goal: to provide an overview of current interventional studies focused on postoperative delirium prevention

Objectives:

1. to outline the types of interventions being tested for delirium prevention
2. To outline the patient populations studied in these interventions

Search Strategy in clinical trials.gov

- Delirium (**2213**)
- Open studies (**838**)
- Interventional studies (**624**)
- Randomized (**178**) → Condition – Delirium (**163**)
- Outcome- delirium (**36**) → Condition – Delirium (**24**)

Focus of intervention and populations

- **Prevention of post-op delirium (n=28)**
- **Types of patients**
    - Elderly
    - Cardiac/major/ortho procedures

Prevention of Postoperative delirium types of interventions

- Dexmedetomidine (n=5)
- Pain management (n=5)
- Anesthetic management (n=5)
- New technologies (n=3)
- Miscellaneous drugs (n=5)
- Non-pharmacologic (n=5)

Treatment trials of critical care sedation in delirium

Riker, 2009	Medical/surgical ICU (mean age=62) mechanically ventilated.	Dexmedetomidine (N) = 244 Midazolam (N) = 122	In subjects delirium-free at baseline lesser prevalence for dexmedtomidine (32.9% vs. 55.0%), p=.03. in subjects with delirium at baseline lesser prevalence for dexmedetomidine (68.7% vs. 95.5%), p<.001. Greater delirium-free days for dexmedetomidine (2.5 vs 1.7), p=.002.
Reade, 2009	Middle aged mechanical ventilation Medical/surgical ICU	Dexmedetomidine (N) = 10 Haloperidol (N) = 10	No differences in duration
Pandharipande, 2007	(median age=60) Medical/surgical ICU mechanical ventilation	Dexmedetomidine (N) = 52 Lorazepam (N) = 51	No difference
Maldonado, 2009	Mechanically ventilated ICU (mean age=57.7) CPB	Dexmedetomidine (N) = 36 Midazolam (N) = 32 Propofol (N) = 31	Lower post-operative delirium compared to both propofol and midazolam (10% vs. 44% vs. 44%), p<.001 (ITT analysis). No differences in duration
Shehabi, 2009	(age>60) CPB mechanically ventilated ICU	Dexmedetomidine (N) = 152 Morphine (N) = 147	Trend less post-operative delirium with dex (8.6% vs. 15%), p=.08. Duration shorter in dexmedetomidine (median days: 2 vs. 5), p=.03.

Dexmedetomidine rationale

- In ICU sedation trials and following cardiac surgery use associated with less delirium
- Mimics natural sleep
- Possible modulation of peri-op stress response

Interventions for Postop Delirium Prevention
Dexmedetomidine

Population	Intervention
≥60 **Elective major surgery** **general anesthesia** **ASA 1-3**	**DEX (infusion during surgery; stopped 30 min before closure)** **Vs.** **Saline** **Examining delirium during first 24 h postop; report a 20% incidence of agitation during this time period**
≥ 68 **Elective major surgery** **General Anesthesia** **MMSE>20 (no dementia)** **ASA 1-3**	**DEX (intraop infusion until 2 hours post extubation)** **Vs.** **Placebo**
Maxillo-facial surgery with free flap **18-80** **ASA 1-2**	**DEX (1 hour before surgery until 24 h postop)** **Vs.** **Saline** **???emergence agitation or postop delirium**
Hip fx – bipolar **≥ 75** **MOCA>23**	**All patients receive peripheral nerve blocks + propofol infusion** **DEX - administered intraoperatively until 30 min before closure; investigators state this is their usual practice** **Vs.** **Saline**
High risk Cardiac **≥60** **No symptomatic cerebrovascular disease** **ICU**	**On ICU arrival trial is testing standard postop sedation protocols vs dex** **Propofol infusion until extubation** **Vs.** **Dex for a maximum period of 24 h**

General comments on dex studies

- Some studies examine agitation in first 24h, others examine in hospital delirium
- Different times and duration of drug administration
- No index of stress measurement
- Primarily elderly/no dementia/not particularly sick or frail

Intervention for postoperative delirium prevention-misc. drugs

≤18 **Open heart** **No renal failure: study primary outcome is kidney function**	**Statin naïve- Atorvastatin 80 mg day prior to surgery, then 40 mg until hospital discharge;** **Using statins- atorvastatin only through day 1 postop, then resumption of previous statin** **Vs.** **Placebo**
≥40 **Thoracic, ortho, vascular procedures; no̅ intracranial /open heart** **General Anesthesia** **PTSD** **Excluded if on beta-blocker or hx of substance abuse**	**Propranolol (60 mg) taken for 14 days starting day of surgery** **Vs.** **Placebo** **Premise: PTSD associated with elevated stress response**
Open heart **≥ 70** **Delirium risk factors: CVA; Euroscore≥5; Abnormal clock draw** **No active delirium or emergency cases**	**Haldol 1 mg (1 day preop; day of surgery; then BID until 72 h postop)** **Vs.** **No Haldol** **Feasibility study**
≥ 65 **Cardiac- CABG or valve**	**Intranasal Insulin (40 IU QID for 7 days or discharge starting 2 h prior to surgery)** **Vs.** **Placebo** **Premise: insulin improves cognition in Alzheimer's; studying POCD as well**
18-90 **CPB** **No off pump procedures or active infections** **Delirium is a secondary outcome**	**Hyperinsulinemic – normoglycemic clamp (80-110mg/dl)** **Vs.** **Standard insulin management**

Comments on miscellaneous drugs

- Cardiac surgery populations
- Studies administer drugs pre and post-op
- Delirium often a secondary outcome in these studies

Intervention for postop delirium prevention
Pain Management

population	intervention
≥75 primary total hip MMSE>23 ASA 1-3	Both groups receive PICA (sufentanyl); oxycodone; parecoxib General Anesthesia with LMA Vs. Lumbar plexus + Sciatica nerve block
≥ 18 Trans-Apical aortic valve replacement No symptomatic cerebrovascular disease	Continuous Thoracic paravertebral block with local anesthetic infusion Vs. IV opioid Premise: decreased opioid utilization will lead to less delirium
≥ 65 Spine, hip, knee	Gabapentin Vs. Placebo Premise: preliminary trial showing efficacy with gabapentin
Hip fx ≥ 50	Femoral Nerve catheter 2-3 days Vs. IV opioids Premise-pain is related to delirium
60-90 Major elective=open abdominal or thoracic Ability to use PCA postop	Both groups receive general anesthesia Epidural- postop PCEA Vs. PCIA Premise: stress response is important in delirium

Comments on pain studies

- Most are built on premise that delirium can be decreased if narcotics are decreased
- Patient populations vary in age
- Unclear what are the long term outcomes of opioid associated delirium

Intervention for postop delirium prevention Technology for intraop management

≥70 **Intermediate-high risk post op delirium (marcantonio risk score ≥6)** **non cardiac surgery** **No emergency cases; no underlying aortic disease**	**Fluid and catechol management by Pulsioflex measurement (goal directed therapy according to pulse contour analysis)** **vs.** **routine fluid management** **Comment: NIRS will be used to document that brain O2 sat is optimized**
≥60 **CPB-complex cardiac including cabg-valve/repeat cardiac/multiple valves/ascending aorta or arch procedures** **No history of delirium**	**NIRS is monitored intraop until 24 h postop** **Maintain NIRS >75% baseline; if below 75% then algorithm used to restore O2 sat levels** **Vs.** **Blinded NIRS**
≥65 **Cardiac/thoracic**	**When cerebral oximetry o2 sat<60% measures are instituted to optimize hemodynamics and hgb** **Vs.** **No intervention**

Comments on technology studies

- Mostly high risk surgeries
- Optimization of perfusion may be appropriate therapeutic goal in these type of cases

Intervention for postoperative delirium prevention-non-pharmacologic

50-89 **Major abdominal/ non-cardiac thoracic** **Post op ICU** **Timed up and go>10 sec**	**9 sessions pre-op home functional prehab PT over three weeks** **Vs.** **No prehab** **Comment: delirium is a secondary outcome**
≥18 **Open heart or complex spine** **ASA 1-3** **MMSE>23**	**Pre and postoperative hypnotherapy session** **vs** **no Rx**
Elective abdominal/urologic/total knee and hip replacement **>75yrs** **Confucius trial**	**Usual Care** **Vs.** **HELP (hospital elder life program):** **structured geriatric consultation;** **2 h training session of the med/surg staff for implementing the HELP program;** **quarterly analysis of delirium cases**
≥50 **Elective knee/hip** **Risk for sleep apnea-stop BANG>2** **No treated sleep apnea**	**CPAP(prior to surgery through day 2 post op)** **Vs.** **No CPAP** **Premise: sleep apnea is a risk factor for delirium**
18-90 **CPB** **Secondary outcome; primary is all cause mortality**	**Remote ischemic preconditioning: RIPC during anesthesia by four 5-min cycles of upper limb ischemia and 5-min reperfusion at a pressure 200 mm Hg,** **Vs.** **Sham**

Non-pharmacologic comments

- Several have high likelihood of being positive given focused populations studied and risk factors modified
- Many studies examine remote ischemic preconditioning in coronary artery disease

Intervention for postop delirium prevention
Anesthesia management

≥ 75 **Hip Fx** **MMSE > 23** **No delirium**	**Xenon (60%; 1 MAC)** **Vs.** **Sevoflurane (1.1-1.4%; 1 MAC)** **Note: 2 other studies looking at Off-pump and on-pump CABG comparing xenon + propofol vs propofol and xenon vs sevoflurane vs propofol, respectively. All these studies are industry sponsored.**
Major surgery (Cardiac & Non-cardiac) **≥60**	**Low dose Ketamine (following induction and prior to incision either 0.5 or 1 mg/kg)** **Vs.** **Saline** **Premise: ketamine effects postop pain; studies show it decreases postop delirium**
Elective Major Surgery-no cardiac or neuro **≥60** **ASA 1-3** **BMI>30**	**Both groups receive remifentanil infusions and anesthesia is guided by narcotrend index monitoring** **Propofol** **Vs.** **Sevoflurane** **Premise: sevoflurane associated with emergence delirium in pediatrics; less delirium with propofol** **Note: similar study comparing propofol vs isoflurane with CSF markers for amyloid pre and 24 h postop**
Hip fx **Spinal anesthesia** **≥65** **STRIDE study**	**Heavy sedation** **Vs.** **Light sedation**
≥65 **Major Non-cardiac** **Exploratory study**	**Light GA** **Vs.** **Deep GA** **Processed EEG used to guide anesthesia**

Comments-anesthetic management

- TIVA vs inhalational is a common theme
- Testing of new anesthetics-xenon
- New uses for old drugs-ketamine

Anesthesia and delirium

- Anecdotal evidence seems strong
- “Grandpa was never the same after surgery”

Is regional anesthesia better?

- Literature is confusing

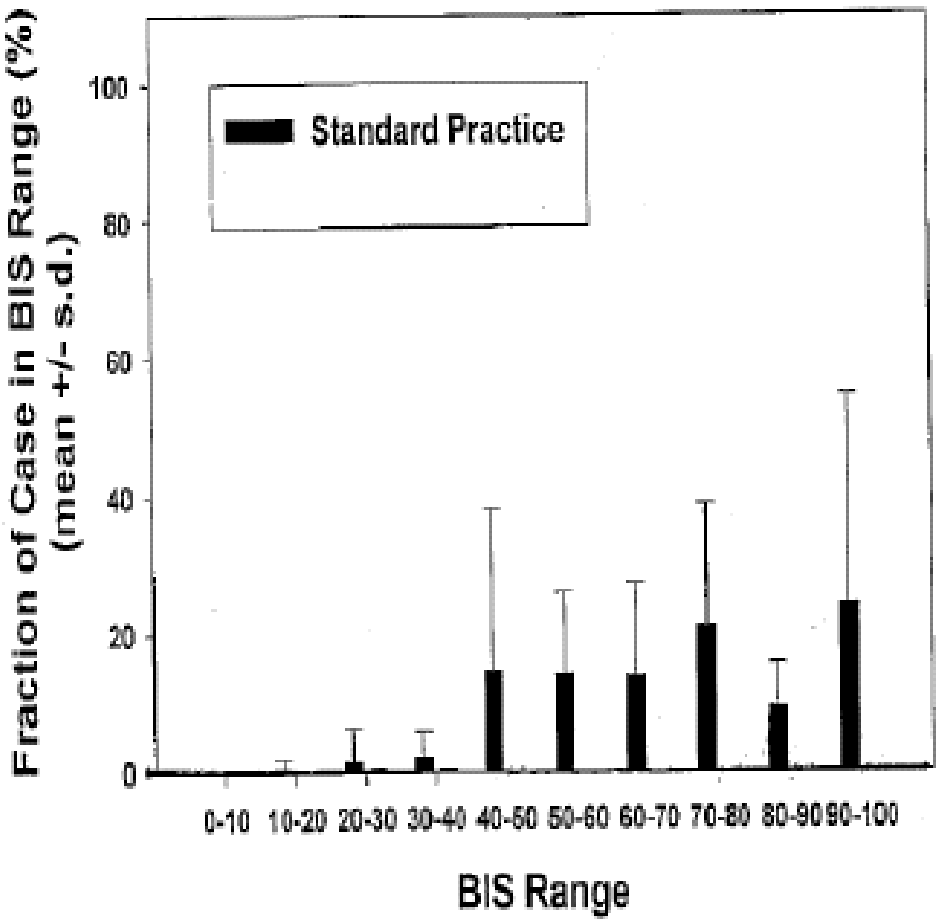
- No differences between spinal and general anesthesia in delirium rates after hip fracture repair

Confounders in literature

- Depth of sedation has not been controlled
- Elderly patients need very little anesthetic to be deeply sedated

General anesthesia commonly occurs during a spinal

- During propofol sedation in hip fracture patients 32.2% of surgical time was spent under GA as defined as BIS <60



Hypothesis

- Depth of sedation is a modifiable factor that may contribute to postoperative delirium

Preliminary RCT

- Prospective randomized double blinded study of elderly patients undergoing hip fracture repair with spinal anesthetic to assess the affects of depth of sedation on postoperative delirium

Results: Postoperative delirium

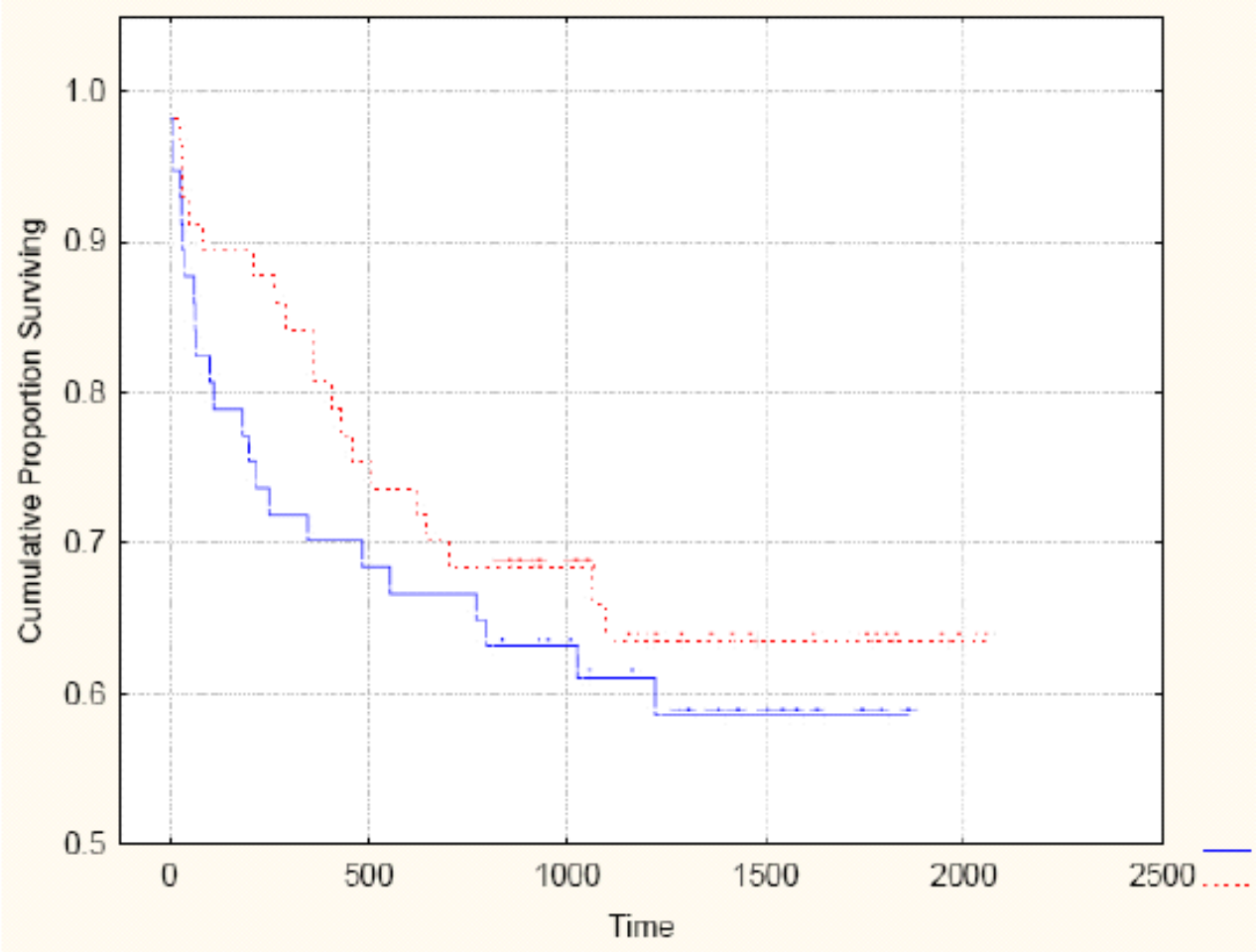
- 23/57 (40.4%) in the deep group
- 11/57 (19.3%) in the light group P=0.02
- Remains significant for higher and lower stratified initial MMSE score groups
- Duration of delirium for all patients
  - 1.4 days (4.0) versus 0.5 days(1.5) $p<0.01$*

Light sedation decreased the risk of delirium

- For every 4.7 patients treated with light sedation, one episode of delirium would be prevented

- In patients with MMSE >20, 3.5 patients treated to reduce one episode of delirium

Trend towards less mortality, underpowered



Limitations

- Underpowered to make conclusions about morbidity and mortality
- No functional outcomes
- Cam score used to measure delirium
- Use of BIS monitor to measure sedation

Aim

The principal objective is to assess the effectiveness of light versus heavy sedation during surgery in elderly patients undergoing hip fracture repair.

- The primary outcome is the impact of intervention on incidence of post-operative delirium during post-operative (in-hospital) Day 1 to Day 5 or to hospital discharge (whichever occurs first).
- The secondary outcomes are mortality at one year (12 months) after surgery and severity of delirium in-hospital using the DRS-R-98.

Outcomes-Others

- Delirium at 1-month (30 days)
- In-hospital delirium at 1-5 days stratified by baseline comorbidities.
- Change in functional outcomes from pre-operative test to 1-month and 1-year follow-up
  - Activities of daily living (ADL)
  - Instrumental ADL (IADL)
  - Grip strength
  - Timed chair rise
  - Timed 3-meter (10 feet) walk
- Change in dementia status between the pre-operative test and 1-year follow-up.

Study size

- Using power analysis from previous study
- 200 patients to determine differences in mortality
- Expect this to take 5 years with 50% enrollment

Intervention

- Randomization of sedation level while under spinal anesthesia to either heavy or light sedation
- Level of sedation is determined using the OAA/S score
- Sedation is provided using propofol

administration of spinal anesthesia

randomization to either light or deep sedation group using web based program

deep sedation
oaa/s score = 0 - 3
suggested starting propofol dose:
90-110 mcg/kg/min

light sedation
oaa/s score =4 or 5
suggested starting propofol dose:
30 mcg/kg/min

Randomization and blinding

- Incorporated a stratification scheme using
  - age (> 80 years or 65 - 80 years)
  - cognitive impairment (MMSE score 24-30 or 15-23).
- All study team members were blinded except the attending anesthesiologist during the case

Observer's Assessment of Alertness/Sedation (OAAS)

Response	Score
Responds readily to name spoken in normal tone	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1
Does not respond to noxious stimulus	0

Collaborators at JHBMC

- Orthopaedics
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- Clinical Trials
  - George Bigelow
- Geriatrics
  - Esther Oh
- Anesthesiology
  - JP Ouanes
  - Mahmood Jaberi
- Psychiatry
  - Karin Neufeld
  - Paul Rosenberg

summary

- Post-op prevention trials focus on the elderly
- Post-op delirium prevention trials primarily test drug interventions:misc drugs=dex=anesthetics
- Dexmedetomidine being tested in all types of elderly surgical populations
- Dex trials demonstrate different modes of administration/timing; lack stress measures; not particularly sick populations

Postoperative delirium prevention

- Anesthesia management delirium trials examine non-cardiac/hip fracture/elderly populations testing anesthetic drugs or techniques
- Pain management trials are primarily focused on regional techniques in targeted populations; unclear about long term ramifications of this type of delirium
- Technology focuses on optimizing perfusion and oxygenation in high risk surgeries
- Miscellaneous drugs focus on cardiac surgery; drug administration is pre and postop; delirium secondary outcome
- Most of the non-pharmacologic interventions tested may be applicable to other populations and several have high likelihood of being positive

Observations concerning underserved populations

- Surgical ICU?
- younger populations prone to delirium?
- Frailty?
- Oncology?
- Alcoholism?
- Emergency cases?
- Stroke and cerebrovascular disease?
- Dementia?