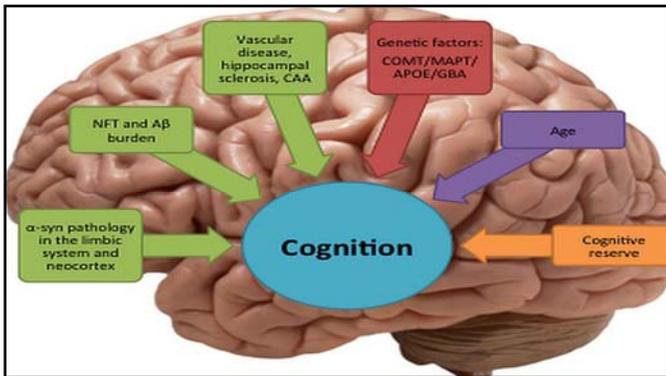


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Postoperative
Cognitive
Dysfunction versus
Delirium?
What is our Role?



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Postoperative Cognitive
Dysfunction and Delirium

- ▶ "Does Anesthesia Fry the Elderly Brain"
- ▶ Study at Duke University 2012



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Duke University Study

- ▶ At discharge, signs of POCD were present in 30-41% of patients
- ▶ At the 3 month mark, young and middle age patients had recovered. However, 12.7% of elderly (>60 years) still demonstrated cognitive impairment.
- ▶ Patients with POCD were more likely to die in the year following their surgery.

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History

- ▶ 1955- Bedford: Recommended to confine operations to necessary cases
- ▶ 1961- Simpson: Concluded that anesthesia had no effect and recorded benefits of surgery
- ▶ 1967- Blundell: Believed anesthetic drugs, fever, low oxygen caused POCD
- ▶ 1970- Finnish study: Showed deterioration in 8% of elderly patients following anesthesia

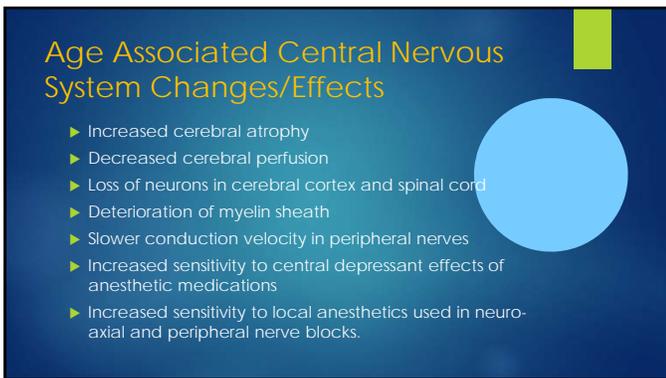
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CNS Structural Changes

- ▶ Brain mass decreases with corresponding decreased cerebral blood flow
- ▶ Decreased receptors
 - ▶ Acetylcholine
 - ▶ Cholinergic neurons in the basal forebrain regulate normal memory
 - ▶ Dopamine
 - ▶ Norepinephrine

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Postoperative Cognitive Disorders

- ▶ Delirium
- ▶ Mild neurocognitive disorder (POCD)
- ▶ Dementia (rare)
 - ▶ Multiple cognitive deficits
 - ▶ Impairment in activities of daily living

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Postoperative Cognitive Impairment

- ▶ 2 Categories
 - ▶ Postoperative Delirium
 - ▶ Postoperative Cognitive Dysfunction

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Delirium versus Cognitive Impairment

<ul style="list-style-type: none"> • Delirium – rapid onset – fluctuation – clouded consciousness – inattention, disorganized thought – not chronic 	<ul style="list-style-type: none"> • Cognitive impairment – variable to insidious onset – not fluctuating – no clouding of consciousness – many domains impaired – persistent/chronic (?)
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Gordon SM, Intensive Care Med 30:1997-2008, 2004
Jackson JC, Intensive Care Med 30:2009-2016, 2004

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Postoperative Delirium and POCD

- ▶ Prior, preoperative geriatric consultation/screening was the only intervention proven to decrease incidence.
- ▶ However, recent research has indicated that preoperative and postoperative pharmacologic and medical management can reduce the incidence.
- ▶ The use of regional anesthesia with low dose propofol and Dexmedetomidine reduces risk.
- ▶ Preoperative levels of education and brain function (cognitive reserve) may predict patients at risk.
- ▶ Reduced white matter integrity is reported to place patients at risk.
- ▶ "Postoperative Cognitive Disorders", Monk and Price, *Curr Opin Critical Care* 2011;Aug;17(4):376-81

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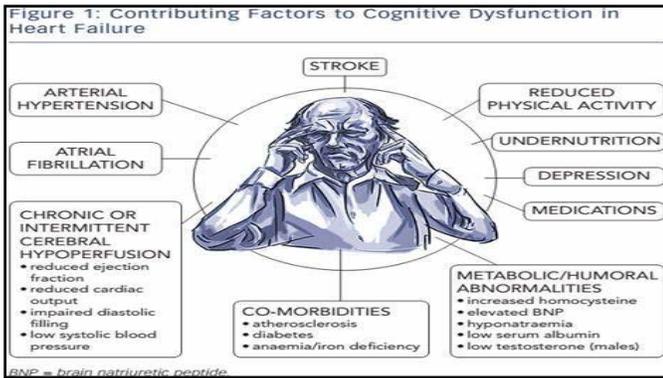
Postoperative Cognitive Disorders

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graph LR
    A((Delirium)) --> B((POCD))
    B --> C((Dementia))
    
```

- **Delirium**
 - ◆ 10-15% of elderly patients after GA
- **Mild neurocognitive disorder - POCD**
- **Dementia (rare)**
 - ◆ Multiple cognitive deficits
 - ◆ Impairment in occupational and social function

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Definitions

- ▶ **Delirium**- Key characteristics are a change in mental status characterized by a reduced awareness of the environment and a disturbance in attention.
- ▶ Is not temporally related to the emergence from anesthesia

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Postoperative Delirium

- ▶ Most common form of perioperative CNS dysfunction
- ▶ Acute confusion, decreased alertness, misperception
- ▶ Twice as common in the elderly
 - ▶ 10-15% of elderly surgical patients
 - ▶ 30-50% if undergoing cardiac or orthopedic surgery
- ▶ Seen after general, regional and MAC anesthesia
- ▶ Results in prolonged hospital stay and protracted postoperative care.

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POD Risk Factors

- ▶ Advanced age
- ▶ Pre-existing dementia
- ▶ Functional disability
- ▶ Mild cognitive impairment
- ▶ Depression
- ▶ Laboratory abnormalities
- ▶ Cardiovascular disease



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Delirium Predisposing Factors

- ▶ Drug withdrawal
 - ▶ Use of benzodiazepines, tricyclic antidepressants
 - ▶ Alcohol abuse
- ▶ Drug interactions
 - ▶ Anticholinergics
- ▶ Pre-existing depression or dementia
- ▶ Metabolic disturbances



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BIOLOGICAL HYPOTHESES OF DELIRIUM

- Decreased Acetylcholine activity in the brain
- Dysfunction of the reticular formation
- Hyperactive Locus ceruleus
- Noradrenergic dysfunction

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POD Precipitating Factors

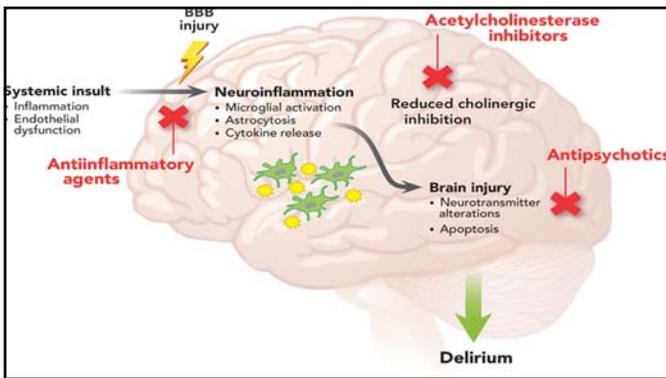
- ▶ Major, complex surgery
- ▶ Emergency surgery
- ▶ Major blood loss
- ▶ Periods of hypotension/hypoxemia
- ▶ Poorly controlled pain
- ▶ Prolonged ICU stay
- ▶ Major postoperative complications
- ▶ Micro-emboli

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Pathophysiology

- ▶ **Delirium**
 - ▶ EEG shows diffuse slowing
 - ▶ Wide variety of disturbances in neurotransmitter systems.
 - ▶ Increased serum anticholinergic activity as well as interaction with melatonin, norepinephrine, and lymphokines
 - ▶ Occurs as a result of the inflammatory response to surgery
 - ▶ Risk factors: > 70, preoperative use of narcotics and benzodiazepines, vision impairment, increased BUN, increased creatinine.

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Can Delirium be Prevented?

- ▶ Marcantonio (2001)- Reduced postoperative delirium by 1/3 in hip fracture patients
 - ▶ Minimize benzodiazepines, anticholinergics, antihistamines, meperidine
 - ▶ Maintain BP greater than 2/3 of baseline
 - ▶ Maintain O2 Saturation > 90%
 - ▶ Maintain Hct > 30%
 - ▶ Mobilize patients ASAP
 - ▶ Provide appropriate environmental stimulation



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Minimizing Delirium Try to Avoid

- ▶ Anticholinergics- atropine, scopolamine
- ▶ Ketamine
- ▶ Benzodiazepines
- ▶ Large doses of barbiturates and propofol
- ▶ Meperidine



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Common and Treatable Causes of Delirium

- ▶ Hypoxemia
- ▶ Hypercarbia
- ▶ Hypotension
- ▶ Pain
- ▶ Sepsis
- ▶ Metabolic



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Pharmacological Treatment- POD

- ▶ Haloperidol remains drug of choice
 - ▶ D2 Dopamine receptor antagonist
 - ▶ Administered at a dose of .5-1 mg IV q 10-15 minutes until behavior is controlled
 - ▶ Careful titration is critical and over-sedation can last up to 72 hours

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Postoperative Cognitive Dysfunction

- ▶ Deterioration of intellectual function presenting as *impaired memory or concentration*.
- ▶ Not detected until days or weeks after surgery
- ▶ Duration of several weeks to permanent
- ▶ Diagnosis is only warranted if:
 - ▶ Corroborated with *neuropsychological testing* and evidence of greater memory loss than one would expect due to normal aging.

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Postoperative Cognitive Function (POCD)

- ▶ Recognized as a complication contributing to peri-operative morbidity and mortality in the elderly.
- ▶ The elderly are the fastest growing segment of the population and undergo 25-30% of all surgical procedures.
- ▶ Cognitive decline is associated with the loss of independence, a reduction in the quality of life, and death.

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Implications of POCD

- ▶ Can lead to abrupt decline in cognitive function
- ▶ Ultimately
 - ▶ Loss of independence
 - ▶ Withdrawal from society
 - ▶ Death

▶ *Seattle Longitudinal Study on Aging*

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Pathophysiology POCD

- ▶ POCD
 - ▶ Age greater than 70
 - ▶ Preoperative cognitive impairment
 - ▶ Altered cerebral perfusion
 - ▶ Cerebral Micro-emboli
 - ▶ Inflammation- high C reactive protein levels
 - ▶ Anesthesia- Regional or General
 - ▶ Immune System Priming
 - ▶ Low educational level
 - ▶ Previous stroke
 - ▶ History of Previous POCD

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POCD Multifactorial?

- ▶ Pre-existing cognitive dysfunction
- ▶ Complexity and Duration of surgery
- ▶ Micro emboli
- ▶ Inflammation
- ▶ Stress, social isolation, immobility

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Independent Multivariate Predictors of One Year Mortality- POCD

Risk	Relative Risk	P value
▶ Baseline comorbidity	16.86	<.001
▶ Volatile vs TIVA	2.97	<.022
▶ Intraoperative Beta Blocker	1.67	<.004
▶ Chronic Beta Blocker	1.53	<.019
▶ Deep Anesthesia Time	1.34	<.007
▶ SBP < 80 mm Hg	1.04	<.008



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Common Drugs Causing POCD

- ▶ Benzodiazepines
- ▶ Methyldopa, Reserpine
- ▶ Hydrochlorothiazide
- ▶ Propranolol
- ▶ Haloperidol
- ▶ Meperidine
- ▶ Atropine, Scopolamine
- ▶ Cimetidine
- ▶ Insulin



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Jevtovic-Todorovic V; Study et al Neuroscience 2003

- ▶ Combination of NMDA antagonist and GABA agonist may result in widespread apoptotic degeneration in the hippocampus.



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Mechanism of Action of GA

Agent	NMDA Ant.	GABA agonist
▶ Ketamine	+	+
▶ N20	+	
▶ Benzos		+
▶ Propofol		+
▶ Inhalation Agents		+

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Is POCD caused by GA or Regional?

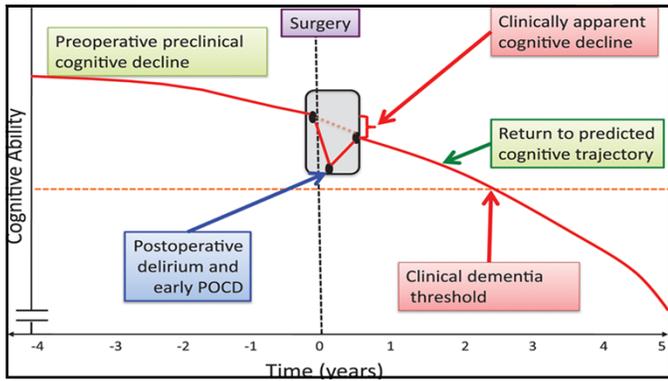
Study	n	Operation	Age (yrs)	POCD	Difference
Hole'80	60	THR	56-84	Yes	Yes
Kaarh'82	60	CAT	>65	Yes	Yes
Riis '83	30	THR	>60	Yes	No
Bigler'85	40	Hip	>60	No	No
Chung'87	44	TURP	60-93	Yes	Yes
Hughes'88	30	THR	50-80	Yes	Yes
Ghonei'88	105	Joint	25-86	Slight	No
Asbjjer'89	40	TURP	60-80	Yes	No
Jones'90	146	THR/TKR	>60	No	No
Nielson'90	60	TKR	60-86	No	No
Camp '93	169	CAT	65-98	No	No
Willia'96	262	TKR	>40	Yes	No

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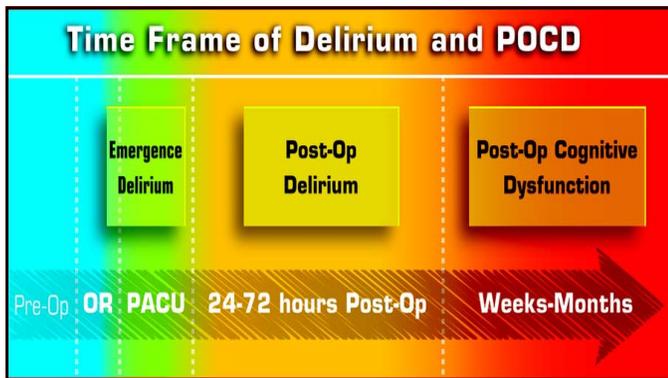
Observed Neurologic Injury during Brain Development Following Sedatives and General Anesthesia

- ▶ Neuronal Cell Death
- ▶ Altered dendritic arrangement
- ▶ Decreased synaptic density
- ▶ Mitochondrial deterioration
- ▶ Altered myelin formation
- ▶ Impaired long term cognitive function

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41

“Is Delirium.... Simply a marker for other factors that may contribute to postoperative cognitive dysfunction risk.... (or does) delirium itself actually contribute to longer- term postoperative cognitive dysfunction?”
 Devinney, Michael et al. *Anesthesiology* 9 :2018 Vol 129, 389-391

42

Separate Disorders or 2 Manifestations of the same underlying spectrum of neurocognitive dysfunction.

- ▶ "Splitters" - 2 completely different disorders
- ▶ "Lumpers" - View these disorders as two parts of the same spectrum of postoperative neurocognitive dysfunction
- ▶ Brown et al provide further evidence in favor of the lumpers position by demonstrating that delirium after cardiac surgery is associated with worse cognitive function at 1 month after surgery

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"Splitters"

- ▶ Syndromes are measured in different ways.
 - ▶ Delirium- assessed by instruments that evaluated attention, level of consciousness and disorganized thinking
- ▶ Syndromes don't necessarily include deficits in the same cognitive domain
 - ▶ Delirium- attention deficits
 - ▶ Cognitive function- memory or executive function
- ▶ Syndromes occur at different times
 - ▶ Delirium- assessed within days of surgery- peak in postop 1-3 days
 - ▶ Cognitive function- typically assessed 1-3 months after surgery
- ▶ Few if any human studies demonstrating these disorders share the same pathophysiologic mechanisms.

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"Lumpers"

- ▶ Several risk factors common to both delirium and cognitive dysfunction
 - ▶ Low education level, poor preop cognitive function and depression
- ▶ Delirium and cognitive dysfunction (occurring between 6-12 weeks after surgery) are both associated with worse cognitive decline in the 3 to 5 year span after anesthesia and surgery
- ▶ Animal studies suggest the possibility of a common pathophysiologic process- neuroinflammation and Alzheimer pathophysiology

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"Lumpers"

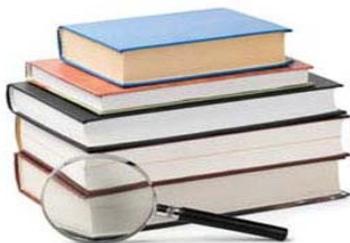
- ▶ Many patients with delirium develop postoperative cognitive deficits, and conversely, many patients with postoperative cognitive dysfunction also had postoperative delirium earlier in their postoperative recovery period.

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POCD and Inhalational Agents

- ▶ There is growing evidence that inhalational anesthetics may be neurotoxic to the aging brain.
- ▶ Volatile anesthetics may augment the pathological processes of Alzheimer's and POCD by affecting amyloid-beta processing.

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Literature Review

48

Royse, CF et al "The Influence of Propofol or Desflurane on Postoperative Cognitive Dysfunction in Patients undergoing Coronary Artery Bypass Surgery". *Anesthesia*. 2011 June;66(6):455-64.

- ▶ Randomized trial of 180 patients
- ▶ POCD measured between days 3 and 7
- ▶ Early POCD significantly higher with propofol compared with desflurane
- ▶ Conclusion: Desflurane associated with reduced early cognitive dysfunction.

49

"Tau phosphorylation and Sevoflurane Anesthesia: An Association to Postoperative Cognitive Impairment". *Anesthesiology*. 2012 Apr;116(4):779-87

- ▶ Study demonstrates, in mice, that sevoflurane exposure is associated with increased tau phosphorylation through specific kinases activation and spatial memory deficits. The data supports a correlation between exposures to this anesthetic agent and cognitive decline.

50

"Comparison of Early Cognitive Function and Recovery after Desflurane or Sevoflurane Anesthesia in the Elderly. A Double-Blinded Randomized Control Trial" *Br J Anaesth*. 2010 Feb;104(2):167-74.

- ▶ 80 patients (65-75 yrs)
- ▶ 40 patients in each group.
- ▶ Results:
 - ▶ According to the Paper-Pencil tests (Well being test, Recall of Digital Span , and Trail making test) were improved in the desflurane group.
 - ▶ Emergence was significantly faster in the desflurane group for "time to open eyes", and "time to extubation".

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MGH Study 01/March/2012

- ▶ Forane versus Desflurane
- ▶ Forane correlated with Alzheimer's disease.
 - ▶ Activation of enzymes and A beta plaques consistent with Alzheimers. There is an impact on neurologic mitochondria which results in POCD.
 - ▶ Desflurane is not associated with mitochondrial injury and enzyme elevations consistent with Alzheimers.
- ▶ MGH in conjunction with Beijing looked at 30 patients- 15 in the Forane group, 15 in desflurane group.
- ▶ 25% of Forane group developed POCD, 0 in Desflurane group.

52

Xiaoguang, Chen et al. "The Recovery of Cognitive Function After General Anesthesia in Elderly Patients. A Comparison of Desflurane and Sevoflurane. *Anesthesia and Analgesia* Dec 2001;93(6) 1489-1494

- ▶ Summary: 118 patients studied. Type of anesthesia and agents used tightly controlled.
- ▶ Desflurane: Faster recovery, eye opening, tracheal extubation, following verbal commands and orientation. Significantly shorter.
- ▶ No difference in agents at the 72 hour mark relative to POCD.

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Postoperative Cognitive Disorder

- ▶ Desflurane
better than Sevoflurane.
- ▶ Forane a poor choice.

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Desflurane vs Sevoflurane Time to return of protective reflexes

- ▶ Choice of inhalational agent can influence the return of protective airway reflexes.
- ▶ McKay et al (Anesthesia Analgesia Volume 100: Issue 3:697-700) found that sevoflurane caused a significant impairment of swallowing compared to desflurane in the postoperative period.

55

Desflurane/Fentanyl compared with Sevoflurane/Fentanyl on Awakening and Quality of Recovery in Outpatient Surgery using a LMA

- ▶ Oliveira et al "Journal of Clinical Anesthesia" 25:8:651-658, December 2013.
- ▶ Results: Desflurane retains faster awakening properties than does sevoflurane when used in combination with fentanyl as part of anesthetic maintenance in outpatient surgery with an LMA. The balanced anesthetic maintenance regimen seems to reduce the potential airway reactivity properties of desflurane.

56

Zhang, Yiyang et al "Anesthetic Isoflurane and Desflurane Differently Affect Mitochondrial Function, Learning and Memory" *Ann Neurol.* 2012 May; 71(5): 687-698.

- ▶ Conclusions:
 - ▶ Isoflurane
 - ▶ Increases ROS levels
 - ▶ Induces opening of mPTP (Parkinson's)
 - ▶ Reduces levels of MMP and ATP (enzymes related to tissue healing).
 - ▶ Causes Caspase 3 Activation (cysteine proteases that play an essential role in apoptosis)
 - ▶ Impairs learning and memory in vitro and in vivo

57

Rorigen, D et al. "Comparison of Early Cognitive Function and Recovery after Desflurane or Sevoflurane Anesthesia in the Elderly: A Double blinded randomized controlled trial" *British Journal of Anaesthesia*, 104(2): 167-74, 2010

- ▶ Conclusions
 - ▶ No difference in Alertness, Divided Attention, Visual Scanning, Working Memory and Reaction Change 6-8 hours and 66-72 hours after operation with either agent.
 - ▶ There were some advantages with Desflurane as demonstrated with the Paper- Pencil Test (Well Being Scale and Trail Making Test)
 - ▶ Either agent safe, slight advantage to Desflurane

58

Li, Xia0-min et al "Resveratrol Pretreatment Attenuates the Isoflurane- induced Cognitive Impairment Through its Anti-Inflammation And Apoptosis Actions in Aged Mice" *J Mol Neurosci* (2014) 52: 286-293

- ▶ Conclusion:
 - ▶ Isoflurane impairs hippocampus dependent cognition
 - ▶ Leads to the overproduction of pro-inflammatory cytokines and neuroapoptosis in the hippocampus
 - ▶ Resveratrol treatment prevents these changes.

59

"Eating Mushrooms can Cut Cognitive Decline Risk"

- ▶ Journal of Alzheimer's Disease, March 2019
- ▶ School of Medicine Singapore
- ▶ Ergothioneine (ET) – Unique antioxidant and anti-inflammatory
- ▶ Not synthesized by humans
- ▶ 6 types of mushrooms identified: golden, oyster, shiitake, white button, and canned mushrooms.

60

Arora, Sona S. et al "Postoperative Cognitive Dysfunction, Alzheimer's Disease and Anesthesia" *International Journal of Neuroscience*, 2014; 124 (4): 236-242

- ▶ Anesthetic Management
 - ▶ Perform a preoperative Cognitive Evaluation: Mini Mental State Exam
 - ▶ Normoglycemia/Screen for sleep disorders
 - ▶ Avoid cholinesterase inhibitors. Use glycopyrrolate
 - ▶ Decrease Inhaled Anesthetic Agents
 - ▶ Cholinergic deficiency plays a role in delirium. Physostigmine can reverse delirium.
 - ▶ Prophylactic Use of Neuroleptics: Haloperidol, Risperidone, and Olanzapine.

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POD/POCD Prevention/Treatment

- ▶ Preoperative assessment of cognitive function.
- ▶ Target high risk individuals
- ▶ Elimination/minimization of benzodiazepines, anticholinergics, antihistamines, meperidine, metoclopramide, Inderal.
- ▶ Encourage early mobilization
- ▶ Keep blood pressure at baseline levels
- ▶ If necessary use Dexmedetomidine for sedation.
- ▶ Preemptive analgesia, use of Tylenol, clonidine, Exparel
- ▶ Ketamine at .5 mgs/kg is associated with lower serum levels of C reactive protein and lower incidence.
- ▶ Associated with stress, anxiety, sleep deprivation, dehydration, PTSD, and pain

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Summary of Guidelines

- ▶ Identify patients at risk
- ▶ Measure baseline cognitive function if possible
- ▶ Carefully titrate all medications
- ▶ Avoid long acting medications- benzodiazepines
- ▶ Maintain baseline blood pressures/oxygen saturation
- ▶ Desflurane or Sevoflurane
- ▶ Effectively manage pain/stress
- ▶ Maintain normo-thermia
- ▶ Minimize anesthetic exposure
- ▶ Utilize regional anesthesia when possible

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