Drug Choices and Outcomes in Neuroanesthesia

or "To Gas, or Not to Gas, That is the Question!"

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Your Anesthetic?
- "Balanced" technique – opiate/volatile?
- Nitrous/narcotic technique?
- TIVA – propofol/opiate
- Does choice of opiate matter?

First – The Basics

Goals of Anesthetic Management
- Hemodynamic stability
- Maintenance of cerebral perfusion pressure
- Control of intracranial pressure
- Optimal surgical conditions (slack brain; no movement)
- Smooth emergence
- Rapid awakening for early neurologic assessment

Disclosures - None
Ideal Neuroanesthetic Technique

• Maintain CBF without affecting autoregulation
• Minimize detrimental changes in Intracranial Pressure (ICP)
• Preserve reactivity of cerebral arterioles to PaCO₂ changes
• Decrease CMRO₂ with cerebral protection effects
• Devoid of seizure activity
• Preserve hemodynamic stability, especially Cerebral Perfusion Pressure (CPP)

Determinants of ICP (and What We Can Control)

• Brain tissue
• Intra- and extracellular fluid (edema)
• CSF
• Blood (arterial/venous)
• Airway or intrathoracic pressure
• Jugular venous pressure
• PaCO₂
• PaO₂
• Anesthetics
• Vasodilators
• Seizures
• Temperature
• Arousal
• Pain

Let’s Assume Everyone Knows:

• Avoid hyperglycemia
• Use isotonic solutions for fluid replacement to avoid cerebral edema
• Maintain normothermia except in extreme conditions (IHAST trial, Todd, 2005, no difference in outcome with hypothermia)

Why Does ICP Matter? Prevent Primary Injury

• Sustained ICP > 20 mm Hg is abnormal
• ICP 20 – 40 mm Hg is considered moderate intracranial hypertension
• ICP > 40 mm Hg is life-threatening
• Increased ICP results in injury due to ischemia from reduced CPP and distortion of intracranial structures such as the brainstem

Normal Values

<table>
<thead>
<tr>
<th>Table 21-1 Normal cerebral physiologic values</th>
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<tbody>
<tr>
<td>CBF</td>
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<tr>
<td>CBF (local)</td>
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<tr>
<td>CBF (cortical)</td>
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<td>CBF (white matter)</td>
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<td>CBF (gray matter)</td>
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<td>CBF (subcortical)</td>
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<td>ICP (supine)</td>
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CBF, cerebral blood flow; CMRO₂, cerebral metabolic rate of oxygen; CVR, cerebral vascular resistance; ICP, intracranial pressure.
Why Does CPP Matter?

CPP, CBF, and Time

Volatile Agents

Effects of Volatile Agents
(Are they all created equal?)

- Sevoflurane preserves autoregulation better than Isoflurane

- Sevoflurane produces less increase in CBV and V_mca than Isoflurane or Desflurane
  Matte BF et. al. Anesthesiology 1999; 91:677-80
  Bedforth NM et. al., Anesth Analg 2000; 91:152-5
  Holmstrom A et al., J Neurosurg Anesthesiol 2004; 16:136-143
Effects of Volatile Agents (Comparative Studies, Intracranial Surgery)

• 1 MAC Desflurane in air\O₂ increased Cerebrospinal Fluid Pressure greater than Isoflurane (18 vs. 8 mm Hg)

Muzzi DA et. al., Anesthesiology 1992; 77:720-724

• Isoflurane or Desflurane 1.0 MAC:
  no change in ICP
  19% decrease in MAP
  22% decrease in CPP.

Fraga M et. al., Anesthesiology 2003; 99:1085-90

• Patients with mass effect: 1.2 MAC Iso or Des:
  No change or difference in CSFP, MAP, or CPP
  Time to respond to commands was 50% shorter with Des (30 vs. 72 minutes, n.s.)

Tayye A et. al., Anesth Analg 2004; 99: 1127-32

Effects of Intravenous Agents

• Patel FD and Sherrard JC in Miller’s Anesthesia, 6th Ed., p. 822

But What About Intravenous Agents?

Effects of Volatile Agents (Comparative Studies, Intracranial Surgery)

A Hint About How We Do It Matters

• Sevoflurane had earlier recovery profile than Isoflurane (moving feet: 24 minutes Sevo vs. 43 minutes Iso). Hemodynamic variables and brain relaxation scores were similar.

Gauthier A et. al., Anesth Analg 2002; 95:1384-8

Effects of Volatile Agents (Sevo vs. Des, Intracranial Surgery)

• In patients with tumors given 1.2 MAC Sevo or Des:
  No difference in emergence time
  Mean extubation time (15 vs 11min) and recovery time (18 vs 12 min) longer with Sevo
  No difference in incidence of pain, shivering, PONV, or hemodynamic events

Effects of Intravenous Agents
(Opiates Compared, Intracranial Surgery)

- In patients with tumors:
  Sufenta (89%) and Alfenta (22%) ↑ CSFP vs Fentanyl
  All ↓ CPP (Fentanyl 14%; Sufenta 25%; Alfenta 37%)
  Marx W et al., J Neurosurg Anesthesiol 1989; Vol 1(1):3-7

- In patients with tumors given boluses of Remifentanil (0.5 mcg/kg or 1.0 mcg/kg) or Alfenta (10 mcg/kg or 20 mcg/kg):
  No change in ICP
  Similar decrease in MAP
  Warner DS et al., Anesth Analg 1996; 83:488-53

- In patients with tumors using Alfentanil, Fentanyl, or Sufentanil:
  No difference in recovery profiles or intraoperative brain conditions
  From RP et al., Anesthesiology 1990; 73:896-904

- In patients with tumors, comparing Remifentanil and Fentanyl:
  No difference in ICP, CPP, MAP (except for intubation), brain condition, or recovery variables.
  Guy J et al., Anesthesiology 1997; 86:514-24

Effects of Intravenous Agents
(Comparative Studies, Intracranial Surgery)

Cautionary Tale for Propofol

- In sedated patients with head trauma (GCS=6-7), Propofol (2mg/kg bolus with 150mcg/kg/min infusion):
  Decreased ICP (11.3-9.2 mm Hg, 18%)
  Decreased MAP (25%)
  Decreased CBF (35-26 ml/100g/min, 25%)
  Decreased CPP (82-59 mm Hg, 28%)
  Pinaud M et al., Anesthesiology 1990; 73:404-9

Volatile vs. Intravenous:
Which is Best?

- Patients with tumors given either Isoflurane (0.5-1.5%) or Propofol infusion, Propofol showed:
  Lower CPP (81 vs. 70 mm Hg)
  Lower CSFP (15.2 vs. 11.6 mm Hg)
  Better recovery variables at 20-30 min

Effects of Intravenous Agents
(Opiates Compared, Intracranial Surgery)

- Remifentanil vs. Sufentanil, Propofol maintenance, elective tumor surgery:
  NO DIFFERENCE IN –
  Extubation time
  Incidence of PONV
  Remi - smoother hemodynamics, greater cost and use of morphine postoperatively
  Djian M et al., Clin Ther 2006; 28:480-88
Volatile vs. Intravenous (Comparisons, Intracranial Surgery)
- In patients with tumors comparing:
  Propofol/Fentanyl
  Isoflurane/N₂O
  Fentanyl/N₂O
  - No differences in mean ICP or brain condition.
  - MAP and CPP was lower with Iso/N₂O.
  - Emergence was more rapid with Fentanyl/N₂O.
  Todd MM et al., Anesthesiology 1993; 78:1005-1020

Volatile vs. Intravenous (Comparisons, Intracranial Surgery)
- Compared to Propofol:
  Des and Iso 0.5 and 1.0 MAC increased CSFP (5 and 4 mm Hg) and decreased CPP (12 and 15 mm Hg)
  Talke P et al., Anesthesiology 1996; 85:999-1004
  Sevo 0.5 and 1.0 MAC increased CSFP (2 mm Hg) and decreased CPP (11-15 mm Hg)
  Talke P et al., Anesthesiology 1999; 91:127-30
  - Propofol infusion, Isoflurane, or Isoflurane switch to Propofol at dural closure
  No differences in hemodynamic or recovery variables.

Volatile vs. Intravenous (Comparisons, Intracranial Surgery)
- In elective tumors combining Fentanyl, comparing Propofol with Iso and Sevo,
  Propofol infusion was associated with:
    Lower ICP (7 mmHg vs 12 or 11)
    Higher CPP (80 mm Hg vs 60 or 63)
    Lower dural tension than Iso (not Sevo)
    Less cerebral swelling after opening dura
  *No difference in ICP or CPP between Iso and Sevo
  Petersen KD et al., Anesthesiology 2003; 98:329-36

Volatile vs. Intravenous (Comparisons, Intracranial Surgery)
- In elective tumor patients, comparing Sevo/Remi to Propofol/Remi:
  no difference in:
  Time to reach Aldrete score = 9
  Brain relaxation scores
  Use of osmotic diuretics
  Less PONV with Propofol
  Higher cost (23%) and postoperative analgesic requirements with Remi groups

Volatile vs. Intravenous (Does Remifentanil Help?)
- Elective craniotomy comparing Sevo-Remi, Sevo/Fentanyl, and Propofol/Remi:
  No difference in – Time to Aldrete score = 9
  Brain relaxation scores
  Use of osmotic diuretics
  Less PONV with Propofol
  Higher cost (23%) and postoperative analgesic requirements with Remi groups

* No benefit to using ultra-short opioid
**And Since we’re Talking About Cost...**

- Current UCH acquisition costs for:
  - Desflurane - $140.05
  - Sevoflurane - $127.37
  - Isoflurane - $10.91
  - Propofol 20 ml - $2.14
  - Propofol 50 ml - $5.34
  - Fentanyl 5 ml - $0.99
  - Sufentanil 100 mcg/2ml - $3.53
  - Remifentanil 1 mg - $43.83

**Compare 3 Opiates, 5 Hours, 70 kg:**

- Fentanyl – 8mcg/kg load, 1.25mcg/kg/hr:
  - Total 1007 mcg = ~$4
- Sufentanil – 1mcg/kg load, 0.3mcg/kg/hr:
  - Total 175 mcg = ~$7
- Remifentanil – 1mcg/kg load, .25mcg/kg/min:
  - Total 5320 mcg = ~$227
- Propofol – 2mg/kg load, 150 mcg/kg/min:
  - Total 612 mg = ~$65

**CBF, ICP, CBV, or CPP?**

- CPP = MAP – ICP
- Want to maintain CPP = 70 – 90 mm Hg
- ICP affected by intracranial volume
- Intracranial volume has 4 components:
  - Tissue volume
  - CSF volume
  - Fluid compartment (edema)
  - Blood volume (arterial and venous)
- CBF reflects arterial volume – how much does this really affect total CBV?

**CBF, ICP, CBV, or CPP?**

- Approximately 10% of CBV is in the arterioles and capillaries – the compartment which reacts to CO₂ and anesthetic agents
- Schendel HH et al., Neurosurgery 1985; 17:663-78
- Hesstad DO et. al. in Handbook of Physiology; American Physiologic Society, 1983
- Comparing 1.4% Iso, 0.8% Hal, or 2.2% Enf:
  - Halothane: ↑ CBV (11%), 1CP (stable)
  - Enflurane: ↑ CBV (9%), 1CP (continued to rise, even after Enf off)
  - Isoflurane: ↑ CBV (10%), 1CP (only for first 20 min, then returned to baseline)
  - Fentanyl: ↓ CBV (8%), 1CP (stable)

**CBF, ICP, CBV, or CPP?**

- In rats though CBF was 2.0-2.6 times greater with Iso than Prop or Pento, CBV was only 10-18% greater with Iso

**Drug Choices and Outcomes in Neuroanesthesia**

- Janik, Daniel, MD

**Comparisons of propofol and volatile agents for maintenance of anesthesia during elective craniotomy procedures: systematic review and meta-analysis**

- Fourteen studies (1,819 patients)
- Brain relaxation scores similar
- ICP lower/CPP higher with Propofol
- PONV less with Propofol
- Postoperative complications similar
- Recovery variables similar
- *Inadequate data to compare neurological morbidity and mortality

**Comparisons of propofol and volatile agents for maintenance of anesthesia during elective craniotomy procedures: systematic review and meta-analysis**

- CBF, ICP, CBV, or CPP?

- In rats though CBF was 2.0-2.6 times greater with Iso than Prop or Pento, CBV was only 10-18% greater with Iso

**Comparisons of propofol and volatile agents for maintenance of anesthesia during elective craniotomy procedures: systematic review and meta-analysis**

- CBF, ICP, CBV, or CPP?
What About Dexmedetomidine?

- Decreases both CBF > CMRO<sub>2</sub>
- Can reduce MAC by up to 90%
- Opioid sparing effect
- Moderate doses do not interfere with neuromonitoring
- Decreases intracranial pressure
- Significantly attenuates hypertensive response to intubation and Mayfield pin placement

Volatile vs. Intravenous Agents
(Is One Really Better?)

- It depends on how you define “better”
  - Quicker emergence (short term outcome)
  - Ease of titration/administration
  - Hemodynamic stability
  - Brain conditions
  - Long-term outcomes (no data)

What About Dexmedetomidine?

- Increases cardiovascular stability
- ETT may be removed earlier in one study
- BUT – it is not an anesthetic and use may confuse bispectral index monitoring

Published Opinions

- Overall, TIVA is similar to volatile anesthetics with regard to hemodynamic stability, emergence times, extubation times, early cognitive function, and adverse events. … Our institutional experience with TIVA in these patients has shown a subjective improvement in brain relaxation and surgical access to the operative site. … The impact of TIVA... in a study group with severely elevated ICP has yet to be evaluated.


Both, sevoflurane and propofol are generally suitable for neurosurgical interventions. The decision to choose either of the two anesthetics should be made on the basis of exact knowledge of their advantages and disadvantages. In patients with no intracranial hypertension the use of sevoflurane might be more reasonable, because cerebral blood flow is improved compared with propofol. When intracranial pressure is high (e.g. large tumor) propofol reduces the intracranial volume and thereby facilitates the surgical approach.

Bekker A, Sturaitis MK, Neurosurgery 2005;57 (ONS Suppl 1)
Tanskanen PE et al, Br J Anaesth 2006;97:658-65
Oztuna I et al, EAUM 2010;23:6-5
Soliman RN et al, Middle East J Anaesthesiol 2011;21:325-34
My Opinion

• For all agents, the ultimate condition of the patient will be determined by the sum of the effects of the chosen agent on CBF, CMRO$_2$, vascular tone, MAP, CO, CSF formation/reabsorption, and CBV.

• The preponderance of evidence is that intravenous agents (Propofol, Barbiturates, Etomidate, Benzodiazepines, synthetic opiates (phenylpiperidines)) have less deleterious, and more salutary effects that are more predictable on intracranial dynamics than volatile agents, especially if MAP is maintained.

My Opinion

• Isoflurane, Sevoflurane, and Desflurane are similar, though the edge goes to Sevoflurane, and their ultimate effects on ICP/CPP are less predictable.

• There is no overwhelming evidence that one technique is superior to any other in terms of short term recovery profile, if the agents chosen are properly administered.

• Choose your poison (agents) wisely given the goals of anesthesia and surgery, and the condition of the patient such as………

• If the patient is wide awake, appearing for elective surgery, and is well-compensated in terms of intracranial dynamics:
  
  Either volatile or TIVA are appropriate taking care to avoid bad things like –
  
  Hypotension (remember CPP)
  Hypertension
  Hypoxemia
  Hypercarbia

  Inadequate anesthesia at critical points

  Remember – it’s more important how you do it, than what you use.
And This:

My Opinion

• If the patient has signs or symptoms of high ICP (altered mental status, head injury, ventriculostomy/ICP monitor in place, midline shift on CT/MRI, etc.):
  - Management of the ICP/CBF/CBV/CPP is critical
  - TIVA is preferable, at least until the dura is opened and the effects of anesthetics on the brain bulk can be assessed directly
  - Keep a very close eye on CPP (>70 mm Hg)

Lower Limit of Autoregulation - Human