Post-Operative Nausea and Vomiting

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WHAT DO YOU GET WHEN YOU COMBINE COGNITIVE BIAS WITH INACCURATE INFORMATION?

OUR BUSINESS STRATEGY! HAHA--HAHAHAHA!!!

I GUESS I SHOULD KEEP MY DAY JOB.

GOOD LUCK WITH THAT.
Conflict of Interest

Regretfully, I have no industry or other financial relationships to disclose
Off-label Use of Medications

The use of one medication for an ‘off-label’ indication will be discussed but will not be recommended or endorsed.
Introduction

The hard fact is that we’re not very good at preventing or treating PONV/PDNV. One study showed that, despite training and feedback, only about half of patients with moderate risk factors and one third of patients with high risk factors receive appropriate prophylactic treatment, even with a simple regimen, one drug per risk factor. Almost all patients received one drug, which was the de facto standard.
Goals and Objectives

1) Review the implications of post-operative nausea and vomiting (PONV)
2) Present current SAMBA guidelines for the prevention and treatment of PONV
3) Present proposed changes to SAMBA guidelines for the prevention and treatment of PONV
Pathophysiology

- Chemoreceptor trigger zone
- Vomiting Center
- CNs VIII and X
- Visual and vestibular systems
Pathophysiology

• Vomiting center is in the lateral medullary reticular formation

• Stimuli from differing afferents can activate the vomiting center, specifically the chemoreceptor trigger zone (CTZ), visceral and cortical afferents
  – CTZ is located in the area postrema and has receptors for dopamine, opiates, acetylcholine, 5-hydroxytryptamine_3 (5HT_3), and substance P
  – Area postrema is outside the blood brain barrier so can be stimulated by chemicals in blood or CSF
Pathophysiology

• Afferents from the pharynx (CN X), visual center and vestibular portion of CN VIII can also activate the vomiting center

• Vestibular system is implicated in motion sickness and has muscarinic and histamine receptors
SAMBA Guidelines

- Released in 2003, revised in 2007, new revision currently in draft stage
- Identifies risk factors
- Recommends methods to reduce baseline risks
- Identifies effective mono and polytherapy for prophylaxis and treatment
Incidence

• 90 million operative procedures yearly in US, 53 million as outpatients. 234 million operative procedures worldwide.

• If untreated, POV will occur in 30%, PON in 50% of the population and up to 80% in high risk population.
  – Patients would pay $56 for a perfect anti-emetic.
  – Those who develop vomiting would pay up to $100.
  – Parents would pay $80 to prevent POV in their children.
  – Almost 50% of patients in a 3 day study reported PONV as interfering with normal postoperative function.

• PONV can delay PACU discharge and can be a cause of unplanned admission following ambulatory surgery.
Risk Factors

Patient factors

Surgical factors

Anesthetic factors
Patient Factors

Female sex
  – Strongest independent predictor

Non-smoker
  – Theorized that smokers may be desensitized to noxious stimuli

History of PONV or motion sickness

Age < 50
Surgical Factors

• Length of surgery

• Type of surgery
  – Laparoscopy
  – Breast surgery
  – Ophthalmologic or ENT procedures
  – Plastic surgery
  – Gynecologic
  – Cholecystectomy
Anesthetic Factors

Dose dependent use of volatile anesthetics
  - No differences in PONV incidence among volatile anesthetics

\( \text{N}_2\text{O} \)
  - Less emetogenic than volatile anesthetics

• Use of postoperative opioids
  - Approximately doubles PONV risk
  - Dose dependent
  - Intra-operative opioids not a major risk factor
Disproven Factors or Limited Relevance

- BMI
- Anxiety
- Naso-gastric Tube
- Supplemental Oxygen
- Peri-operative Fasting
- Migraine

- Music therapy
- Isopropyl alcohol inhalation
- Esomeprazole
- Nicotine patch to non-smokers
- Cannabinoids
Factors With Conflicting Evidence

- ASA Physical Status
- Menstrual cycle
- Level of anesthetist’s experience
- Muscle relaxant antagonists
# PONV Risk Scoring

## Risk Factors and Points

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>1</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>1</td>
</tr>
<tr>
<td>History of PONV</td>
<td>1</td>
</tr>
<tr>
<td>Postoperative opioids</td>
<td>1</td>
</tr>
</tbody>
</table>

**Sum = 1-4**

![Bar Chart for Number of Points]
POV Risk Scoring in Children

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery &gt; 30 minutes</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt; 3 years</td>
<td>1</td>
</tr>
<tr>
<td>History of PONV or PONV in relatives</td>
<td>1</td>
</tr>
<tr>
<td>Strabismus surgery</td>
<td>1</td>
</tr>
<tr>
<td><strong>Sum =</strong></td>
<td><strong>0 - 4</strong></td>
</tr>
</tbody>
</table>

Number of Points
<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>1</td>
</tr>
<tr>
<td>Nausea in PACU</td>
<td>1</td>
</tr>
<tr>
<td>Age &lt; 50 years</td>
<td>1</td>
</tr>
<tr>
<td>History of PONV</td>
<td>1</td>
</tr>
<tr>
<td>Postoperative opioids</td>
<td>1</td>
</tr>
<tr>
<td><strong>Sum =</strong></td>
<td><strong>1-5</strong></td>
</tr>
</tbody>
</table>

**Number of Points**

PDNV Risk Scoring
Methods to Reduce Baseline Risk

- Avoidance of general anesthesia
- Induction and/or TIVA with propofol
- Avoidance of $N_2O$ and volatile anesthetics
- Minimizing intraoperative and postoperative opioids
- Adequate hydration
- Neostigmine no longer recognized as a risk factor
PONV prophylaxis

- First line agents
  - 5-hydroxytryptamine (5HT₃) receptor antagonists
  - Corticosteroids
  - Butyrophenones
  - Anticholinergics
  - Neurokinin 1 receptor antagonists
  - Other medications
5HT₃ Receptor Antagonists

- Selectively bind 5HT₃ receptors and competitively block emetogenic signals to vomiting center
  - Cytotoxic agents increase the release of 5HT₃ from enterochromaffin cells in small intestine
  - Those cells are in close proximity to vagal afferents that then travel to brain stem via nucleus tractus solitarius which then activates the vomiting center

- Duration of activity depends on affinity for receptor, not half life

- Genetic polymorphisms affect individual response
  - Metabolized via cytochrome P450 mono-oxygenase isoenzymes CYP2D6 and CYP3A4
5HT$_3$ Receptor Antagonists

- Most effective for prophylaxis when given at the end of surgery

- Most studies done with ondansetron

- Favorable side effect profile
  - Majority are associated with QT prolongation
  - Dolasetron has black box warning in Canada secondary to severe arrhythmias
Palonosetron

• Novel 5HT₃ receptor antagonist
  – Half life of 40 hours

– Greater affinity for 5HT₃ receptor
  • Unique interactions with receptor that trigger effects that persist beyond the time it is bound
    – May cause long term alteration in 5HT₃ receptor
Palonosetron

• Recent randomized, double blind, placebo controlled studies
  – Palonosetron 0.075mg reduced incidence of PONV in first 24 hours after surgery
  – Significantly reduced severity of nausea

• Tolerable side effect profile
  – No QT prolongation when compared to placebo
Corticosteroids

Dexamethasone has been shown to be equally as effective as ondansetron and droperidol

- Antiemetic effect thought to be from central inhibition of nucleus tractus solitarius or prostaglandin antagonism

Should be given at induction of anesthesia as antiemetic effects are late

No evidence of adverse effects after single doses though significant increases in blood glucose 6-12 hours post-operatively have been noted. Use in labile diabetics is relatively contraindicated.

Methylprednisolone is effective but no more so than dexamethasone.
Butyrophenones

• Droperidol is a centrally acting dopamine antagonist

• Equivalent in efficacy when compared to ondansetron and dexamethasone

• Short half life

• Most effective when given at end of surgery

• Haloperidol is antiemetic in low doses, 0.5-2 mg IM or IV.
Butyrophenones

Haloperidol has the advantage to be given intra-muscularly

Haloperidol is not FDA approved as an antiemetic nor for IV administration

Mentioned only because of recent droperidol shortages
Black Box Warning

- Placed in 2001 warning of serious arrhythmogenic effects and death
- Based on 273 reports with 127 adverse events
  - Death
  - Life-threatening events
  - Prolonged hospitalization
- Majority of case reports were from outside the US
Black Box Warning

• Multiple confounding factors
  – Polypharmacy
  – Droperidol doses > 25mg
  – Several cases reported more than once
• Only 5 patients that received less than 2.5mg had reported arrhythmias
• Few studies have show QT prolongation after large bolus doses of droperidol, but none leading to arrhythmias
Black Box Warning
Promethazine

Should not be administered intra-arterial or subcutaneously because of the risk of severe tissue injury including gangrene.

There is also the risk that the drug can leach from the vein during IV administration and also result in tissue injury.

If administered IV it should be diluted and administered into a properly functioning IV.

The preferred route of administration is deep intramuscular injection.
Anticholinergics

• Scopolamine is a centrally acting anticholinergic
  – May cause drowsiness, visual disturbances and dry mouth

• Randomized, double blind, placebo controlled study compared transdermal scopolamine (TDS) to ondansetron and droperidol
  – TDS had comparable prophylactic effect when compared to ondansetron and droperidol
    • No increased need for rescue therapy
  – Dry mouth occurred more frequently in TDS group
  – Drug is actively available from patch for up to 72 hours
  – TDS must be placed a minimum of 2-4 hours prior
Neurokinin -1 Receptor Antagonists

• Apretitant similar to ondsansetron for 24 hours after surgery
• Significantly more effective at 24 and 48 hours after surgery
• 80mg dose may be the most effective dose
Other Medications

Dimenhydrinate and meclizine are effective.

Metaclopramide – weak antiemetic and not effective.

Alpha2-agonists- weak antiemetics

Gabapentin – 1 hr prior to surgery as effective as dexametasone – combination better than either alone.

Midazolam - as effective as ondansetron.
P6 Stimulation

• P6 acupuncture point is located 2 Chinese units proximal to the distal skin crease of the wrist
  – Many proposed mechanisms of action
    • Stimulation of endogenous opioids
    • Increased vagal modulation
    • Stimulation of reflexes that affect LES sphincter and gastric relaxation
P6 Stimulation

• Several randomized, double blind, placebo and sham controlled trials
  – P6 stimulation decreased incidence of nausea, but does not significantly reduce incidence of emesis
    • Decreased use of antiemetic rescue therapy
  – Seems to be most effective in early postoperative period
  – One study showed patients had better pain control
P6 Stimulation with Neuromuscular Blockade Monitoring

• Recent randomized, double blind study
  – NMB blockade monitoring at P6 point
  – NMB blockade at ulnar nerve
  – 1Hz frequency with constant 50mA current

• Significantly decreased incidence of early PONV, specifically nausea

• Inconsistent data in pregnant patients

• 1 cun (Chinese unit) = width of a person’s thumb at the knuckle
Commercially Available P6 Stimulator

[Image of Reletex PCN-3 and Reletex PCN-7 devices]
Prophylaxis

- Routine prophylaxis is usually not warranted in patients with low risk for PONV

- Patients at moderate risk should receive prophylaxis and those at high risk should receive multiple agents
## Antiemetic Doses and Timing in Adults

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aprepitant</td>
<td>40mg po</td>
<td>At induction</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>4-5 mg IV</td>
<td>At induction</td>
</tr>
<tr>
<td>Dimenhydrinate</td>
<td>1 mg/kg IV</td>
<td></td>
</tr>
<tr>
<td>Droperidol</td>
<td>0.625-1.25 mg IV</td>
<td>End of surgery</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>0.5mg/kg IM</td>
<td>End of surgery</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>40mg IV</td>
<td></td>
</tr>
<tr>
<td>Ondansetron</td>
<td>4mg IV 8mg SDT</td>
<td>End of surgery</td>
</tr>
<tr>
<td>Palonosetron</td>
<td>0.075 mg IV</td>
<td></td>
</tr>
<tr>
<td>Scopolamine</td>
<td>TD patch</td>
<td>Prior evening or 2 hrs prior to surgery</td>
</tr>
</tbody>
</table>
Antiemetic Doses for prophylaxis of POV in Children

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>150ug/kg up to 5 mg</td>
</tr>
<tr>
<td>Dimenhydrinate</td>
<td>0.5 mg/kg up to 25 mg</td>
</tr>
<tr>
<td>Droperidol (black box warning)</td>
<td>10-15ug/kg up to 1.25 mg</td>
</tr>
<tr>
<td>Ondansetron (approved age 1 month and older)</td>
<td>50-100ug/kg up to 4 mg</td>
</tr>
</tbody>
</table>
Combination Therapy for Adults

- Droperidol + dexamethasone
- $5\text{-HT}_3$ receptor antagonist (‘tron’) + dexamethasone
- ‘Tron’ + droperidol
- ‘Tron’ + droperidol + dexamethasone
- Ondansetron + TDS
Combination Therapy for Children

Ondansetron 0.05mg/kg + dexamethasone
  0.015mg/kg

Ondansetron 0.1mg/kg + droperidol
  0.015mg/kg
Example interventions

Drug A = dexamethasone 4 mg
Drug B = ondansetron 4 mg
Drug C = droperidol 1 mg
Drug D = dimenhydrinate 1 mg/kg

Given drug examples are used to illustrate how the algorithm may be implemented but may not represent the most favorable approach.

TIVA = total intravenous anesthesia, i.e., propofol induction and maintenance, no nitrous oxide

<table>
<thead>
<tr>
<th>Estimated</th>
<th>Risk for</th>
<th>PONV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Medium</td>
<td>High</td>
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</table>

<table>
<thead>
<tr>
<th>Prophylaxis</th>
<th>Risk for</th>
<th>PONV</th>
</tr>
</thead>
<tbody>
<tr>
<td>None – Wait and see</td>
<td>Drug A + Drug B or TIVA</td>
<td>Drug A + Drug B + TIVA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Risk for</th>
<th>PONV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Drug B 2) Drug C when drug B doesn’t work</td>
<td>1) Drug C 2) Drug D when drug C doesn’t work</td>
<td>1) Drug C 2) Drug D when Drug C doesn’t work</td>
</tr>
</tbody>
</table>
# SAMBA CLINICAL OUTCOMES REGISTRY SCOR DATABASE

## PONV – The Emory Clinic ASC - 2012

<table>
<thead>
<tr>
<th>PONV Score</th>
<th># Cases</th>
<th>Prophylactic Antiemetics</th>
<th>Antiemetic rescue in PACU (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>None given</td>
<td>1 agent</td>
</tr>
<tr>
<td>0</td>
<td>134</td>
<td>106</td>
<td>26</td>
</tr>
<tr>
<td>1</td>
<td>1241</td>
<td>853</td>
<td>315</td>
</tr>
<tr>
<td>2</td>
<td>1889</td>
<td>948</td>
<td>491</td>
</tr>
<tr>
<td>3</td>
<td>661</td>
<td>38</td>
<td>157</td>
</tr>
<tr>
<td>4</td>
<td>90</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>
Treatment

- If no prophylaxis was given, recommended treatment is 5HT$_3$ receptor antagonist.
- If prophylaxis was given and PONV still occurs, treat with an antiemetic from a different pharmacologic class.
- Do not repeat 5HT$_3$ receptor antagonist within 4-6 hours of last dose.
### SAMBA CLINICAL OUTCOMES REGISTRY
### SCOR DATABASE
### PDNV – The Emory Clinic ASC – 2012

<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>( PONV ) Score</th>
<th>( \text{Nausea at Callback} ) (% of patients reached)</th>
<th>( \text{Vomiting at Callback} ) (% of patients reached)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>0</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>20 (2%)</td>
<td>7 (1%)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>58 (3%)</td>
<td>19 (1%)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>45 (7%)</td>
<td>18 (3%)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>10 (11%)</td>
<td>7 (8%)</td>
</tr>
</tbody>
</table>
SAMBA Guidelines

1. Identify patients’ risk for PONV
2. Reduce baseline risk factors for PONV
3. Administer PONV prophylaxis using one to two interventions in adults at moderate risk for PONV
4. Administer prophylactic therapy with combination (>2) interventions/multimodal therapy in patients at high risk for PONV
5. Administer prophylactic antiemetic therapy to children at increased risk for POV; As in adults, use of combination therapy is most effective.

6. Provide antiemetic treatment to patients with PONV who did not receive prophylaxis or in whom prophylaxis failed.

7. Ensure PONV prevention and treatment is implemented in the clinical setting

8. Use general multimodal prevention to facilitate implementation of PONV guidelines
References