Postoperative Nausea and Vomiting: Update on Prevention, Rescue, and Novel Strategies

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• No conflicts of interest to disclose (sadly)

Question 1
52 yo male ½ PPD smoker presents for ORIF of the mandible following an accident at his job site. What is/are the recommended PONV prophylaxis for this patient?

a. Dexamethasone 4 mg IV at the end of the case
b. Ondansetron 4 mg IV at the end of the case
c. No prophylaxis indicated
d. Dexamethasone 4 mg + Ondansetron 4 mg at the beginning of the case
e. Droperidol 0.625 mg IV at the end of the case

Overview
• Understand risk stratification for PONV
• Review Updated Guidelines that address PONV
  • Controversies and Future Directions
• Review therapies for PONV
  • Pharmacologic and non-pharmacologic
  • Prophylaxis therapy
  • Approach to Refractory PONV
• Understand PONV in the setting of postoperative pain control strategies

PONV: Does it matter?
• Incidence of PONV
  • General Incidence: 30%, Range 10-80%
  • Risk Factor Dependent
• Cost(s) of PONV
  • Prolonged PACU stay +/- unanticipated hospital admission
  • Increase overall healthcare costs
  • Poor Cost Effectiveness analysis in available literature
• Patient Satisfaction related to occurrence of PONV
  • Pain and PONV are the top two patient concerns
  • Patients are “willing to pay” for preventing PONV!
Assessing PONV Risk

Updates to PONV Guidelines

- Implemented Grading System advocated for by ASA
  - A: High quality evidence
  - B: Moderate quality evidence
  - C: Low quality evidence
- 1: Strong recommendation
- 2: Weak recommendation

Risk Factors Revisited

PATIENT FACTORS:
- Female (OR 2.57, CI 2.32-2.84)
- Hx of PONV (OR 2.09, 1.90-2.29)
- Nonsmoker (OR 1.82, 1.68-1.98)
- Hx of motion sickness (1.77, 1.55-2.04)
- Age (0.88/decade, 0.84-0.92)
  - <50 increased risk

Risk Factors Revisited

ANESTHESIA FACTORS:
- Volatile Anesthetics (1.82, 1.56-2.13)
- Longer Duration of Anesthesia (1.46/hr, 1.30-1.63)
- Postop Opioid Use (1.47, 1.31-1.65)
- Nitrous Oxide Use (1.45, 1.06-1.98)
PONV and Pediatric Patients

- 2007 Guidelines
  - Surgery >30 minutes
  - Age >3
  - Hx of PONV in patient, parent, or sibling
  - Strabismus surgery
  - ~ 9%, 10%, 30%, 55%, 70%

- 2012 Update: validated at a different institution in patients not undergoing strabismus surgery
  - 0, 1, 2, 3 Risk Factors -- excluding strabismus surgery -- ~ 3.4%, 11.6%, 28.2%, 42.3%

- SAMBA/ASA Guidelines support use of this simplified risk profile for pediatric patients

Question 2

Which of the following patients has the highest risk of PONV?

a. 2 yo boy with maternal history of PONV undergoing strabismus surgery
b. 34 yo M undergoing laparoscopic cholecystectomy with a history of motion sickness
c. 42 yo F undergoing laparoscopic hysterectomy with a history of nausea with all prior surgeries
d. 51 yo F undergoing laparoscopic cholecystectomy with a ½ PPD smoking habit
e. 8 yo M undergoing cholesteatoma resection with no familial issues with anesthesia

Mitigating Risk of PONV

- Recognizing Patient Factors
  - Setting expectations with patient based on RFs

- Reducing Anesthesia Factors (IMPACT Trial, NEJM 2004)
  - 5199 high risk patients, 4123 randomized to 1 of 64 treatment combos
  - Ondansetron 4 mg, Dexamethasone 4 mg, Droperidol 4 mg, Propofol replacing volatile, omission of N2O, remi replacing fentanyl
  - Use of one antiemetic reduces PONV by 26% (RR 26%, CI 23-29%)
  - Use of TIVA reduces PONV risk by 19%
  - Omission of N2O reduces PONV risk by 12%
  - Combination antiemetic therapy reduces incidence of PONV
  - 52% with none given → 37% with 1 → 28% with 2 → 22% with 3

Agents use for PONV Prophylaxis

Ondansetron

- A serotonin 5HT3 receptor antagonist
- “Gold Standard” of PONV prophylaxis
- Recommended dose of 4 mg IV = 8 mg ODT
- Administered at the end of surgery
- NNT 5-6 for prevention of vomiting
- NNT 7 for prevention of nausea
- Risks: of QTc prolongation with dose >16 mg
- Side Effects: NNH 32 for headache, 31 for elevated liver enzymes, 23 for constipation
- FDA pulled 32 mg IV from market due to QTc prolongation
Ondansetron

- Zofran™ developed in 1980’s
- FDA Approved Jan 1991
- Generic approved by FDA in Dec 2006
- Wholesale Cost: $0.10 - $0.76 USD
- At CHCO: $0.17/vial, Pt charge $17.50
- At UCH: $0.34-$2.08/vial, Pt charge $9.60

Dexamethasone and PONV

- Quantitative Systematic Review (2000), 1,976 pts, 17 studies
  - NNT Adults 7.1 (Dose 8-10 mg IV), Peds 3.8 (Dose 0.1 mg/kg IV)
- Dose Ranging Study (Br J Anes 2011), 106 F pts, Gyn surg
  - Prospective, double blind, Saline // Dex 0.05mg/kg // Dex 0.1mg/kg
  - Dose-dependent increase in Quality of Recovery (QOR) score
- Metaanalysis (Br J Anes 2013) also suggests dose-dependent analgesic effect of Dex >0.1 mg/kg
  - Utility in a multimodal analgesic/opioid-sparing approach
- Concern for wound infection risk? Hyperglycemia?
  - Hyperglycemia 6-12 hours postop in all pts; wound infection risk yields mixed picture
  - Consider omitting Dexamethasone in patients with unstable DM

Droperidol

- Potent D2 dopaminergic receptor antagonist
- Droperidol is as effective as ondansetron
- NNT 5 for PONV prevention (0-24 hrs)
- Most effective when administered at the end of surgery
- Black box warning (FDA 2001): QT prolongation and subsequent risk of Torsades de Pointes
  - Only at large doses; evidence v poor/absent for low doses
  - Ondansetron prolongs QTc equally at prophylactic doses
- Lowest doses of 0.625 or 1.25 mg IV are highly effective without a clinically significant risk of CV SE (Eur J Anes 2012)
  - Is it time to remove the BBW?

Scopolamine and PONV

- Anticholinergic transdermal patch
- Onset of action 2-4 hours, effect lasts 24 hours
- Approx as useful as ondansetron, droperidol only when applied at least 2-4 hours preoperatively
- NNT 6 for prevention of PONV
- Side effect profile undesirable
  - Visual disturbance NNH 5.6
  - Dry mouth NNH 13
  - Dizziness NNH 50

Phenergan/promethazine and PONV

- Phenothiazine class
- Dose 12.5-25 mg IV recommended
- Lack of new data, overall paucity of studies
- 1990s/2000s data shows mild antiemetic effect
- No good evidence to support routine use of promethazine for PONV prevention
- Serious adverse consequences of infiltration (necrosis, gangrene)

Dimenhydrinate and PONV

- Antihistamine class
- Recommended dose 1 mg/kg
- Efficacy similar to ondansetron, dexamethasone, and droperidol
- Lack of data for dose-finding, dose response, and side effect profile
- SAMBA/ASA guideline does not make a recommendation on the use of antihistamines for treatment of PONV
**NEW AGENTS**

**Aprepitant/Fosaprepitant & PONV**
- **Emend™ (Merck 2003)**
  - NK-1 receptor antagonist with high affinity and selectivity
  - Blocks action of substance P at neurokinin-1 receptors
  - Substance P also found in high concentrations at chemo trigger zone/vomiting center in the brain
  - IV formulation = fosaprepitant
  - PO formulation = aprepitant, 40 mg PO or 80 mg PO
  - t1/2 = 40 hours
  - CHCO Cost 40 mg PO: $84.71/tablet, $490.21 charge to Pt; IV formulation (fosaprepitant) $253.70/vial
  - UCH Cost 40 mg PO: $83.00/tablet, $350.00 charge to Pt; IV formulation $250.00/vial

**Aprepitant, cont’d**
- 2 RCT achieved similar 0-24 hour reduction in PONV when compared to ondansetron
- RCT in 104 craniotomy patients (A+A 2011) showed aprepitant 40 mg PO + dexamethasone was more effective than ondansetron + dexamethasone at reducing POV only
- Dose-finding study in laparotomy patients undergoing Gyn surgery found 40 mg PO less effective than 80 mg PO
- SAMBA/ASA Conclusions: clinical experience with aprepitant limited, role in routine use is unclear, cost is high compared to other effective therapies, more data needed

**Palonosetron**
- 2nd generation 5HT3 receptor antagonist
  - Unique receptor binding properties
    - An allosteric antagonist, exhibits cooperative receptor binding, causes long-lasting functional changes to receptor
  - T ½ = 40 hours
  - Does NOT affect QTc interval!
  - Studies mostly in oncology/CINV w/ doses 0.25 mg
    - Lower doses (0.075 mg) may be effective for PONV prophylaxis

**Neostigmine and PONV**
- Early metaanalyses suggested that high dose neostigmine (>2.5 mg) and intrathecal neostigmine associated with PONV
- Updated metaanalysis 933 pts (A+A 2005) suggests that neostigmine in large or small doses does not increase PONV significantly
  - Overall vomiting (0-24 hrs postop): RR 0.91, CI 0.70-1.18
  - Overall nausea (0-24 hrs): RR 1.24, CI 0.98-1.59
  - Also not significantly higher in early (0-6 hr), delayed (6-24 hr)
- Current SAMBA/ASA guidelines no longer recommend avoidance of neostigmine in clinically useful doses

**Supplemental Oxygen and PONV**
- Systematic Review of 10 trials, 1729 patients
  - “PONV” = any nausea, vomiting, retching in 0-24 hours
  - 860 pts received 30-40% FIO2, 869 pts received 80% FIO2
  - In patients to received 80% FIO2, relative risk for overall PONV was 0.91, CI 0.77-1.06:
    - Same results for early and delayed PONV
  - SAMBA/ASA guidelines no longer recommend 80% supplemental O2 for reliable reduction of PONV
Peds Anesthesia and PONV

- Intraoperative subhypnotic propofol infusion (~25 mcg/kg/min) reduced PONV in children when added to either dexamethasone or 5HT3 receptor blocker
- NSAID use in Tonsillectomy and Adenoidectomy population reduces emesis (OR 0.49, CI 0.29-0.83)
  - Without increasing the risk of post-tonsillectomy hemorrhage!
- Adequate hydration (30 mL/kg vs. 10 mL/kg) resulted in less PONV in pediatric strabismus repair patients

Ineffective Therapies for PONV

- Music Therapy
- Alcohol swab inhalation
- NGT decompression intraoperatively
- PPI use
- Administering nicotine patch to nonsmokers
  - Actually increases PONV!

Single Agent Prophylaxis - Summary

- "Low Risk" = 10-20% incidence of PONV??
- With introduction of generic ondansetron and safe side effect profile of equally efficacious antiemetics, the conversation changes

Combination Therapy

- Most commonly studied:
  - Ondansetron + 2nd agent (usually dexamethasone or droperidol)
    - Do not exceed 10 mg of dexamethasone
  - Dexamethasone as 2nd agent
  - Conclusion: any combination therapy consisting of either ondansetron or dexamethasone is better than a single agent
- Effects are additive
- Administration of combination therapy is not associated with any increased risk of side effects (QTc prolongation, dystonia, CNS SE)

Recommended Combo Therapy

Non-pharmacologic Therapies - I

- Pericardium 6 ("P6")

  - 2009 BJA Study, 200 pts, female, gyn surg, prospective, observer-blind, RCT
    - 4 groups: 24h acustim pre- and post-induction, sham acustim pre- and post-induction
    - PONV 33% vs. 66% (P<0.001), Rescue therapy 39% vs. 61% (P<0.001)
    - Acustim PONV RR 0.29 (CI 0.16-0.52), Acustim Rescue RR 0.38 (0.21-0.66)

Table 4. Pharmacologic Combination Therapy for Adults and Children

<table>
<thead>
<tr>
<th>Adults</th>
<th>Combination</th>
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<tbody>
<tr>
<td>Droxidone + dexamethasone</td>
<td>(A1)</td>
</tr>
<tr>
<td>5-HT3 receptor antagonist + dexamethasone</td>
<td>(A2)</td>
</tr>
<tr>
<td>5-HT3 receptor antagonist + droperidol</td>
<td>(A1)</td>
</tr>
<tr>
<td>5-HT3 receptor antagonist + dexamethasone + droperidol</td>
<td>(A2)</td>
</tr>
<tr>
<td>Ondansetron + caspiperidone</td>
<td>(A1)</td>
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<tr>
<td>Ondansetron, 0.05 mg/kg + dexamethasone, 0.015 mg/kg</td>
<td>(A1)</td>
</tr>
<tr>
<td>Ondansetron, 0.1 mg/kg + droperidol, 0.015 mg/kg</td>
<td>(A1)</td>
</tr>
<tr>
<td>Tropisetron, 0.1 mg/kg + dexamethasone, 0.5 mg/kg</td>
<td>(A1)</td>
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<table>
<thead>
<tr>
<th>Combinations in children</th>
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<tbody>
<tr>
<td>Ondansetron, 0.05 mg/kg + dexamethasone, 0.015 mg/kg</td>
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</tr>
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<td>Tropisetron, 0.1 mg/kg + dexamethasone, 0.5 mg/kg</td>
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</table>
**Pericardium 6, cont’d**

- 2011 A+A Study, 264 pts, prospective, double blind, placebo-controlled trial of electrostimulation
  - 4 groups: single twitch, double burst stim, train of four, and tetany applied over the P6 pressure point
  - Early PONV, opioid consumption, patient satisfaction all significantly improved with P6 Tetanic stimulation
  - Late PONV not reduced
- Cochrane (2009) metaanalysis, 40 studies, 4858 pts
  - Compared to sham tx, P6 acupoint stim reduced nausea (RR 0.69, CI 0.57-0.83), vomiting (RR 0.70, 0.59-0.83), and need for rescue antiemetics (RR 0.69, 0.57-0.83)
  - Compared to antiemetic medications, no significant reduction or increase in N/V/rescue.

**Nonpharmacologic Therapies - II**

- Ginger
  - 5 trials, 363 pts (AJOG 2006)
  - 1 gram PO given 1 hour prior to induction (compared to placebo) reduced nausea (RR 0.69, CI 0.54-0.89) and vomiting (RR 0.61, CI 0.45-0.84)
- Noni Fruit (Morinda Citrifolia Linn)
  - 100 high risk pts, preliminary, prospective, double-blinded RCT (2010 J Med Assoc Thai)
  - Capsule preparation of boiled dried fruit, 150 mg vs. 300 mg vs. 600 mg vs. placebo
  - Early PONV 80% placebo vs. 48% w/ 600 mg (P<0.04)

**Cost Effectiveness Data**

- A critical consideration especially in today’s healthcare environment
- PONV therapy C/E studies are highly variable, low-powered (lack reliability), and not always aimed at assessing C/E
- Studies conducted prior to availability of generic ondansetron
- New guidelines call for updated C/E data
- Willingness to pay data (WTP)
  - $100 to prevent experiencing PONV
  - Parents willing to pay $80 to prevent PONV in their children
- Patient Satisfaction Data (do we even need data?!?)

**Established PONV in PACU**

- 2001 Systematic Review of 18 trials, 3809 pts
Treating Established PONV

- Rescue meds after prophylaxis (2005 J Clin Anes)
- Original study: RCT, double blind multicenter study of prophylaxis (N=2061) with 4 arms (placebo, droperidol 0.625, droperidol 1.25, ondansetron 4 mg)
- Looked ‘backwards’ at the use of rescue meds in PACU:
  - droperidol 0.625-1.25 mg, ondansetron 4 mg, metoclopramide 10 mg, promethazine 6.25-12.5 mg, dimenhydrinate 25-50 mg
- Outcome = “Complete Response”
  - No Nausea, No emesis, No need for further rescue medication

Ondansetron as prophylaxis

<table>
<thead>
<tr>
<th>Rescue drug</th>
<th>No. of patients receiving rescue</th>
<th>Complete response [n (%)]</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Droperidol 0.625 mg</td>
<td>61</td>
<td>54 (88.5)</td>
<td>1.06 (0.77-1.48)</td>
</tr>
<tr>
<td>Droperidol 1.25 mg</td>
<td>34</td>
<td>30 (88.2)</td>
<td>1.05 (0.77-1.47)</td>
</tr>
<tr>
<td>Ondansetron 4 mg</td>
<td>40</td>
<td>22 (55)</td>
<td>0.41 (0.15-1.05)</td>
</tr>
<tr>
<td>Metoclopramide 10 mg</td>
<td>34</td>
<td>30 (88.2)</td>
<td>1.05 (0.77-1.47)</td>
</tr>
<tr>
<td>Promethazine 6.25-25 mg</td>
<td>36</td>
<td>28 (77.8)</td>
<td>0.21 (0.07-0.63)</td>
</tr>
<tr>
<td>Dimenhydrinate 25-50 mg</td>
<td>20</td>
<td>15 (75)</td>
<td>0.26 (0.08-0.85)</td>
</tr>
</tbody>
</table>

Droperidol as prophylaxis

Rescue Therapy Conclusions

- Choose a different class of medication that used for prophylaxis to treat refractory PONV
  - Probably do not choose metoclopramide
- If >6 hours, consider 2nd dose of 5HT3 antagonist
- Poor studies
- No prospective RCTs (needed)
- ? Inhaled isopropyl alcohol, ? aromatherapy while waiting for rescue medication to take effect
  - Poor studies (low N, poor design, anecdotal only)
  - Minimal downsides, immediate therapy

PONV Conclusions

- Prophylaxis is warranted in all patients if no contraindications
- Two-agent prophylaxis is indicated in patients with a moderate risk (>20%) of PONV
- Recognizing and discussing patient risk is important
- Reducing anesthetic contributions to PONV is effective and important

- Nonpharmacologic techniques are effective therapies to treat PONV
- Refractory PONV can be treated with
  - Second or third agent of different class
  - A second dose of 5HT3 receptor blocker if >6 hours
Questions? Thoughts? Comments?

Go Broncos!