


## 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?

- Dexamethasone 4 mg IV at the end of the case
- Ondansetron 4 mg IV at the end of the case
- No prophylaxis indicated
- Dexamethasone 4 mg + Ondansetron 4 mg at the beginning of the case
- Droperidol 0.625 mg IV at the end of the case



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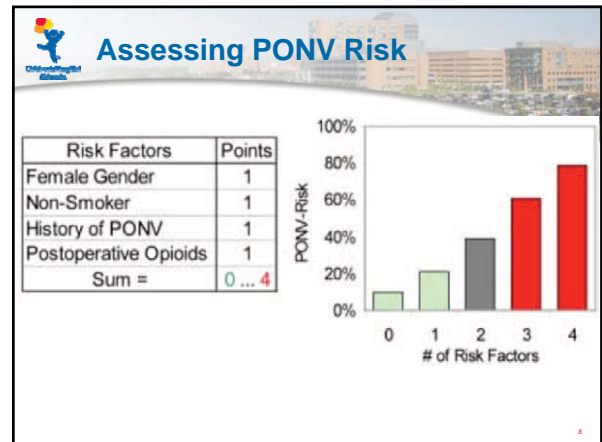
### Overview

- 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!



### 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

### Table 1. Risk Factors for PONV in Adults

Evidence	Risk factors
Positive overall	Female sex (B1) History of PONV or motion sickness (B1) Nonsmoking (B1) Younger age (B1) General versus regional anesthesia (A1) Use of volatile anesthetics and nitrous oxide (A1) Postoperative opioids (A1) Duration of anesthesia (B1) Type of surgery (cholecystectomy, laparoscopic, gynecological) (B1)
Conflicting	ASA physical status (B1) Menstrual cycle (B1) Level of anesthetist's experience (B1) Muscle relaxant antagonists (A2)
Disproven or of limited clinical relevance	BMI (B1) Anxiety (B1) Nasogastric tube (A1) Supplemental oxygen (A1) Perioperative fasting (A2) Migraine (B1)

### 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 POV 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

13




## Question 2

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

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


14



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15



## 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


16



## Agents use for PONV Prophylaxis



17




## Ondansetron

- A serotonin 5HT<sub>3</sub> 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

18

## 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), 1976 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 A 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 A 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



**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
- t<sub>1/2</sub> = 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

26

**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*

27

**Palonosetron**

- 2<sup>nd</sup> generation 5HT<sub>3</sub> receptor antagonist
- Unique receptor binding properties
  - An allosteric antagonist, exhibits cooperative receptor binding, causes long-lasting functional changes to receptor
- T<sub>1/2</sub> = 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

28

**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*

29

**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% FIO<sub>2</sub>, 869 pts received 80% FIO<sub>2</sub>
- In patients to received 80% FIO<sub>2</sub>, 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 O<sub>2</sub> for reliable reduction of PONV*

30

### 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

# of Risk Factors	PONV Risk (%)
0	~10%
1	~20%
2	~40%
3	~60%
4	~80%

- "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 + 2<sup>nd</sup> agent (usually dexamethasone or droperidol)
    - Do not exceed 10 mg of dexamethasone
  - Dexamethasone as 2<sup>nd</sup> 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

**Table 4. Pharmacologic Combination Therapy for Adults and Children**

**Adults**

- Droperidol + dexamethasone<sup>47</sup> (A1)
- 5-HT3 receptor antagonist + dexamethasone<sup>47,120,189,192,327,47,120,189,192,327</sup>(A1)
- 5-HT3 receptor antagonist + droperidol<sup>47,140,188,257</sup> (A1)
- 5-HT3 receptor antagonist + dexamethasone + droperidol (A2)
- Ondansetron + casopitant<sup>118,117,117,118</sup> or TDS<sup>187</sup> (A1)

**Combinations in children**

- Ondansetron, 0.05 mg/kg, + dexamethasone, 0.015 mg/kg<sup>328,329</sup> (A1)
- Ondansetron, 0.1 mg/kg, + droperidol, 0.015 mg/kg<sup>330</sup> (A1)
- Tropisetron, 0.1 mg/kg, + dexamethasone, 0.5 mg/kg<sup>331</sup>(A1)

### 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)



### 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.

### Pericardium 6 Pressure Point

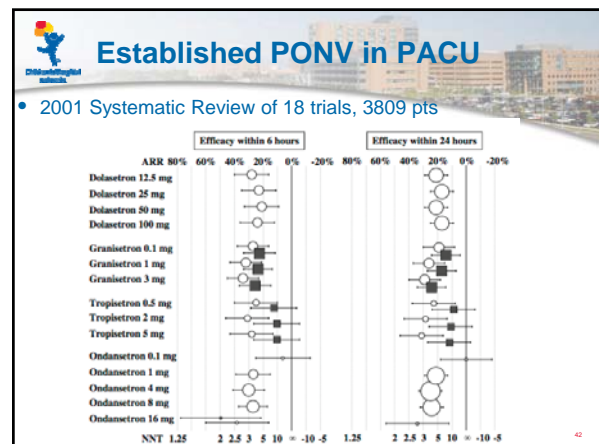
### Nonpharmacologic Therapies - II

- 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!?)

### Refractory PONV



### 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


Rescue drug	No. of patients receiving rescue	Complete response [n (%)]	P	OR (95% CI)
<i>Prophylaxis with ondansetron 4 mg (n = 515)</i>				
Ondansetron 4 mg	28	13 (46)		
Droperidol 0.625-1.25 mg	46	30 (65)	.14	0.40 (0.15-1.0)
Metoclopramide 10 mg	34	22 (65)	.2	0.41 (0.14-1.18)
Promethazine 6.25-25 mg	36	28 (78)	.02	0.21 (0.07-0.63)
Dimenhydrinate 25-50 mg	20	15 (75)	.08	0.26 (0.08-0.95)

### Droperidol as prophylaxis

<i>Prophylaxis with droperidol 0.625-1.25 mg (n = 1028)</i>				
Droperidol 0.625-1.25 mg	61	34 (56)		
Ondansetron 4 mg	36	27 (75)	.08	0.42 (0.17-1.04)
Metoclopramide 10 mg	78	40 (51)	.61	1.20 (0.61-2.34)
Promethazine 6.25-25 mg	60	46 (77)	.02	0.38 (0.18-0.84)
Dimenhydrinate 25-50 mg	32	25 (78)	.04	0.35 (0.13-0.94)

### 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 2<sup>nd</sup> 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!*