

# Research we can all use to Treat PONV *(Part II)*



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# Postoperative Nausea & Vomiting (PONV)

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- Major Problem affecting patients but also pockets
  - Incidence ranges from 16-87%
  - Pain and PONV are the number one reasons that delay patient discharge from the hospital following an outpatient surgical procedure
  - Conventional antiemetic therapies can also lead to delay in discharge
  - Non-traditional antiemetic therapies have shown promise in treatment of PONV in female GYN general anesthesia patients

# SIGNIFICANCE

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- ❑ Major problem facing patients and health care providers today.
- ❑ Average lost revenue to the institution of approximately \$415 per patient (Kenny 1994).
- ❑ Annual cost of \$253,270 - \$1,519,617
- ❑ Represents the lost revenue from performing 96,576 surgeries

# PONV

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- Earlier IPA studies showed efficacy in treating PONV in general population of surgical patients but not clear if treatment would be effective in groups of patients identified as high risk for PONV
  - Female Gender
  - Non-smoker
  - History of Motion Sickness
  - History of Prior PONV
  - General Anesthesia > 60 minutes
  
- Unclear of efficacy of using IPA treatment strategies in patients given prophylactic antiemetics
- Study designed to investigate IPA in patients identified as high risk for PONV (3+ risk factors) who have been administered prophylactic antiemetics (ondansetron)

*Pellegrini JE, Deloge J, Bennett J, Kelly J. Comparison of isopropyl alcohol (IPA) versus promethazine in the treatment of PONV in patients identified as high risk for PONV. (Accepted for Publication AANA J) 2008*

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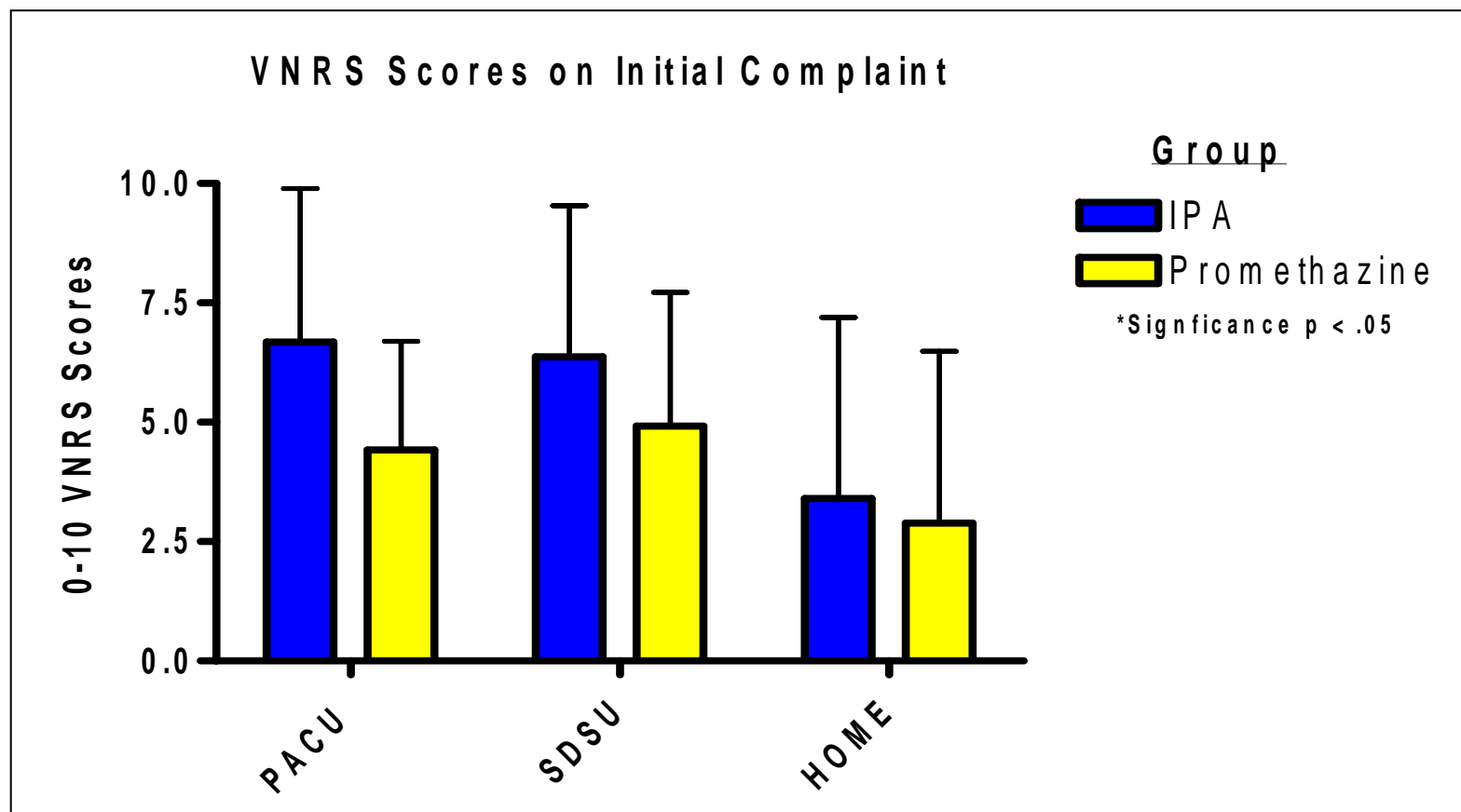
- Study designed using similar design as Cotton et al study (discussed in Part I)
  - Subjects followed for 24 hour postoperatively
  - Clinical site moved to allow for better control
  - Primary measured variables
    - Severity of Nausea
      - 0-10 Verbal Numeric Rating Scales for Nausea
        - Baseline, entry to PACU, SDSU, immediately before treatment and every 5 mins thereafter X 30 min then every 15 min thereafter post-event
    - Demographic variables
      - Risk factors for PONV
        - Gender and motion sickness
        - Covariate risk factors also measured
        - N2O, BMI, hydration status (preoperatively), use of oral gastric tube
    - Incidence of nausea
  - Recorded all medications administered preoperatively, intraoperatively and postoperatively
    - Standardized induction & maintenance protocol
    - Change made to treatment regimen for control group
      - Promethazine administered for primary treatment in control group and secondary treatment in IPA group
      - Promethazine used as rescue treatment in IPA group
  - All subjects administered 4 mg IV ondansetron 15-30 minutes prior to conclusion of surgery
  - Designed to take advantage of multi-modal therapy

	IPA (N= 42)	Promethazine (N= 43)	<i>P Value</i> <i>*Sig p&lt;.05</i>
Age (years) ( <i>Mean ±SD</i> )	33.98 +/- 10.9	37.09 +/- 11.0	.052
Weight (kg) ( <i>Mean ±SD</i> ) BMI median kg/m <sup>2</sup> ( <i>range</i> )	75.43 +/- 17.4 27 (22-34)	74.84 +/- 13.3 27 (21-33)	.939 .947
Total Hours NPO Before Surgical Procedure	11.9 ± 2.2	12.2 +/- 2.5	.688
<b>Gender</b> (N)			
Female	30	33	.763
Male	12	10	
Surgical time (minutes) ( <i>Mean ±SD</i> )	50.57 +/- 34.32	57.63 +/- 44.3	.416
Anesthesia time (minutes) ( <i>Mean ±SD</i> )	90.45 ± 39.5	101.1 ± 48.7	.272
PONV risk factors (N)			.676
3 risk factors	24	26	
4 risk factors	12	9	
5 risk factors	6	8	
Time from PACU admission to PONV event (minutes) ( <i>Mean ±SD</i> )	90.9 ± 101.8	78.8 ± 76.7	.664
<b>History of motion sickness</b> (N)			.723
Yes	26	25	
No	16	18	
Primary Volatile Agent Used (N)			.326
Desflurane	18	25	
Sevoflurane	22	16	
Isoflurane	2	2	
Opioids Morphine Eq ( <i>Mean±SD</i> )			.375
Perioperative	24.05 ± 16.4	21.5 ± 9.1	
PACU	8.8 ± 5.7	9.3 ± 5.6	
SDSU	4.4 ± 2.5	4.1 ± 1.9	.736
<b>N2O Use</b> (N)			.049*
Yes	25	16	
No	17	26	
<b>Oral Gastric Tube Use</b>			.668
Yes	16	19	
No	26	24	

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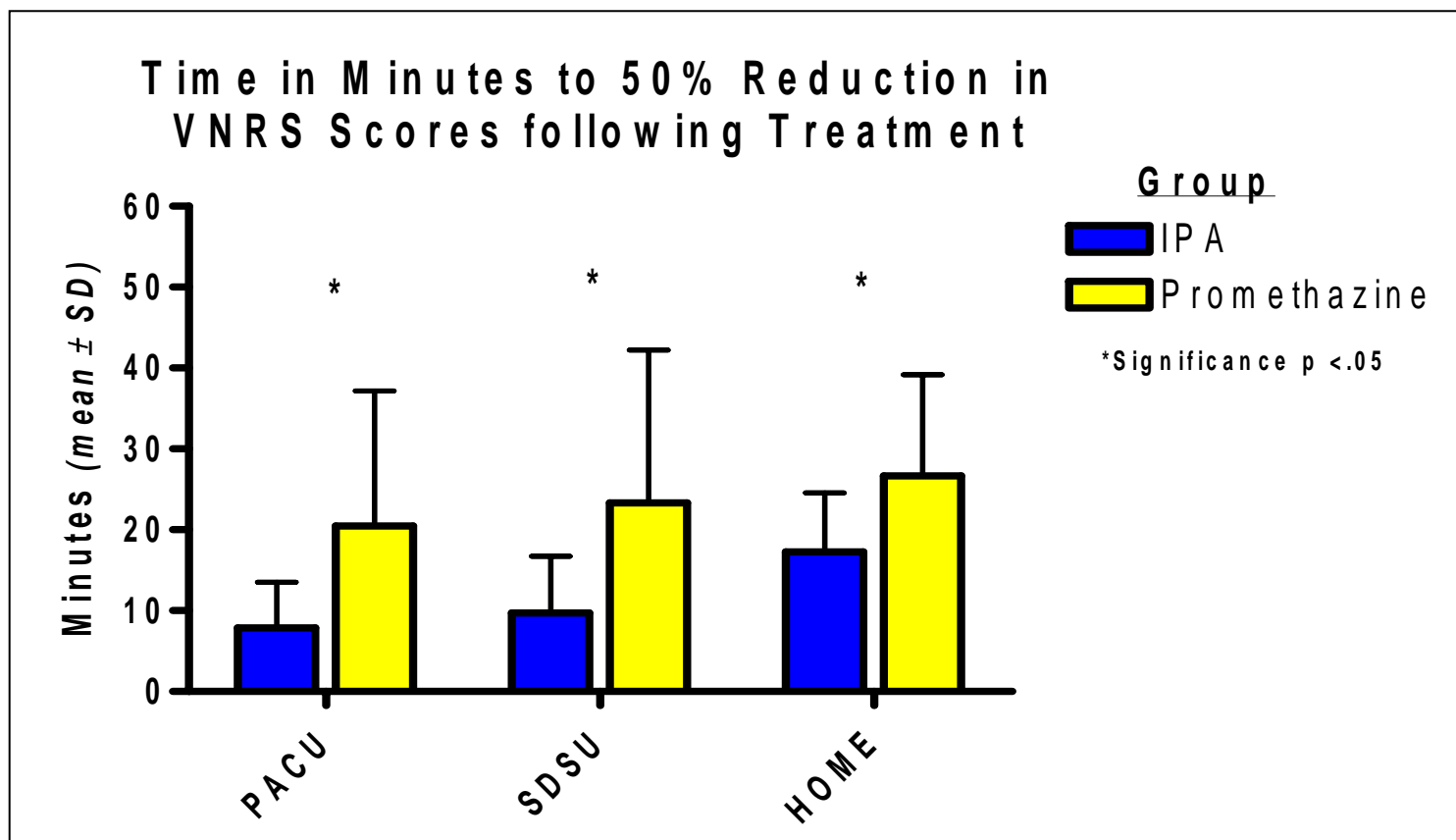
	IPA (N= 42)	Promethazine (N=43)	P Value <i>*Sig p&lt;.05</i>
<b>Nausea Events</b>			
PACU N (%)	7 (17%)	10 (23%)	.448
SDSU N (%)	17 (41%)	12 (28%)	.088
HOME N (%)	19 (47%)	10 (23%)	.019*
<i>Overall Incidence of Nausea</i>	<b>76%</b>	<b>61%</b>	<b>.119</b>
<b>Emetic Events</b>			
PACU N (%)	0	0	1.0
SDSU N (%)	3 (7%)	2 (5%)	.756
Home N (%)	5 (12%)	5 (12%)	.969
<b>Promethazine Requirements <i>median (range)</i></b>			
PACU	0	12.5 (0-25)	.002*
SDSU	12.5 (0-25)	25 (0-50)	.033*
HOME	12.5 (0-25)	12.5 (0-25)	.214
<i>IPA Group Promethazine Use</i>			
SDSU N (%)	<b>4 (23%)</b>		
Home N (%)	<b>3 (16%)</b>		
	<i>(% IPA failures)</i>		

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## □ More Results

- Both groups reported satisfaction with nausea treatments
- Side effects
  - No subject required treatment for any side effects
    - No side effects reported in those subjects administered IPA only
    - 72% of subjects administered promethazine reported sedation
    - 45% of subjects administered promethazine reported dry mouth

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## □ Discussion

- Overall relative risk of PONV (based on risk factors) approximately 60-70%
  - Ondansetron prophylaxis reduced PONV incidence
    - 20-25% in PACU & SDSU (*limited pharmacodynamics*)
- No untoward effects from IPA/Ondansetron
- Difficulty with SDSU 5 min measurements of VNRS
- Validated results of Winston & Cotton studies
- IPA viable option in high risk patients
- IPA prophylaxis
  - One study has analyzed IPA prophylaxis and showed efficacy when compared to control (*Teran & Hawkins 2008*)
    - IPA administered following extubation
    - Current study analyzing effect of IPA prophylaxis administered immediately before induction in GYN population undergoing procedures < 30 minutes

# PONV Prophylaxis

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- Many practitioners administer an antiemetic in the preoperative or intraoperative period in an effort to prevent PONV
  - Most common regimens employed include:
    - Ondansetron 4 mg IV administered 15-30 minutes before the conclusion of surgery
    - Droperidol 0.625-1.25 mg IV administered 30 minutes before surgery conclusion
    - Combination of antiemetics and steroids
      - Ondansetron with droperidol/ondansetron with metoclopramide etc.
      - Often secondary antiemetic substituted with dexamethasone
    - Combination shown to be more effective than when single agent used
      - Studies show effectiveness in preventing PONV ranges between 20-80%
        - Dependant on risk factors present

# PONV Prophylaxis

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- ❑ Risk Factors for PONV
- ❑ Based on multiple studies have identified a multitude of factors both intrinsic and extrinsic
- ❑ Most commonly used factors to identify patients as high risk for PONV
  - Previous history of PONV
  - History of motion sickness
  - Receipt of general anesthesia for > 60 minutes
  - Female Gender
  - Non-smoking status
- ❑ Secondary factors
  - GYN/intraabdominal laparoscopic surgical procedures
  - Use of Nitrous Oxide
    - ❑ Controversial – studies indicate that if N<sub>2</sub>O limited to 50% or less no increased risk is present

# PONV Prophylaxis in High Risk Groups

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- Majority of procedures are outpatient
  - Typically PONV prophylaxis performed in immediate preoperative or intraoperative period
    - Expensive
    - Side effects
    - Multimodal approach more efficacious than unimodal
      - Combination can increase side effect profile
        - Most commonly unimodal therapy initiated in practice
  - Problem in providing PONV prophylaxis to “high risk” patients
    - Only see patients on day of surgery
      - Cannot achieve adequate serological levels of antiemetic medication prior to receiving surgical and anesthesia stimulus that could invoke the PONV response
    - Multi-modal antiemetic therapy often results in sedation, somnolence, hypotension etc. which can delay discharge to home
      - Rationale used by many practitioners to use uni-modal therapy in the outpatient surgical setting
  - Solution- Need identified to find “over the counter medication” that we could instruct high-risk patients to self-administer before they present for surgery
    - Meclizine viable candidate
      - H-1 antagonist
      - Inexpensive
      - Low side effect profile
        - Studies indicate safety when co-administered with ondansetron

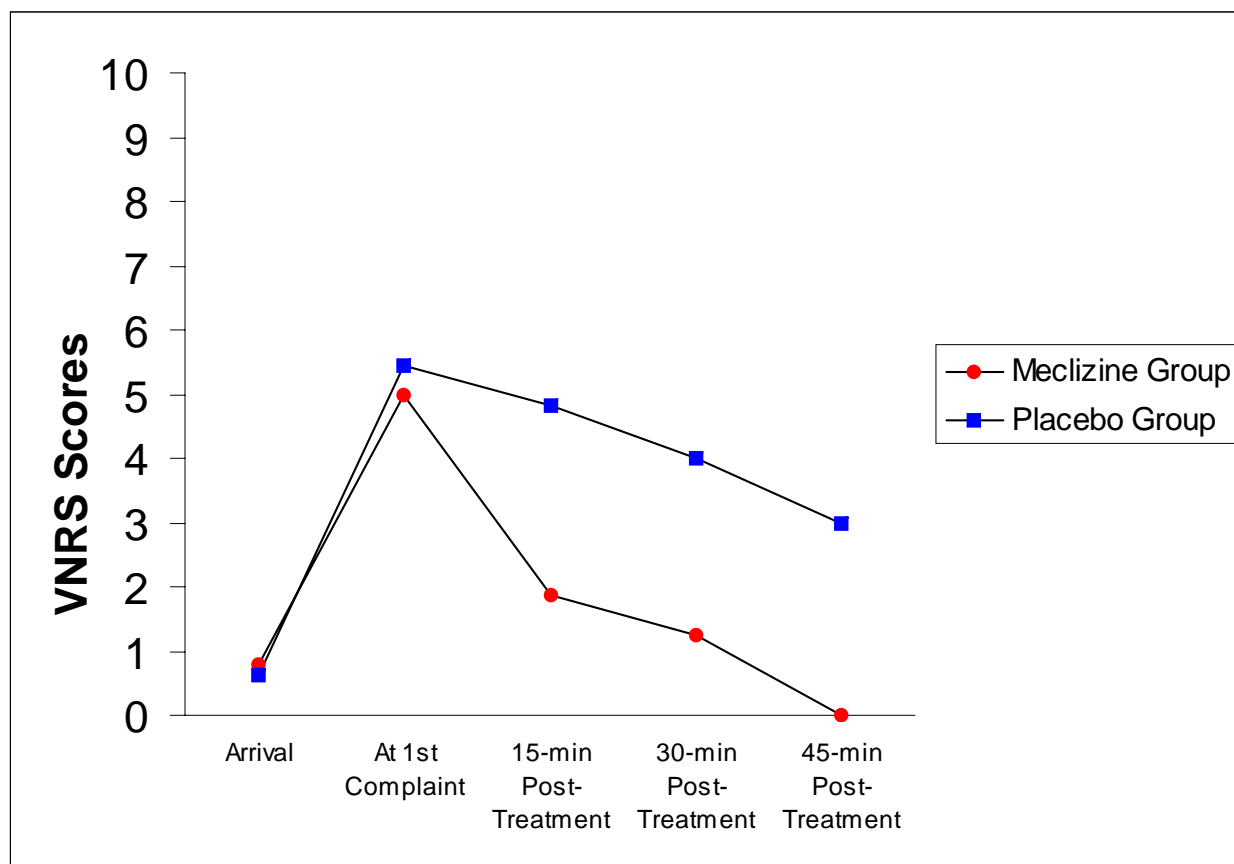
*Forrester CM, Benfield DA, Matern CE, Kelly JA, Pellegrini JE. Meclizine in combination with ondansetron for prevention of PONV in a high risk population. AANA J 2007; 75(1): 27-33.*

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- Double-blind placebo controlled trial on 77 subjects identified as high risk for PONV
  - Administered 50 mg meclizine or placebo with sip of H2O approximately 30 minutes prior to induction of GETA
  - Standardized induction & anesthesia maintenance
    - All subjects administered 4 mg IV ondansetron 30 minutes prior to extubation
- Measured variables
  - Demographic Variables
    - Age, Ht, Wt, Risk Factors, Preoperative & Postoperative fluid deficit, BMI, Surgical & Anesthesia times
  - Analgesic & anti-emetic requirements
  - 0-10 Verbal Numeric Rating Scale for Nausea
  - Incidence of Nausea & Emesis
  - Time interval to nausea events
    - PACU
    - SDSU
    - Ward (*small sample admitted overnight*)
    - Home

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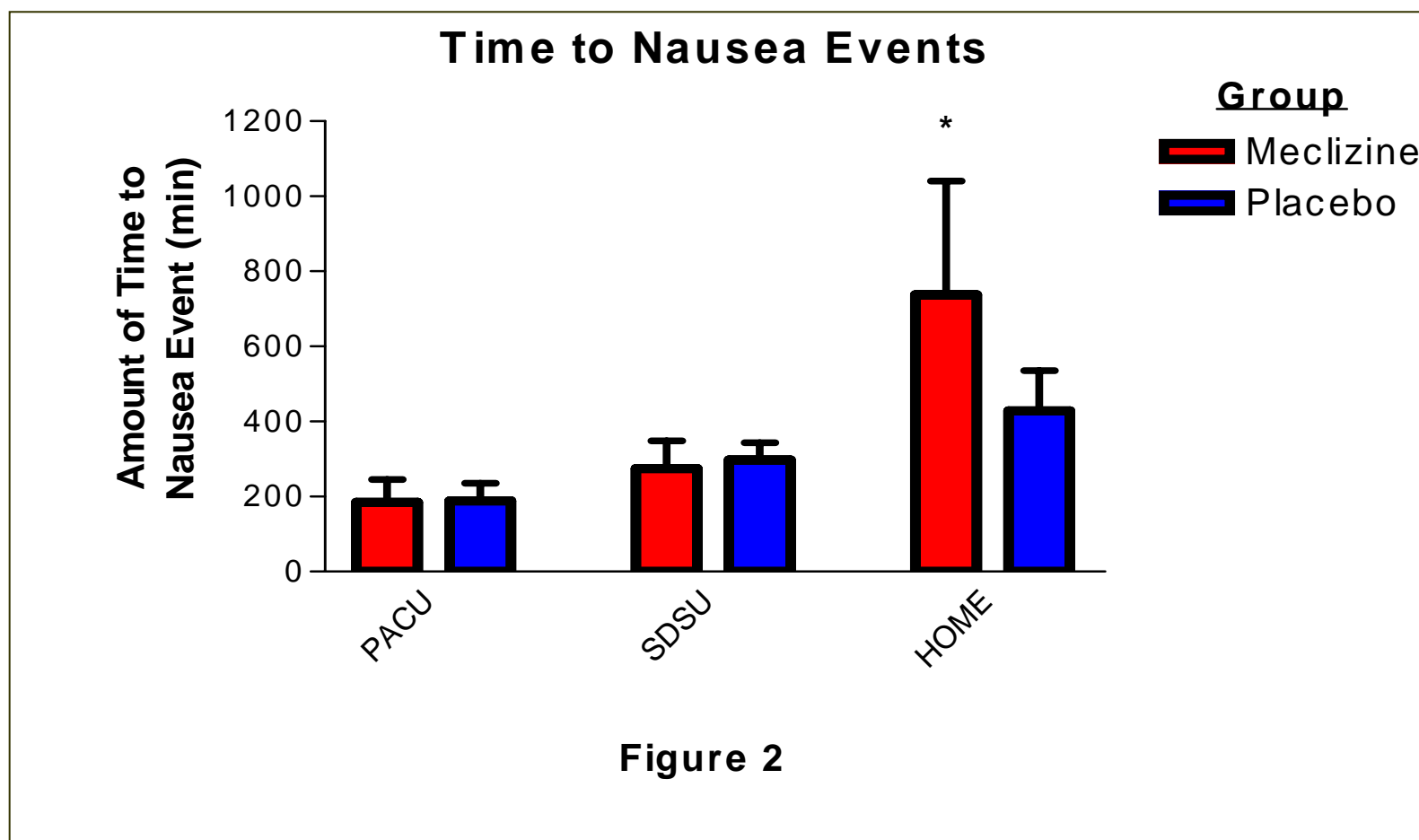
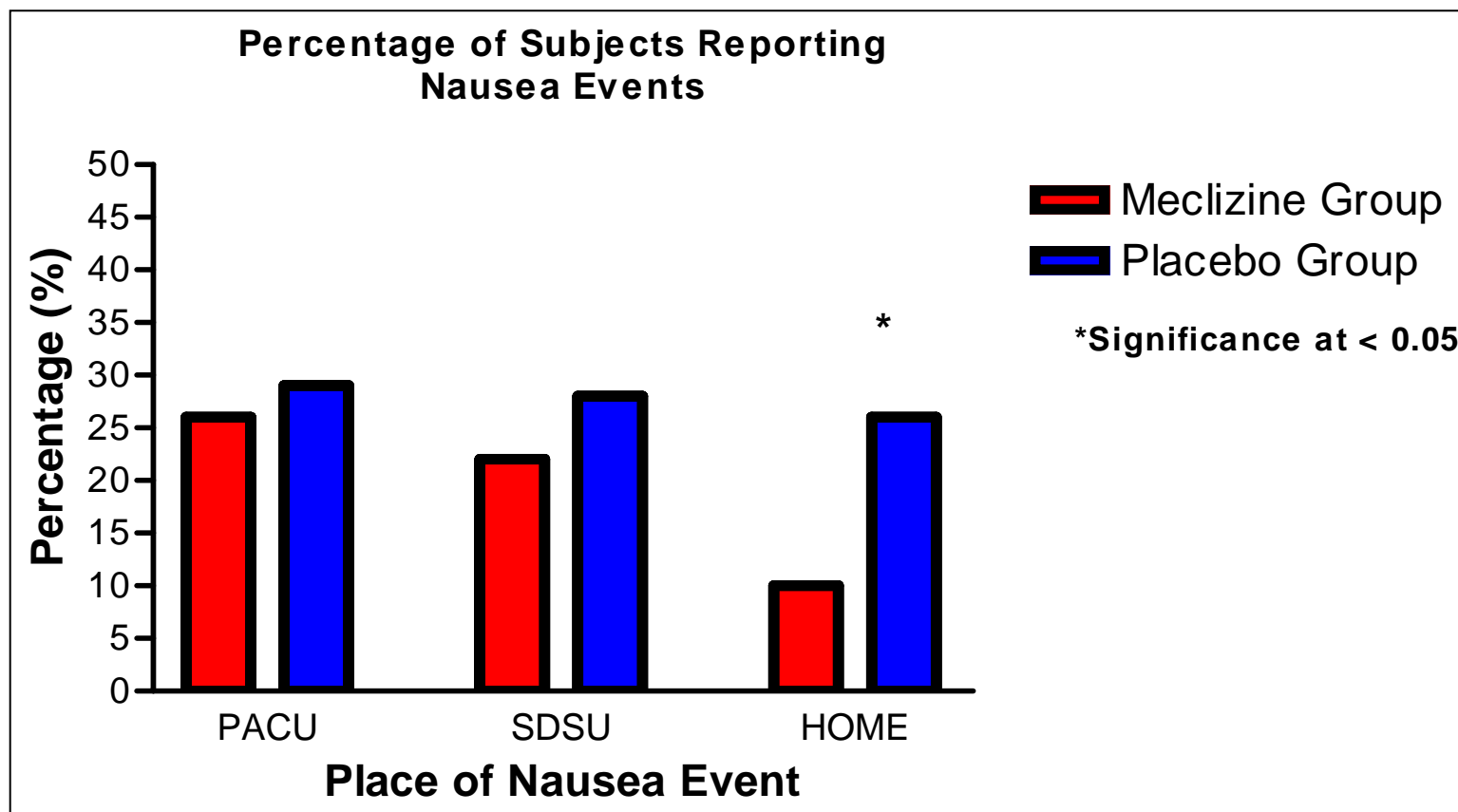


Figure 2

*Forrester CM, Benfield DA, Matern CE, Kelly JA, Pellegrini JE. Meclizine in combination with ondansetron for prevention of PONV in a high risk population. AANA J 2007; 75(1): 27-33.*

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□ Results

- No differences in demographic variables
- No differences in analgesic or anti-emetic requirements in hospital
- No differences in emetic occurrences
- No side effects noted from meclizine
  - Side effect (headache) noted in 16% of meclizine group and 20% of placebo group
    - Attributed to ondansetron administration
- No differences in overall incidence of nausea in PACU & SDSU but significant difference noted following discharge to home
  - Indicating possible delay in efficacy for meclizine
- Identified need for future study analyzing effect of administering meclizine using bi-phasic modality to ensure adequate serum levels are present in PACU & SDSU
  - The night before and the day of surgery

## PONV Prophylaxis in High Risk Groups

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- ❑ Multimodal antiemetic therapy more effective than unimodal therapy
- ❑ Earlier study indicated combination of meclizine and ondansetron administered the day of surgery effective in only preventing PONV following discharge to home
- ❑ Hypothesized that administration of 50 mg meclizine the night before & in the immediate preoperative period would be more effective in preventing in-hospital PONV

*Bopp EJ, Estrada JL, Kilday JM, Spradling JC, Daniel C, Pellegrini JE.  
Meclizine for prevention of PONV in a high risk population. (Submitted  
for publication AANA J. 2008)*

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- ❑ Double-blind placebo controlled trial on 70 subjects identified as high risk for PONV
  - Identified as high risk for PONV during preoperative interview (*2-3 days before surgery*)
  - Informed consent obtained at interview & issued pharmacy prepared “bubble packs” that contained either meclizine (50 mg) or placebo
    - ❑ Instructed to take contents of “bubble pack” with sip of H<sub>2</sub>O the night before surgery
      - Pregnancy precautions
    - ❑ Administered second dose of meclizine (50 mg) or placebo the morning of surgery with sip of H<sub>2</sub>O approximately 30 minutes prior to induction
  - Standardized induction & anesthesia maintenance
    - ❑ All subjects administered 4 mg IV ondansetron 30 minutes prior to extubation
- ❑ Measured variables
  - Demographic Variables
    - ❑ Age, Ht, Wt, Risk Factors, Preoperative & Postoperative fluid deficit, BMI, Surgical & Anesthesia times
  - Analgesic & anti-emetic requirements
  - 0-10 Verbal Numeric Rating Scale for Nausea
  - Incidence of Nausea & Emesis
  - Time interval to nausea events
    - ❑ PACU
    - ❑ SDSU
    - ❑ Ward (*small sample admitted overnight*)
    - ❑ Home
  - Satisfaction scores for nausea control
  - Stanford Sleepiness Scale
    - ❑ Baseline, Preop, PACU, SDSU & 24 Hrs postop

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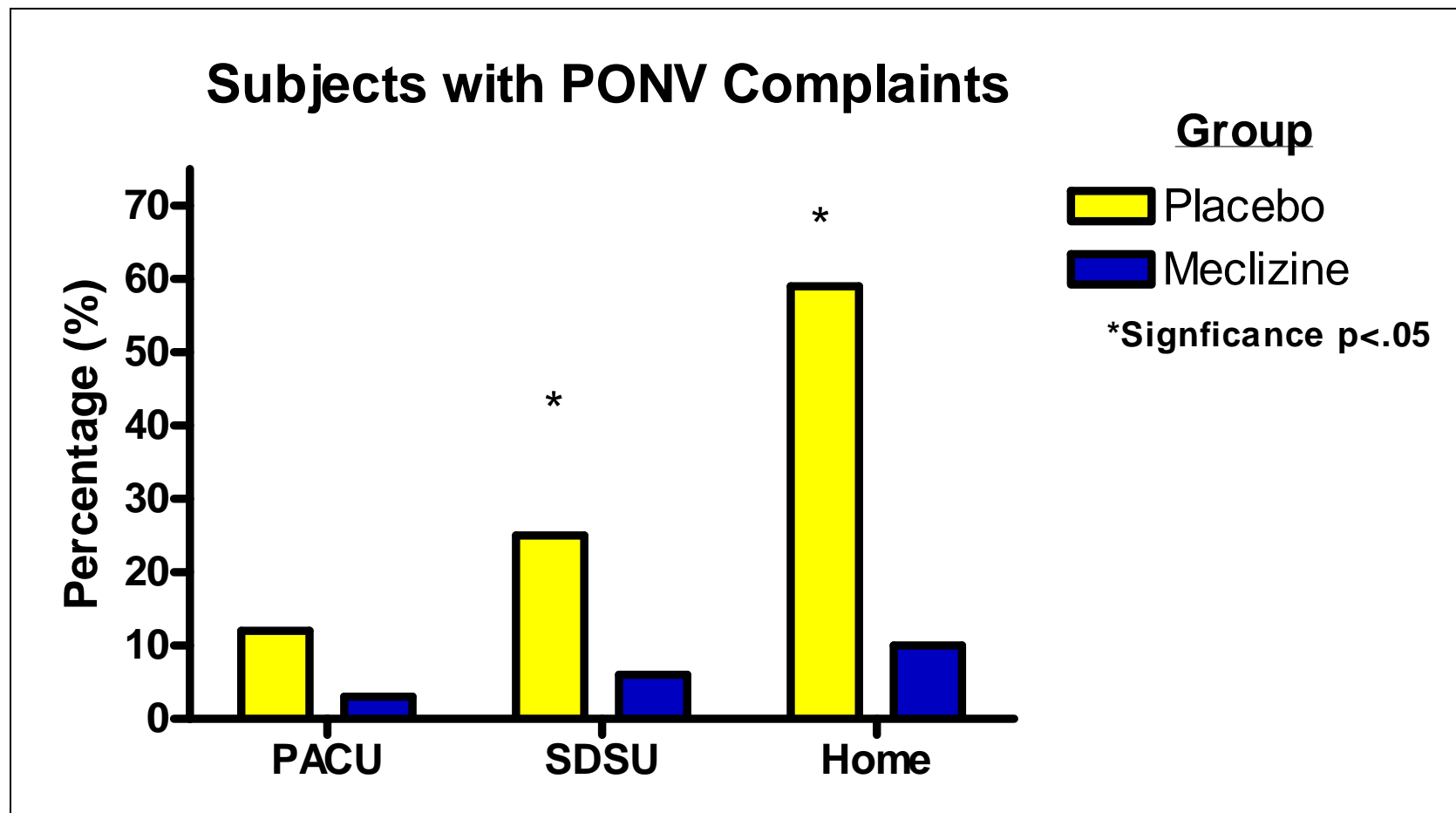
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□ Results

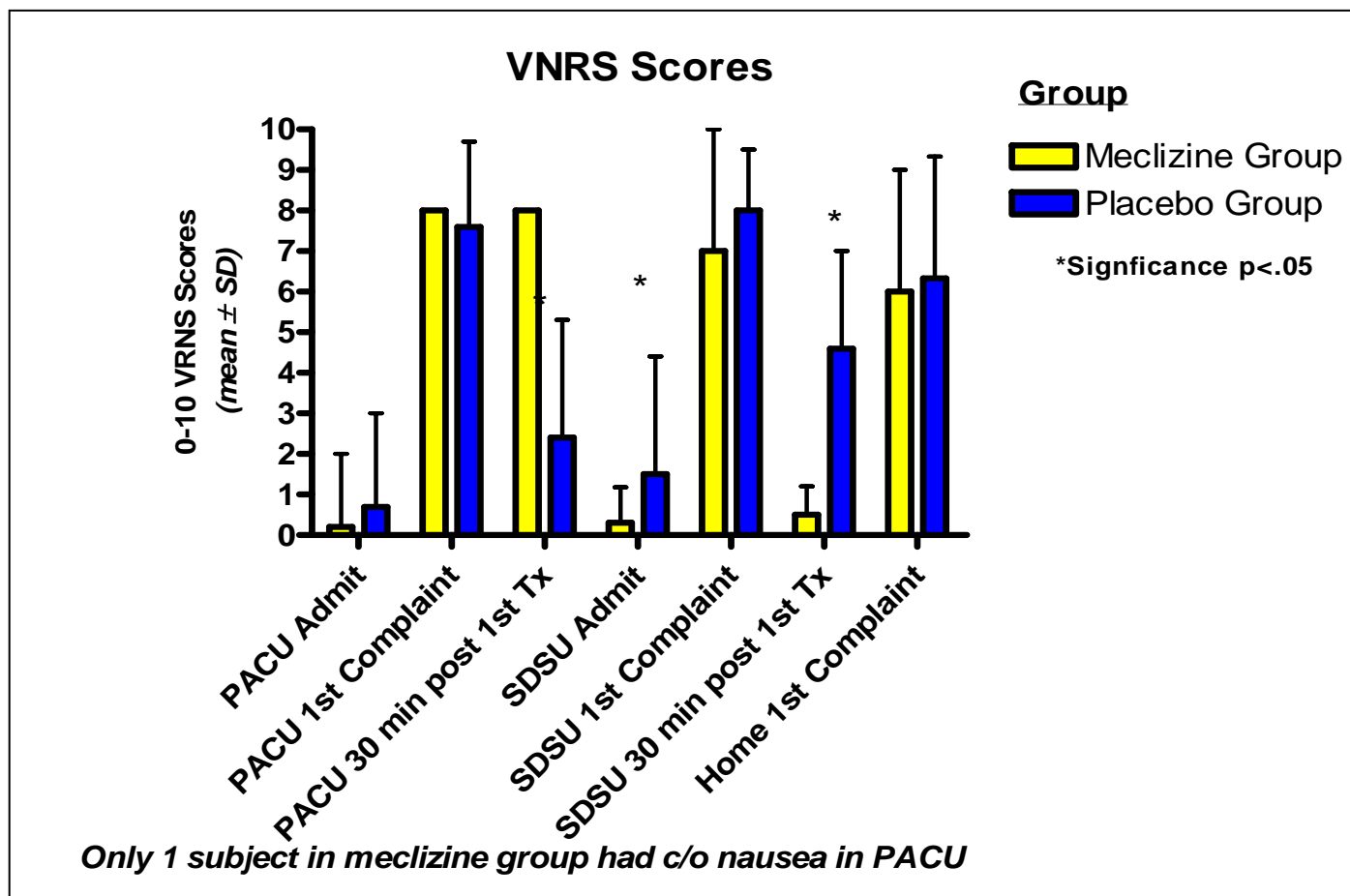
- Predominantly only 3 risk factors identified for population
- Satisfaction scores
  - 85% of meclizine group reported “complete satisfaction with nausea control” as compared to 54% of the placebo group (p=.004)
- No differences in:
  - Demographic variables
  - Surgical & Anesthesia times
  - Anesthetic & Analgesic regimens
  - Sleepiness Scales
    - No differences in SS between groups
  - In patient ward admission requirements
    - 11 subjects for living on small ship
    - 2 subjects for increased analgesic requirements
    - 1 subject because no “ride home” available
  - Sub analysis of Ward admission data performed and showed similar postoperative trends as those reported in home and SDSU settings

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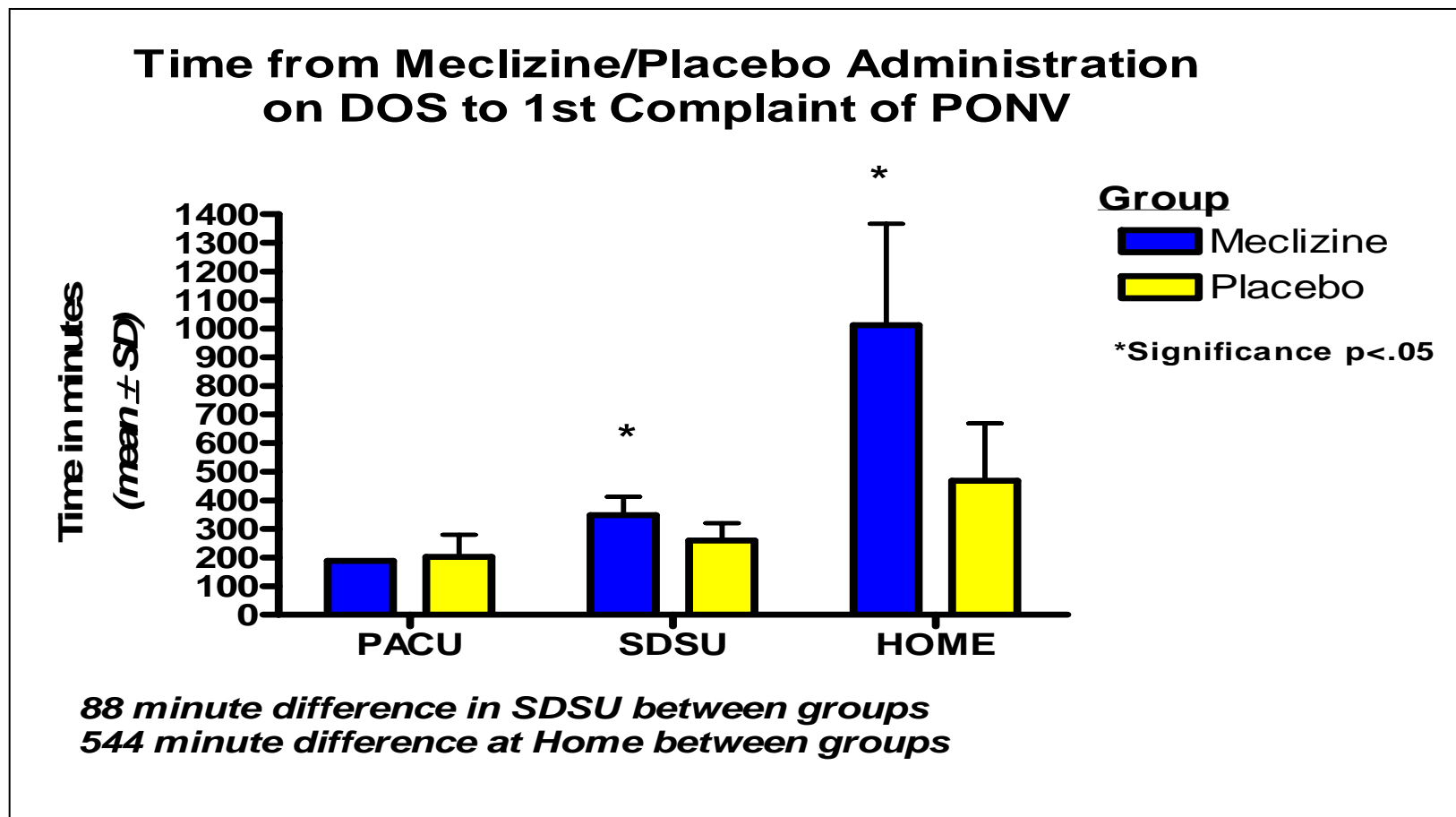
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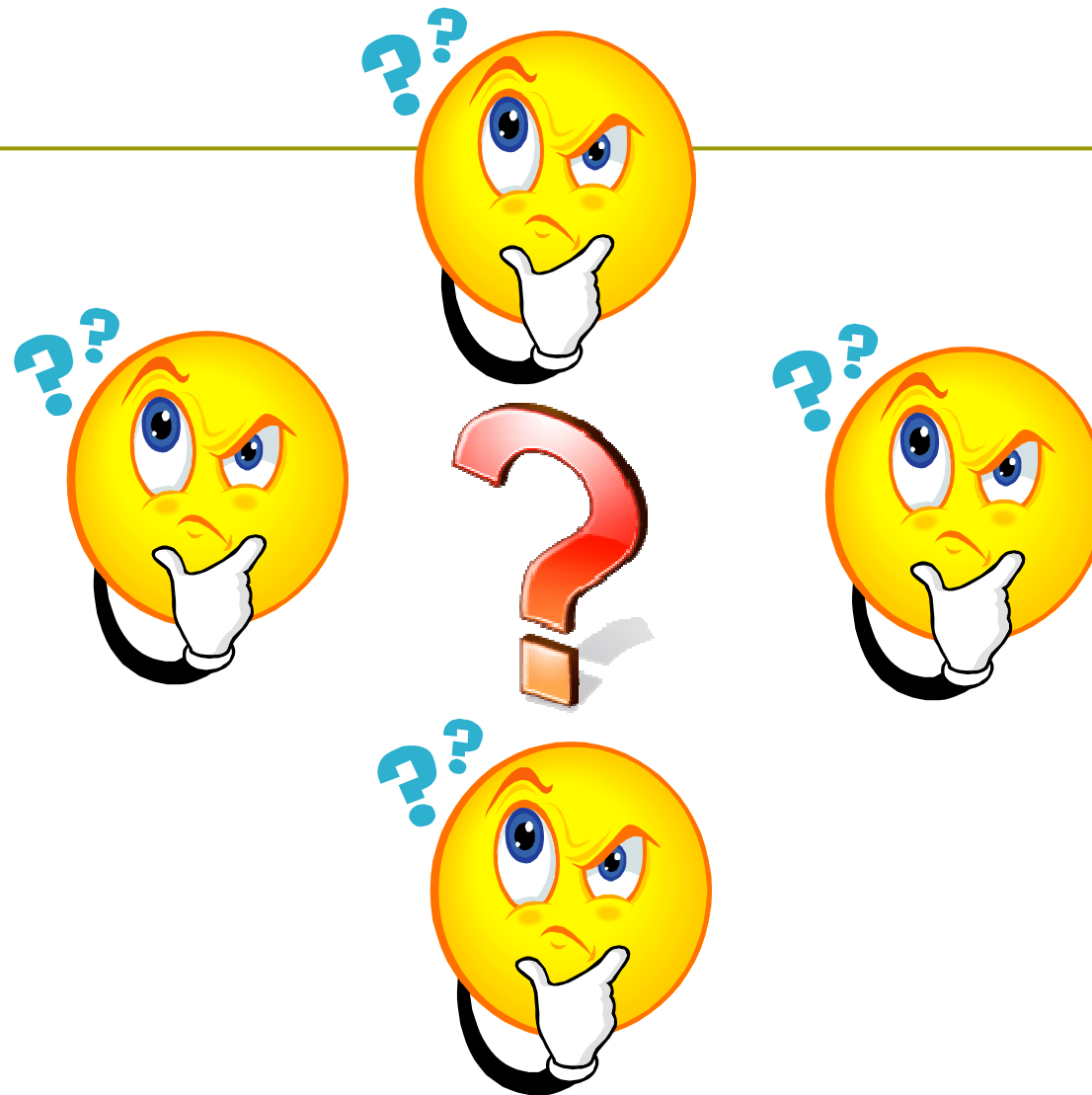
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- ❑ A total of 88 subjects enrolled but 9 subjects excluded from analysis due to failure to adhere to study protocol
  - Failed to take prescribed medication “bubble pack” the night before surgery
- ❑ Showed effectiveness of self-administration of meclizine before surgery
- ❑ No increase in side effects noted from combination of meclizine and ondansetron
- ❑ Combination resulted in significant higher satisfaction scores
- ❑ Pregnancy tests - concern

# Discussion

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- ❑ IPA and ondansetron shown as viable options for treatment of PONV in groups of high risk patients
- ❑ Meclizine best administered using bi-phasic modality rather than DOS
- ❑ No increase in side effect profiles for any treatment regimen
- ❑ All techniques described were found to be
  - Simple
  - Effective
  - Safe
  - Very inexpensive



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