Critical Review Form
Therapy

Does End Tidal CO2 Monitoring During Emergency Department Procedural Sedation and Analgesia With Propofol Decrease the Incidence of Hypoxic Events? A Randomized, Controlled Trial, *Ann Emerg Med* 2010; 55:258-264

Objectives: **"To determine whether physicians use of real-time capnography is associated with a 15% decrease in the incidence of hypoxia compared with standard monitoring alone during emergency department (ED) sedation with propofol". (p. 259)**

Methods: **Prospective randomized controlled trial at Albert Einstein Medical Center (Philadelphia) from November 2006 to February 2008 enrolling consecutive patients > 18 years old selected for propofol sedation Exclusion criteria included severe COPD, chronic oxygen requirements, hemodynamic instability, respiratory distress, pregnancy, inability to provided informed consent, allergy to morphine, fentanyl or propofol, or judgment of attending physician that procedural sedation could compromise patient safety.**

Patients were randomly assigned to the study (standard monitoring and capnography) or control group (standard monitoring and blinded capnography). Exhaled CO_2 was measured using a Capnostream 20™ via nasal-oral CO_2 cannula which simultaneously displays oximetry, CO_2 waveform and $ETCO_2$ value.

All patients received 3L/min oxygen via nasal cannula. No fewer than 30-minutes pre-procedure they also received 0.5 µg/kg fentanyl or 0.05 mg/kg of morphine. Sedation was initiated using 1 mg/kg propofol then 0.5 mg/kg boluses until desired level of sedation (using ideal body weight).

All data was collected by trained research assistants who had no role in the patient's care using a standardized data collection instrument. Level of alertness was measured using the modified Ramsey scale. Before the study, nurses and physicians received training to identify respiratory depression via capnography. Research assistants also noted the time and nature of any interventions for respiratory depression or hypoxia, as well as any sedation-related adverse events including hypotension, bradycardia, arrhythmia, vomiting, prolonged ED stay, or admission.

Hypoxia was defined as oximetry ≤ 93%. Respiratory depression was defined a priori as $ETCO_2$ ≥ 50 mm Hg, absolute ↑ or ↓ from baseline $ETCO_2$ ≥ 10%, or loss of waveform for >15 seconds. If > 35% of data was lost then the patient was not included in the analysis. To identify a 15% decrease in hypoxia from baseline 20% to 5%, 72 patients were needed in both arms with 80% power and one-sided ∞= 0.05.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes. "Patients were randomly assigned to the study group (standard monitoring and capnography) or control group (standard monitoring and blinded capnography) by research associates using a computer-generated randomization list". (p. 259)
2.	Was randomization concealed (blinded)?	Yes. "Research associates and treating physicians were blinded to the randomization choice until after enrollment". (p. 259)
3.	Were patients analyzed in the groups to which they were randomized?	There is no clear statement of intention-to-treat but the CONSORT diagram (Fig 2, p. 261) demonstrates an ITT analysis.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	"Patient characteristics were similar between the two groups (Table 1)". (p. 261) including initial and total propofol dose, Ramsey score, and length of sedation. However, the blinded capnography group appears older (median 31 years vs. 37 years) and heavier (81 kg vs. 75 kg). Furthermore, the investigators offer no information on other prognostic variables like co-morbid illness burden, illness severity, or % with OSA.
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	

1.	Were patients aware of group allocation?	Not clearly stated but presumably yes. Even if they were not blinded, unless they were informed before and after the procedure (see 95% CI above) patients likely would not remember what happened during PSA.
2.	How precise was the estimate of the treatment effect?	See 95% CI above.
2.	Were clinicians aware of group allocation?	No. See I-A-2 above. Clinicians did have access to $ETCO_2$ after randomization and could have deduced group allocation at that point.
3.	Were outcome assessors aware of group allocation?	No. " Before study blinding was broken, three investigators evaluated each graph to code the presence or absence of hypoxia and respiratory depression". (p. 260).
4.	Was follow-up complete?	No loss to follow-up is reported in Fig 2, although 18 subjects were excluded with > 35% missing data.
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect? **Wash U JC Table** Hypoxia → 17(25) 27(42) 17%(13-33) **6 (3-91)** No Hypoxia → 22(32) 10(16) 16%(2-36)	• 210 subjects were screened and 132 patients analyzed (68 capnography, 64 blinded capnography). • 44 subjects (33%, 95% CI 25% - 41%) had a hypoxic event. • RD was significantly more common in the blinded capnography group and capnography significantly reduced the number of hypoxic events with NNT = 6 (see Table at left). • Capnometry (respiratory depression) was 100% sensitive and 64% specific in predicting hypoxia. • In patients with hypoxia the median time from onset of respiratory depression to hypoxia was 60 seconds (range 5 to 240 seconds). • A loss of waveform was most likely to lead to hypoxia and the majority of patients who developed respiratory depression had a Δ $ETCO_2$ > 10% from baseline - most below the baseline. • Physicians informed of capnography results were non-significantly more likely to intervene to improve respiratory status: 24/68 (35%) of capnography vs. 14/64 (22%) of blinded capnography for difference 13% (95% CI – 2% to 27%).

Blinded Capnography (%)	Capnography (%)	ASR (95% CI)	NNT (95% CI)
Hypoxia → 17(25)	27(42)	17%(13-33)	**6 (3-91)**
No Hypoxia → 22(32)	10(16)	16%(2-36)	

III.	How can I apply the results to patient care (answer the questions posed below)?	
1.	Were the study patients similar to my patient?	Uncertain since the investigators do not provide sufficient demographic data to judge (co-morbid illness, illness severity, OSA %, etc). Urban academic ED so patients and PSA practices probably very similar to Wash Univ., but difficult to judge objectively with scant demographic data provided.
2.	Were all clinically important outcomes considered?	No patient-important outcomes are reported. Future studies will need to assess the short and long-term sequale of PSA-associated hypoxic events like ED length of stay, preventable admissions, and unanticipated death (Green 2010).
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. Since 36% of abnormal $ETCO_2$ readings were "noise" (no respiratory events) and since the Capnostream 20™ retails at $4950 one would have to conduct a cost-benefit analysis. ▪ What is the value of detecting a respiratory event up to 4-minutes earlier? ▪ What is the patient-important outcome of a 20-second episode of hypoxia? ▪ How much would a lawsuit cost if a preventable PSA-related brain-injury or mortality occurred? Nonetheless, lacking the benefit of a formal cost analysis, $ETCO_2$ monitoring is standard practice in the operating room. Why should EM settle for a lesser standard pending definitive evidence?

Limitations

1) **Incomplete description of patient population including co-morbid illness burden, acute illness severity, proportion with obstructive sleep apnea, ED length of stay, hospital LOS, and patient satisfaction with sedation.**

2) **Lack of any cost-benefit analysis or discussion.**

3) **No adjustment for baseline prognostic inequities between groups.**

Bottom Line

One-in-three patients at an urban academic ED undergoing propofol PSA experience a hypoxic event (oxygen saturation ≤ 93%) and capnography significantly predicts the development of hypoxia with NNT 6 and up to 4-minutes advanced notice compared with pulse oximetry or clinical observation alone. Future research will need to explore the patient-important clinical impact of transient PSA-associated hypoxia and assess the cost-benefit of capnography in the ED setting.