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A Randomized Controlled Trial of Capnography During Sedation in a Pediatric Emergency Setting

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Abstract

Objective—Data suggest that capnography is a more sensitive measure of ventilation than standard modalities and detects respiratory depression before hypoxemia occurs. We sought to determine if adding capnography to standard monitoring during sedation of children increased the frequency of interventions for hypoventilation, and whether these interventions would decrease the frequency of oxygen desaturations.

Methods—We enrolled 154 children receiving procedural sedation in a pediatric emergency department. All subjects received standard monitoring and capnography, but were randomized to whether staff could view the capnography monitor (intervention) or were blinded to it (controls). Primary outcome were the rate of interventions provided by staff for hypoventilation and the rate of oxygen desaturation <95%.

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Results—Seventy-seven children were randomized to each group. Forty-five percent had at least one episode of hypoventilation. The rate of hypoventilation per minute was significantly higher among controls (7.1% vs. 1.0%, $p=.008$). There were significantly fewer interventions in the intervention group than in the control group (OR 0.25; 95% CI 0.13, 0.50). Interventions were more likely to occur contemporaneously with hypoventilation in the intervention group (2.26, 95% CI 1.34, 3.81). Interventions not in time with hypoventilation were associated with higher odds of oxygen desaturation $<95\%$ (OR 5.31; 95% CI 2.76, 10.22).

Conclusion—Hypoventilation is common during sedation of pediatric emergency department patients. This can be difficult to detect by current monitoring methods other than capnography. Providers with access to capnography provided fewer but more timely interventions for hypoventilation. This led to fewer episodes of hypoventilation and of oxygen desaturation.

Keywords

End-tidal carbon dioxide; Hypoxia; Respiratory depression; Hypopnea

1. Introduction

Capnography, or continuous end-tidal carbon dioxide (ETCO₂) monitoring, is a sensitive indicator of ventilation that can alert a provider to hypoventilation more often and earlier than other modalities.^{1–3} In non-intubated patients, it is measured passively via a nasal-oral cannula in a continuous and objective manner.^{4, 5} Capnography can detect hypoventilation and apnea before it becomes apparent by clinical examination or pulse oximetry, yet is infrequently used in monitoring children during sedation in an outpatient or pediatric emergency department (PED) setting despite promotion by agencies such as the Joint Commission.^{2, 6–13} The detection of apnea or hypoventilation can be significantly delayed by use of pulse oximetry alone, particularly if patients receive supplemental oxygen.^{1, 14–18}

Children in the PED frequently need medications for procedural sedation, which induces a state of attenuated pain, anxiety and motion to facilitate procedures such as fracture reduction or drainage of abscesses.^{19–21} While sedation is generally safe, it may lead to hypoventilation due to alterations in a patient's respiratory rate or tidal volume. While the normal respiratory rate varies by age, providers may follow trends with impedance plethysmography or clinical examination. However, tidal volume is less easy to quantify. Hypopnea, a decline in tidal volume, is not detectable by monitoring either respiratory rate or other standard parameters and is difficult to detect on physical examination. However, hypopnea commonly occurs during sedation and often precedes hypoxemia.^{2, 7, 22, 23}

This is the first randomized trial to examine the effects of capnography on detecting hypoventilation and preventing hypoxemia during sedation among children in the PED. We hypothesized that the addition of capnography to standard monitoring would significantly improve recognition of hypoventilation by providers caring for sedated children. This improved recognition might increase the rate of interventions to prevent continued hypoventilation and reduce the rate of oxygen desaturations, thus improving patient safety.

2. Methods

2.1 Study Design and Setting

This was a randomized, controlled trial of capnography in a PED within an urban, tertiary care academic center from September 1, 2011 to January 31, 2013. The PED is staffed by 13 pediatric emergency medicine attendings, 6 fellows, and approximately 50 registered nurses.

2.2 Population

Children aged 1 – 20 years given intravenous medications to induce sedation were eligible for inclusion. Exclusion criteria included intubation, administration of baseline supplemental oxygen without preceding hypoxemia, and conditions associated with abnormal ETCO_2 values, such as lower airway disease (e.g. asthma), diabetic ketoacidosis, moderate to severe dehydration, and major trauma. Subjects were also excluded if they did not tolerate the capnography cannula or if the patient cried for >20% of the sedation. Crying can interfere with the accuracy of capnography measurements and typically occurs in under-sedated patients, thus the investigators felt the risk of hypoventilation was low.

2.3 Study Protocol

All PED staff received training on the interpretation of capnography. Appropriate noninvasive interventions for hypoventilation (e.g., instructing patient to take deep breaths) were also discussed. Interventions were not mandated, thus all interventions were at the discretion of the treating team.

Either the principal investigator or a research assistant obtained consent from the patients and/or a parent and collected data on all patients. Study personnel were typically present during the afternoon and evening on both weekdays and weekends and approached all eligible subjects. The cannula for capnography monitoring (Smart CapnoLine Plus, Oridion, Bedford, MA) was placed in the nostrils and over the lip of patients in both the intervention and the control groups and attached to the Nellcor® Oximax® NPB-75 portable capnograph (Covidien, Mansfield, MA). Subjects tolerating the cannula were then randomized via sequentially numbered, sealed, opaque envelopes in a 1:1 ratio into one of two groups by study personnel: those in which the treating team was blinded to the screen on the capnograph (control group), and those in which the capnograph was viewable by all staff (intervention group). A statistician provided blocked randomization using Proc Plan (Sas 9.2, Cary, NC), with a 7-digit random seed; group assignments were allocated to patients in a random sequence within blocks of six.

2.4 Measurements

The patients' American Society of Anesthesiologists (ASA) classification, age, weight, indication for sedation, physician providing sedation and medications administered were recorded. The ASA classification is a five-category scale to assess a patient's fitness for anesthesia. Each patient received standard monitoring with a 3-lead electrocardiograph, impedance plethysmography and pulse oximetry. A nurse and physician certified to perform sedation were present and documented the heart rate, respiratory rate, oxygen saturation and blood pressure every 5 minutes. Vitals signs and ETCO_2 readings were recorded every 30

seconds by study personnel, who were not involved in the sedation. Recordings began immediately before administration of medications for sedation and continued until sedation ended. Medications and dosages administered were also recorded throughout the sedation.

Study personnel held the capnograph out of the sight of providers for the control group. For the intervention group, the monitor was placed within sight of the treating staff. Alarms on the capnograph alerted providers in the intervention group to ETCO_2 levels $<30\text{mmHg}$ and $>50\text{mmHg}$, the limits for hypopnea and bradypnea, respectively.^{2, 3, 24} Alarms on the capnograph were silenced in the control group. The treating staff controlled the main cardiorespiratory monitor and its alarm settings for all patients. Any staff intervention related to either airway or ventilatory management was documented within each 30-second time interval. These included verbal or physical stimulation, bag-valve mask ventilation, airway repositioning (jaw thrust or head tilt), use of a shoulder roll, supplemental oxygen or reversal agents.²¹ Study personnel did not inform the treating staff of any abnormal values. This study was approved by the Human Research Protection Program and registered at ClinicalTrials.gov (NCT01463527).

2.5 Outcomes

Primary outcomes were the rate of hypoventilation as defined by capnography $<30\text{mmHg}$ without hyperventilation or $>50\text{mmHg}$, the rate of staff interventions (defined above) and the rate of oxygen desaturations as defined by pulse oximetry $<95\%$ in each group over time. Secondary outcomes were the rate of persistent hypoventilation, defined as two consecutive abnormal ETCO_2 measurements, and pulse oximetry readings $<90\%$. We also studied timely interventions, defined as an intervention occurring concurrent with or in the 30-second interval following hypoventilation. Interventions occurring outside of this timeframe were defined as delayed.

2.6 Data Analysis

Based on prior data²² and using repeated measures design, we estimated that with 77 patients per group and an average of 4 observations per patient, we would have 80% power to detect a difference of 0.20 in the proportion of interventions for hypoventilation: 0.50 in the intervention and 0.30 in the control group. Using the same approach, with 77 patients per group, we estimated that we would have 80% power to detect a statistically significant difference in the proportions of children with at least one oxygen desaturation $<95\%$: 0.30 in the intervention group vs. 0.50 in the control group.

Data were entered into Excel (Microsoft Corp, CA); analyses were performed using SAS 9.2 (SAS Institute Inc. Cary, NC). Baseline characteristics of the two groups (intervention and control) were described. Student's t-test was used for continuous variables and chi-square/Fisher's exact test for categorical variables. Statistical significance was established with a two-sided alpha of 0.05. Any statistically significant or clinically meaningful differences were added to the multivariate analysis.

The outcomes were summarized by group as the average rates per patient minute of sedation, as well as minimum and maximum rates. Because of the repeated observations on the same patient, we used the generalized estimating equations (GEE) approach²⁵, which is

an extension of logistic regression for correlated binary outcomes. Measures taken on the same subject over time are not independent because of the common source of variance, and to account for this, GEE bring together the outcomes at each time point using a working correlation matrix. For each outcome, we modeled, the average rate of an event per minute of sedation, using the following primary predictors: the group, time of sedation (bounded by the median sedation time of 35 minutes) and the interaction of group by time as the main independent predictors. A full model also included patient ethnicity, age, gender, provider, respiratory rate, use of a shoulder roll at the start of sedation, length of sedation and medication dosage. The final reduced model included statistically significant effects and other clinically important variables. Odds ratios (OR) and 95% confidence intervals (95% CI) were reported for each predictor in the models. The mean predicted rates of outcomes at each time point for the randomized groups were obtained from the final GEE models and plotted superimposed on the observed rates (i.e., proportion with outcomes in a given minute of sedation).

3. Results

There were 194 children approached for enrollment. Twenty-seven potential subjects were excluded: 18 refused to participate, 4 were not sedated or study personnel were unavailable, 3 didn't tolerate the cannula, and in 2 the cannula interfered with the procedure (e.g., nasal laceration). Thirteen patients were excluded after randomization (7 controls, 6 cases): 11 for crying during >20% of the sedation, 1 was <1 year of age, and 1 used a pacifier which obstructed the cannula. Additional children were randomized until our sample size was met. There were 154 patients in the analysis, 77 randomized to each group. Basic characteristics of the groups are outlined in Table 1. The overall rates per patient minute of sedation for each outcome are shown in Table 2.

3.1 Hypoventilation

All episodes of hypoventilation were due to hypopnea (ETCO₂ values <30mmHg without hyperventilation). Subjects had from 0 to 148 episodes of hypoventilation while sedated. The rate or the proportions of subjects with an episode of hypoventilation during a minute of sedation increased over time in both groups, but this change in rate was significantly greater in the controls (change in rate of hypoventilation per minute: 7.1% vs. 1.0%, $p=.008$; OR=1.06, 95% CI 1.02, 1.11) [Figure 1]. Medication dosage per kilogram, length of sedation, gender, respiratory rate, and use of a shoulder roll were not significantly associated with this outcome. The rate of persistent hypoventilation, defined as two consecutive abnormal values (30 seconds apart), also increased over time and was significantly greater among controls (7.5% vs. 1.0%, $p=0.02$; OR=1.06, 95% CI 1.01, 1.12) [Figure A.1].

3.2 Interventions

Only 6 patients received supplemental oxygen. No patients received bag-valve mask ventilation, intubation or reversal agents. For the most frequent methods of intervention, the odds of verbal or physical stimulation in the intervention group were significantly lower than in controls after adjusting for age and length of sedation (OR of 0.31; 95% CI: 0.17, 0.57). Subjects with longer sedations were more likely to receive an intervention (OR: 1.02

per minute increase; 95% CI: 1.005, 1.03). For each additional year in age there was a 10% increase in the likelihood of having an intervention (OR: 1.10; 95% CI: 1.04, 1.10).

When interventions that could be used to correct hypoventilation were combined (stimulation and airway repositioning) similar results were found (Figure 2). Overall, the odds of receiving one of these interventions in the intervention group were significantly lower than in controls after adjusting for age and length of sedation (OR: 0.25; 95% CI 0.13, 0.50). The intervention group was more likely to receive timely interventions compared with the control group (OR: 2.26; 95% CI 1.34, 3.81) [Figure A.2]. For every 10-minute increase in sedation duration, the overall odds of receiving a timely intervention decreased 14% (OR per 10 minutes 0.86; 95% CI 0.75, 0.99).

3.3 Oxygen Desaturation

While the rate of oxygen desaturations significantly dropped over time in both groups ($p=0.02$), there was no statistically significant difference between the groups ($p=0.80$) [Figure A.3]. However, delayed interventions (those not timed concurrently with hypoventilation) were significantly associated with higher odds of an oxygen desaturation $<95\%$ (OR 5.31; 95% CI: 2.76, 10.22) [Figure 3] and $<90\%$ (OR 6.19; 95% CI 1.36, 28.11) when compared to timely interventions. Higher medication dosage per kilogram was associated with higher odds of oxygen desaturation $<90\%$ (OR 2.53; 95% CI: 1.23, 5.22). Thus, for every 1mg/kg increase in medication dosage the odds of an oxygen desaturation increased 153%.

4. Discussion

This is the first randomized trial in children to assess the impact of the addition of capnography to standard monitoring during sedation in a PED. We found that capnography benefited patients by reducing the rate of hypoventilation in subjects over time, improving the timeliness of interventions and impacting the frequency of oxygen desaturations when timely interventions were performed.

It is important to note that all episodes of hypoventilation in this study were caused by hypopnea. The low ETCO_2 values seen in hypopnea are due to an increasing proportion of dead space ventilation as tidal volume declines. Many prior studies have failed to account for this form of hypoventilation, including only bradypnea and apnea.^{8–10, 26–29} While bradypnea and apnea can be detected by changes in respiratory rate, hypopnea may not be detectable by either physical examination or respiratory monitors.^{2, 23} Although apnea is reportedly uncommon, in two studies capnography detected apnea in 25% of patients, while staff detected none of these events.^{23, 30} Capnography has been shown to be a superior method by which to detect all types of hypoventilation.

Nevertheless, current guidelines do not recommend capnography to routinely monitor all patients receiving sedation.^{31–33} Clinical practice guidelines for the monitoring and safe practice of sedation vary by specialty and institution.^{31, 32} Although anesthesiologists consider capnography essential to monitor patients undergoing general anesthesia, the device has not been routinely applied by non-anesthesiologists, where sedation is associated

with significant risks of oxygen desaturations, apnea, and airway obstruction.^{27, 34–39} Furthermore, emergency services are delivered in an environment where the need for efficiency and the frequent distractions may threaten patient safety.⁴⁰ Despite its reported ease of use and of interpretation among pediatric specialists, capnography is not universally available or utilized for either intubated or non-intubated patients.^{11, 41} In a survey of pediatric emergency medicine fellowship programs, only 53% had capnography available for non-intubated patients and 61% never used capnography during sedation.¹¹

In our study, while the increase in hypoventilation over time could be explained by the completion of procedural stimulation prior to the abatement of sedation, it is unclear why this was significantly different between the groups. Staff may have been more perceptive to capnography trends in the intervention group and acted prior to cutoff values for hypoventilation. However, these would not have met the definition of timely interventions and there was not a rise in the proportion of these events.

Sedation can lead to hypoxemia from hypoventilation.^{8, 10, 20, 39, 42} Although shown to be underreported, oxygen desaturation occurs in up to 25% of children during sedation and can effect cerebral oxygenation.^{20, 23, 43–45} Both chronic and intermittent hypoxemia can adversely affect development, behavior, and academic achievement in childhood.⁴⁶ Mild hypoxemia (pulse oximetry <95% for >60 seconds) has been reported to precede more serious adverse events.^{47, 48} In our prior study, 50% of children who received sedation in the PED had hypopnea and were 6.6 times more likely to have oxygen desaturations. More importantly, hypopnea occurred on average 3.7 minutes prior to oxygen desaturation, providing a window of opportunity to intervene.²²

While we hypothesized that capnography would increase staff interventions due to its increased sensitivity for hypoventilation, patients in the intervention group had fewer interventions. Only one other study has reported the effect of capnography on staff interventions. Deitch evaluated adult emergency department patients receiving sedation and found an increase in interventions among physicians viewing the capnograph.⁴⁹ The threshold at which a provider intervenes for hypoventilation is variable. Overall, there was a higher frequency of interventions in our study compared with that of Deitch. Our providers may feel reassured by capnography; in contrast it may heighten awareness among adult providers. A qualitative investigation of staff participants was undertaken to better explain these findings and is detailed in a separate report. The majority of interventions in our sample were simple, noninvasive maneuvers. Since no study patients experienced severe deterioration of their vital signs, this demonstrates that hypoventilation can be easily corrected, especially when detected early.

Unlike prior randomized controlled studies, there was no significant difference in the rates of oxygen desaturation between groups.^{23, 49, 50} The proportion of patients with an oxygen desaturation during sedation was lower in children than in adults in these studies. In contrast to Lightdale's study, our staff were not mandated to intervene for abnormal capnography, perhaps approximating actual clinical circumstances more accurately and accounting for these differences.²³ Although it is not surprising to find that the majority of interventions in the intervention group were related to abnormal capnography, the association between

delayed interventions and oxygen desaturations has not been previously described. Providers who were blinded to capnography provided more interventions, but more often remote from episodes of hypoventilation. This supports prior arguments regarding the delays and difficulties of detecting hypoventilation through our current monitoring standards.

5. Limitations

There are several potential limitations to our study. Our primary outcome was a pulse oximetry reading <95%, with a reading <90% as a secondary measure. While the direct patient morbidity associated with oxygen desaturations are unknown, the administration of supplemental oxygen without the ability to continuously monitor a patient's ventilatory status can mask continued respiratory depression and can lead to respiratory arrest. Similarly, a consensus panel on pediatric sedation emphasized intervention-based definitions of adverse events versus absolute numerical cutoffs.²¹ There were fewer oxygen desaturations in this study than in our prior study from which we estimated our sample size; thus we may have been underpowered to detect a significant difference between groups in the rates of hypoxemia.²²

This was a convenience sample of patients. Neither providers nor study personnel were blinded to group assignment after consent and randomization. Study personnel were present during the sedation and collected observations of interventions. The Hawthorne effect could influence the behavior of staff during sedation. However, this could have influenced both groups. While staff in the control group may have been more vigilant in their monitoring, it is unclear how this would affect their ability to detect hypoventilation. As our results opposed our original hypothesis, this is less of a concern. Interventions were defined at the outset and less subjective in nature, thus reducing the potential bias of non-blinded observations.

No serious adverse events were recorded. Since this study was not powered to detect these rare events, we are unable to predict how capnography may impact staff behavior and patient outcomes for these less frequent events. Also, ketamine was used in the majority of subjects as we do not have access to propofol in our PED. While ketamine is typically considered safe for sedation, hypopneic hypoventilation due to this medication has been rarely studied.^{22, 26, 29, 45, 51} Similarly, while a large proportion of our subjects also received midazolam, we previously found no differences in the rates of hypoventilation with this common combination of medications in comparison to ketamine alone.^{22, 29, 52} Different sedative medications may lead to different frequencies of events.

6. Conclusions

In summary, hypopneic hypoventilation is common among children receiving sedation in a PED and is difficult to detect other than by capnography. Providers with access to capnography during sedation provided fewer, but more timely interventions for hypoventilation. This was associated with fewer episodes of hypoventilation and fewer episodes of oxygen desaturation. While larger studies are needed to assess the impact of capnography on more serious adverse events, capnography may improve the quality of care among children during sedation.

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Abbreviations

CI	Confidence interval
ETCO₂	End-tidal carbon dioxide
OR	Odds ratio
PED	Pediatric emergency department
SD	Standard deviation

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Figure 1.

Proportion of subjects with hypoventilation during every 30-second interval of the sedation in the control and intervention groups.

Figure 2.
Proportion of subjects receiving an intervention in each 30-second interval of the sedation in the control and intervention groups.

Figure 3.

Proportion of subjects experiencing an oxygen desaturation <95% in every 30-second interval during the sedation based on timely and delayed interventions.

Figure A.1.

Proportion of subjects with persistent hypoventilation during every 30-second interval of the sedation in the control and intervention groups.

Figure A.2.

Proportion of subjects receiving an appropriately timed intervention in each 30- second interval of the sedation in the control and intervention groups.

Figure A.3.
Proportion of subjects experiencing an oxygen desaturation <95% in every 30 second interval during the sedation in the control and intervention groups.

Table 1

Characteristics of intervention and control arms.

Variable	Intervention N=77	Control N=77	P Value
Mean Age, years (SD)	8.6 (5.1)	8.2 (4.8)	0.61
Gender			
Male	46 (59.7%)	43 (55.8%)	0.62
Female	31 (40.3%)	34 (44.2%)	
Ethnicity/Race			
White	44 (57.1%)	46 (59.7%)	0.99
Black	13 (16.7%)	13 (16.7%)	
Hispanic	15 (19.5%)	14 (18.2%)	
Other	5 (6.5%)	4 (5.2%)	
ASA Classification			
1	75 (97.4%)	73 (94.8%)	0.68
2	2 (2.6%)	3 (3.9%)	
3	0 (0%)	1 (1.3%)	
Mean duration of sedation, minutes (SD)	36.9 (17.9)	35 (14.8)	0.48
Weight, kg (SD)	35.8 (20.8)	35.8 (21.8)	0.99
Indication for sedation			
Fracture reduction	43 (55.8%)	42 (54.5%)	0.56
Laceration repair	13 (16.9%)	16 (20.8%)	
Incision and drainage of abscess	16 (20.8%)	12 (15.6%)	
Arthrocentesis	2 (2.6%)	3 (3.9%)	
Dislocation	1 (1.3%)	4 (5.2%)	
Other	2 (2.6%)	0 (0%)	
Sedation Medications			
Ketamine	76 (98%)	75(98%)	1.0
Mean dose ketamine (mg/kg)	1.45	1.32	0.19
Median times ketamine administered during sedation(min, max)	2 (0, 6)	2 (0, 6)	0.78
Midazolam	32 (41.6%)	31 (40.3%)	0.87
Final Disposition			
Discharged	72 (93.5%)	73 (94.8%)	1.0
Admitted	5 (6.5%)	4 (5.2%)	
Mean respiratory rate, breaths per minute (SD)	26.3 (0.3)	24.4 (0.3)	<0.01
Any episode of hypoventilation	34 (44.2%)	36 (46.8%)	0.87
Any episode of oxygen desaturation	23 (29.9%)	23 (29.9%)	1.0
Any Interventions, Total	38 (49.4%)	39 (50.7%)	0.87
Verbal or physical stimulation	28 (36.4%)	33 (42.9%)	0.41
Head tilt or Jaw thrust	3 (3.9%)	11 (14.3%)	0.02
Shoulder roll	13 (16.9%)	11 (14.3%)	0.66

Variable	Intervention N=77	Control N=77	P Value
Supplemental oxygen	4 (5.2%)	2 (2.6%)	0.68

Table 2

Rate of Outcomes of Interest: Events per Patient Minute of Sedation (Minimum, Maximum)

Outcomes	Intervention	Control	P-value
	(Total Patient Minutes: 2165)	(Total Patient Minutes: 2132)	
Hypoventilation	0.092	0.138	0.28
	(0 – 1.882)	(0 – 1.148)	
Persistent hypoventilation	0.004	0.010	0.004
	(0 – 0.088)	(0 – 0.260)	
Oxygen desaturation < 95%	0.016	0.024	0.30
	(0 – 0.176)	(0 – 0.400)	
Oxygen desaturation < 90%	0.004	0.004	0.90
	(0 – 0.058)	(0 – 0.088)	
Any intervention	0.390	0.396	0.94
	(0–2.084)	(0 – 2.030)	
Shoulder Roll	0.280	0.256	0.85
	(0 – 2.084)	(0 – 2.030)	
Verbal or Physical	0.038	0.132	0.0003
Stimulation	(0 – 2.084)	(0 – 1.500)	
Head tilt or Jaw thrust	0.004	0.038	0.02
	(0 – 0.176)	(0 – 1.412)	
Supplemental Oxygen*	0.076	0.016	0.09
	(0 – 1.942)	(0 – 1.412)	
Appropriate intervention	1.805	1.617	0.003
	(0.235 – 2.067)	(0.038 –2.047)	

* Note: only 4/77 patients in intervention group and 2/77 patients in control group have received supplemental oxygen.

Upper panel corresponds to overall rates (total number of events/total number of records per group);

Lower panel corresponds to min-max of individual rate per group.