A Pilot Study on the Effect of Nasal Continuous Positive Airway Pressure on Arterial Partial Pressure of Carbon Dioxide During Spinal Anesthesia with Intravenous Sedation for Total Knee Arthroplasty

Stephen B. Smith, MD,* Shawn Carr, CRNA,* Stacey Psikula, CRNA,* Anita Das, PhD,†
and Katherine Grichnik, MD, MS‡

BACKGROUND: Deep sedation of surgical patients may be associated with hypoventilation, airway collapse, and hypercarbia, although the extent of hypercarbia is rarely quantified. In this prospective, randomized, controlled clinical pilot study, we assessed the efficacy of nasal continuous positive airway pressure (nCPAP) for reducing arterial partial pressure of carbon dioxide ($Paco_2$) among deeply sedated, spontaneously ventilated patients undergoing total knee arthroplasty (TKA) under subarachnoid block (SAB), versus standard airway management in a control group.

METHODS: Forty ASA status I–III patients underwent deep sedation with propofol to level 2 on the Modified Observers Assessment of Alertness/Sedation Scale during TKA performed under SAB. Nasal or oral airways were placed at the discretion of the anesthesia team, but they were not used in conjunction with nCPAP. Baseline arterial blood gas analysis (ABG-1) was performed after Modified Observers Assessment of Alertness/Sedation Scale level 2 was reached. Patients were then randomized to receive nCPAP (nCPAP group, $N = 20$) or standard oxygen mask management (control group, $N = 20$). A second ABG (ABG-2) was performed 30 minutes later to assess the effect of nCPAP on $Paco_2$. The primary efficacy end point was change in $Paco_2$ from baseline to the 30-minute time point.

RESULTS: Baseline (ABG-1) $Paco_2$ values were similar between nCPAP and control groups with median values of 54.5 and 56.1 mm Hg, respectively. There was a significant decline in $Paco_2$ in the nCPAP group (median of −4.6 mm Hg [10th–90th quantile, −14.55 to 3.85]) as compared with the control group (median of 0.95 mm Hg [−4.75 to 9.85]; $P = 0.015$; 95% confidence interval [CI] for location shift = −9.5 to −1.3). Within the control group, $Paco_2$ was similar from ABG-1 to ABG-2 (median [10th–90th quantile] = 56.1 mm Hg [47.2–67.0] vs 56.6 mm Hg [46–68.8]; $P = 0.52$; 95% CI for the median = −3.4 to 3.4). Forty percent of all patients received an airway before ABG-1. The baseline $Paco_2$ value of patients receiving an airway was not different from that of patients without an airway (median [10th–90th quantile] = 56.0 mm Hg [46.0–68.4] vs 54.1 mm Hg [45.6–65.6], respectively; $P = 0.33$; 95% CI for location shift = −2.30 to 7.20).

CONCLUSIONS: Deep sedation of TKA patients during SAB resulted in moderate hypercarbia (mean and median $Paco_2$ = 55). There was a trend showing that nCPAP treatment reduced $Paco_2$ versus treatment for control group patients receiving standard airway management; however, estimated treatment difference varied widely, from 1.4 to 12.6 mm Hg. Among control group patients, the initial $Paco_2$ during deep sedation was similar to the $Paco_2$ when measured after a 30-minute period of continued deep sedation. Finally, baseline $Paco_2$ among deeply sedated patients who received an airway was not different from that of patients who did not receive an airway.   (Anesth Analg 2015;120:479–83)

Nasal continuous positive airway pressure (nCPAP) has been shown to be a highly effective means of relieving upper airway obstruction of patients with obstructive sleep apnea (OSA). The upper airway of a patient with OSA acts as a Starling resister, with a collapsible segment in the oropharynx and variable airflow obstruction during the respiratory cycle.[1] Application of nCPAP creates a pneumatic splint in the hypopharynx that reduces obstruction.[2]

The upper airway of a deeply sedated patient exhibits many similarities to that of a patient with OSA. Deep IV sedation causes varying degrees of upper airway obstruction related to alteration of pharyngeal muscle activity, and reduction in respiratory drive and lung volume.[3] Propofol, commonly used as an intraoperative sedative/hypnotic drug due to its favorable pharmacokinetic and pharmacodynamic features, is associated with upper airway collapse through a disproportionate decrease in genioglossus tone as assessed by electromyography.[4,5] These effects may be augmented by the supine position, respiratory consequences of regional anesthesia, and the effects of other sedatives and opiates

administered during anesthetic care.[6] Airway collapse may result in hypoventilation and hypercarbia. Undesirable physiological effects of hypercarbia include hypertension, tachycardia, increased pulmonary vascular resistance, acidosis, and cerebral vasodilation. The clinical impact of these effects is not clear but may be important in association with preexisting cardiac, pulmonary, or neurologic conditions. The benefit of postoperative CPAP treatment in OSA patients has been studied extensively.[7] However, there have been no studies, to our knowledge, that have investigated the effect of intraoperative nCPAP application in deeply sedated surgical patients.

The purpose of this study was to assess the efficacy of CPAP in reducing arterial partial pressure of carbon dioxide ($Paco_2$) increase associated with deep IV sedation of adult patients undergoing total knee arthroplasty (TKA) under subarachnoid block (SAB). We hypothesized that nCPAP would decrease $Paco_2$.

METHODS
Patients
After IRB approval of the study protocol, 40 patients gave informed written consent to be included in this prospective, randomized, controlled clinical trial conducted at New Hanover Regional Medical Center in Wilmington, NC. Inclusion criteria were ASA physical class I, II, or III patients scheduled to undergo TKA who were older than 21 years and younger than 70 years, with a body mass index (BMI) <40. Qualified study participants consented to an anesthetic plan consisting of preoperative femoral nerve block (FNB), SAB using intrathecal morphine with bupivacaine, and IV sedation during the operative procedure. Exclusion criteria included prior diagnosis of OSA, prior stroke with residual neurologic deficit, prior diagnosis of chronic obstructive pulmonary disease, a recent respiratory infection, or current pregnancy. Additionally, patients with chronic opioid or benzodiazepine dependency were excluded. This study was registered with ClinicalTrials.gov by Stephen B. Smith, MD, on June 5, 2012 (Identifier NCT01622647).

Randomization
A random number generator program was used to assign sequential qualified study cases to control group ($N = 20$) or nCPAP group ($N = 20$) before collection of additional demographic information and before anesthetic and surgical care. The group assignment of each individual study patient was not known by the anesthesia team until after sedation and the start of the surgical procedure. After study group assignment, baseline data were collected, including age, gender, height, weight, and BMI. A questionnaire was completed to obtain a STOPBANG score.[8] STOPBANG score and BMI, proven measures of OSA risk, were assessed to verify group similarity and identify potential risk for airway obstruction during sedation. Anesthetic care in the operating room was provided by 1 of 2 certified nurse anesthetists (CRNAs) working with an anesthesiologist. Participating CRNAs and anesthesiologists were blinded to all arterial blood gas (ABG) results until after completion of all study cases.

Clinical Procedures
The anesthesia protocol was designed to mirror the anesthesia approach used for a large majority of patients undergoing TKA at the sponsoring facility, a community orthopedic specialty hospital. This included SAB and intraoperative deep IV sedation using propofol infusion. Additionally, intrathecal morphine and FNB were provided as components of a multimodal postoperative analgesia program used at the facility. FNB was performed 30 to 60 minutes before the operation using 20 mL of 0.5% ropivacaine, with procedural sedation using midazolam and/or fentanyl at the clinical discretion of the anesthesiologist. After transfer to the operating room, SAB was performed using bupivacaine 0.75% in dextrose 7.5%, dosed at the discretion of the anesthesia team, with the addition of 150 μg preservative-free morphine. Patients received additional midazolam and/or fentanyl as needed before the completion of the SAB procedure. After SAB induction, an infusion pump was used to deliver propofol. Dosage was titrated between 30 and 100 μg/kg/min to maintain sedation level at or near level 2 on the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale. All patients received supplemental oxygen using a facemask until the time that ABG-1 was collected. Nasal or oral airways were placed at the discretion of the anesthesia team, but they were not used in conjunction with nCPAP.

Five minutes after surgical skin incision, a baseline analysis (ABG-1) was collected from all study patients by radial artery puncture. Analysis was performed by a technician using the *i-STAT* 1 analyzer (Abbott Laboratories, Abbott Park, IL). Immediately after ABG-1 was collected, the CRNA opened a sealed group assignment envelope and those patients randomized to the nCPAP group were fitted with an nCPAP mask connected to a CPAP machine (RESMED ESCAPE-S8 model, ResMed Corp, San Diego, CA). Airway pressure was set to 8 cm of water, a mid-range setting on the device, for all CPAP group patients, and oxygen was added to the system via flowmeter as needed to maintain SaO_2 at least 98%. Patients randomized to the control group continued to receive supplemental oxygen via mask. Thirty minutes after ABG-1, a second specimen (ABG-2) was collected from all study patients.

The primary objective of this study was to assess the efficacy of CPAP for reducing the $Paco_2$ increase associated with deep IV sedation among patients undergoing TKA under SAB. Secondarily, the protocol facilitated evaluation of any change of $Paco_2$ after an additional 30-minute period of deep sedation among 20 control subjects.

Statistical Analysis
There are limited published data on the extent of hypercarbia that occurs during deep sedation of surgical patients, and we know of no published data concerning the impact of nCPAP during deep sedation. No formal sample size calculation was completed. Rather, a sample size of 40 subjects was chosen for a pilot study to provide an initial assessment of a $Paco_2$ increase during deep intraoperative sedation and the effect of nCPAP treatment. The primary end point for comparison of the control group and nCPAP group was change from baseline in $Paco_2$ measured 30 minutes after the institution of nCPAP in the test group. Additional data, including baseline $Paco_2$, STOPBANG questionnaire score, BMI, gender, patient age, and drug dosage, were collected. Continuous data are expressed as median, along with 10th and 90th quantiles. Ninety-five percent confidence intervals (CIs) for the median were determined based on order statistics. Continuous data

were compared between groups using the Mann-Whitney U test, and categorical data were compared using Fisher exact test. The location shift parameter and 95% CI for the location shirt parameter were calculated using the Hodges-Lehmann approach. The Wilcoxon signed rank test was used to compare $Paco_2$ values at ABG-1 and ABG-2. A value of $P < 0.05$ was considered statistically significant. Analysis was performed using JMP software, a product of SAS Institute, Cary, NC.

RESULTS

Forty adult patients completed the study protocol (20 in each group) between July 2012 and July 2013. The baseline $Paco_2$ values for the full study population ($N = 40$) to the time of ABG-1 ranged from 38 to 76 mm Hg (median $Paco_2$ [10th–90th quantiles] = 55 mm Hg [45.8–67]). Table 1 presents a comparison of study group demographic information and data collected to the time of ABG-1. The groups were similar with respect to demographic characteristics, STOPBANG score, BMI, and dosing of midazolam and fentanyl, and there was a similar degree of hypercarbia during deep sedation in both groups.

$Paco_2$ values at ABG-1 (baseline) and ABG-2, as well as the change in $Paco_2$ values between these 2 time points, are presented in Table 2. After a 30-minute period of continuous sedation at MOAA/S level 2, ABG-2 revealed no difference in $Paco_2$ compared with baseline ABG-1 values in the control group (median change from baseline $Paco_2$ [10th–90th decile] = control: 0.95 [−4.75, 9.85]; $P = 0.52$; 95% CI median = −3.4 to 3.4). In contrast, after a 30-minute period of nCPAP treatment, there was a significant decline in $Paco_2$ in the nCPAP group compared to baseline ABG-1 values (median change from baseline $Paco_2$ [10th–90th decile] = control: 0.95 [−4.75, 9.85] vs −4.60 [−14.55, 3.85]; $P = 0.015$; 95% CI for the location shift = −9.5 to −1.3). The distribution of study

group patients with mild, moderate, and severe hypercarbia (defined as 42–49, 50–59, and ≥60 mm Hg, respectively) at ABG-1 and ABG-2 is presented in Figure 1.

As noted, an oral or nasal airway was placed in 16 study patients before ABG-1. Table 3 presents $Paco_2$ values at ABG-1 by airway use. There was no difference in BMI or gender based upon airway use among study patients. The baseline $Paco_2$ value of patients who received an airway was similar to that of those who did not receive an airway (median [10th–90th quantile] = 56.0 [46.0–68.4] vs 54.1 [45.6–65.6], respectively; $P = 0.33$; 95% CI for location shift = −2.30 to 7.2). The $Paco_2$ at ABG-1 with and without airway use was also evaluated according to subsequent study group randomization. Among patients who were later randomized to the control group, the baseline $Paco_2$ value of those who received an airway was similar to the baseline $Paco_2$ of those who did not receive an airway (median [10th–90th quantile] = 56.4 [45.8–68.5] vs 56.1 [48.7–63.5], respectively; $P = 0.68$; 95% CI for the location shift = −6.2 to 9.8). Likewise, among patients who were later randomized to the nCPAP group, the baseline $Paco_2$ value of those who received an airway was similar to the $Paco_2$ among those who did not receive an airway (median [10th–90th quantile] = 56.0 [51.2–60.6] vs 53.2 [44.9–72.5], respectively; $P = 0.21$; 95% CI for the location shift = −2.8 to 9.3).

DISCUSSION

The principle aim of this study was to investigate the efficacy of nCPAP for reducing hypercarbia that accompanies deep sedation. During deep sedation of surgical patients, we observed a statistically significant reduction in $Paco_2$ among patients treated with nCPAP for 30 minutes versus control group patients, although the estimated difference ranged rather widely, from 1.4 to 12.6 mm Hg. For the purposes of this discussion, designations described in 1 published study

Table 1. Study Group Demographics and Study Data at ABG-1

	Control ($n = 20$)	nCPAP ($n = 20$)	P value
$Paco_2$ (mm Hg) at ABG-1	56.1 (47.2–67.0)	54.5 (45.3–66.6)	0.40[a]
Age, years	63 (52.0–68.5)	66 (56.5–68.5)	0.22[a]
Female, n (%)	11 (56%)	13 (65%)	0.75[b]
BMI, kg/m^2	28.5 (24.3–35.3)	31.2 (24.8–38.7)	0.18[a]
SB Points	3 (1.5–5)	4 (1–5)	0.60[a]
Pre-SAB midazolam (mg)	5 (3.5–6)	5 (3–7)	0.86[a]
Pre-SAB fentanyl (µg)	50 (0–100)	50 (0–75)	0.48[a]
Airway use before ABG-1, n (%)	10 (50%)	6 (30%)	0.33[b]
(note: airways removed after ABG-1 among TEST group, but maintained in control group)			

All continuous values are presented as median with 10th and 90th quantile.
ABG = arterial blood gas; BMI = body mass index; SB Points = STOPBANG questionnaire score; SAB = subarachnoid block (spinal); airway = nasal or oral airway adjunct; nCPAP = patients treated with nasal CPAP.
[a]Mann-Whitney U test.
[b]Fisher exact test.

Table 2. Study Group Changes in $Paco_2$ Between ABG-1 and ABG-2

	Control ($n = 20$)	nCPAP ($n = 20$)	P value[a]	Location shift and 95% CI[b]
$Paco_2$ (mm Hg) at ABG-1	56.1 (47.2–67.0)	54.5 (45.3–66.6)	0.40	−2.2 (−7.0 to 3.2)
$Paco_2$ (mm Hg) at ABG-2	56.6 (46.0–68.8)	48.2 (41.3–59.6)	0.01	−6.6 (−12.6 to −1.4)
Change in $Paco_2$ from ABG-1 to ABG-2	0.95 ([−4.75] – [+9.85])	−4.60 ([−14.55] – [+3.85])	0.01	−5.2 (−9.5 to −1.3)

All continuous values are presented as median with 10th and 90th quantile.
nCPAP = patients treated with nasal CPAP.
[a]Mann-Whitney U test.
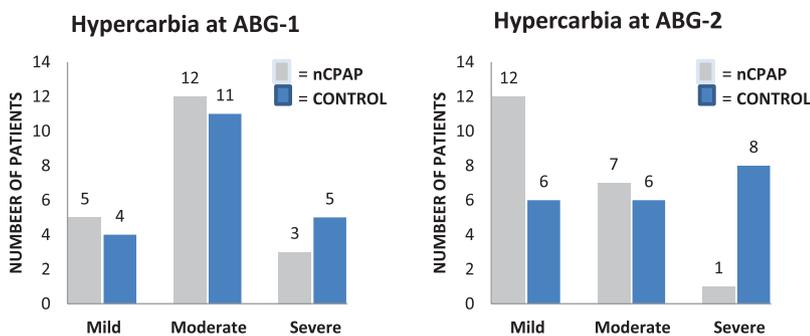[b]Calculated using the Hodges-Lehmann approach.

Figure 1. Hypercarbia severity at ABG-1 and ABG-2. nCPAP = patients treated with nasal continuous positive airway pressure (N = 20); control = no nCPAP (N = 20); mild = Paco$_2$ <50 mm Hg; moderate = Paco$_2$ ≥50 to <60 mm Hg; severe = Paco$_2$ ≥60 mm Hg.

Table 3. Paco$_2$ at ABG-1 Among Patients With and Without an Airway Adjunct

	With AW (N = 16)	Without AW (N = 24)	P value	Location shift and 95% CI[c]
Paco$_2$, mm Hg (median, 10th–90th)	56.0 (46.0–68.4)	54.1 (45.6–65.6)	0.33[a]	2.25 (−2.30 to 7.20)
Male gender	7 (43.8%)	9 (37.5%)	0.75[b]	NA
Female gender	9 (56.3%)	15 (62.5%)		
BMI	31.0 (24.8–35.6)	28.9 (23.9–36.4)	0.46[a]	1.15 (−2.0 to 4.9)

All continuous values are presented as median with 10th and 90th quantile.
nCPAP = patients treated with nasal CPAP; AW = airway adjunct; BMI = body mass index.
[a]Mann-Whitney U test for nonparametric data.
[b]Fisher exact test.
[c]Calculated using the Hodges-Lehmann approach

may be used to categorize hypercarbia as mild, moderate, or severe based upon Paco$_2$ ranging from 42 to 49, 50 to 59, and ≥60 mm Hg, respectively.[9] During MOAA/S level 2 sedation, moderate or severe hypercarbia was identified in 80% of control group patients and 75% of nCPAP patients when assessed by ABG-1. After a 30-minute period of continued sedation, ABG-2 demonstrated moderate or severe hypercarbia in 70% of control group patients, but in only 40% of patients treated with nCPAP during this interval. The hypothesis that nCPAP treatment would reduce hypercarbia associated with deep sedation was confirmed; however, further investigation is required to provide a more robust estimate of treatment effect.

There are limited published data that quantify a Paco$_2$ increase during deep IV sedation of adult patients. The data collected in this study may be a useful contribution in that regard. DeOliveira et al.[10] reported a similar range of Paco$_2$ increase in a deeply sedated patient population with a lower BMI that was younger and all female. The clinical importance of moderate hypercarbia in this range is not clear. Deleterious effects of acute hypercarbia may include cerebral vasodilation with increase in intracranial pressure, stimulation of the sympathetic nervous system with tachycardia, and both peripheral and pulmonary vasoconstriction. Hypercarbia may provide a beneficial effect by shifting the oxyhemoglobin dissociation curve to the right, thereby promoting oxygen release in tissues. It has been postulated that this may improve healing and reduce wound infection.[11–13] Underlying medical conditions may therefore influence any detrimental impact of hypercarbia. Our protocol excluded patients with conditions associated with greater tendency to develop hypercarbia during deep sedation, including chronic obstructive pulmonary disease, OSA, and BMI >40. Further studies may be useful to determine whether patients with these and other risk factors may develop increased hypercarbia during deep sedation and whether they may derive greater benefit from nCPAP treatment.

Comparison of ABG-1 and ABG-2 in the control group allowed us to observe whether Paco$_2$ changed after an additional 30-minute period of deep sedation. Rather than increasing further with ongoing deep sedation, Paco$_2$ was unchanged at ABG-2 as compared with ABG-1. This suggests a tendency for Paco$_2$ to plateau at a higher level than normal during a constant level of deep sedation.

In keeping with routine practice at the sponsoring facility, the study protocol incorporated a multimodal analgesia plan that included intrathecal morphine and FNB. A study by Abboud et al.[14] found that ventilatory responses to CO$_2$ showed no evidence of depression attributable to either 0.1 or 0.25 mg of intrathecal morphine. Our protocol also permitted the anesthesia team to place an oral or nasal airway when judged to be clinically indicated, but specific criteria for airway placement were not specified. An airway was placed in 40% of all study patients during deep sedation before ABG-1. The degree of hypercarbia associated with deep sedation at ABG-1 was similar across both groups irrespective of the use of an airway. It may be anticipated that an airway reduces upper airway obstruction in a manner similar to nCPAP and, therefore, placement would similarly reduce Paco$_2$. However, this was not observed. Studies have shown that nCPAP treatment not only splints the upper airway pneumatically to reduce obstruction but also reduces the work of breathing, and it may increase pulmonary functional residual capacity.[15,16] We propose that these mechanisms likely contributed to the Paco$_2$ reduction observed with nCPAP treatment but not observed after airway placement. Six of the patients treated with an airway before ABG-1 were randomized to receive nCPAP treatment after ABG-1, and in all 6 patients, ABG-2 revealed a reduction in Paco$_2$ versus ABG-1. The number of such cases was insufficient to assess statistical significance. These issues may warrant further scientific investigation.

The STOPBANG questionnaire has been validated as a useful tool to screen for patients at risk for OSA and, potentially,

at increased risk for airway obstruction during sedation. We used the questionnaire to assess and compare the likely tendency for upper airway obstruction between study groups and the groups had similar scores. One-quarter of our study population had a STOPBANG score of 5 or 6, equally distributed between study groups. Based upon the findings of Chung et al.,[17] who compared STOPBANG score and subsequent diagnosis of OSA by portable polysomnography, it is likely that a significant proportion of the patients in our study had undiagnosed OSA that was moderately severe or severe.

There were several limitations to this study. First, propofol was titrated to achieve a sedation level at or near MOAA/S level 2 in all study patients. It is possible that drug titration using Bispectral Index monitoring may have allowed maintenance of a more standardized level of deep sedation. Second, our study protocol did not restrict airway placement for care of patients deemed to need it. This provision was a potentially confounding variable in the assessment of the effect of nCPAP on $Paco_2$ during deep sedation, but it provided some insight into airway effects on $Paco_2$ during deep sedation. The population size in this pilot study was insufficient to separately correlate variables such as BMI or STOPBANG score with $Paco_2$ during sedation in a statistically significant manner, and how these variables may influence the effectiveness of nCPAP. Finally, we selected a standardized, mid-range pressure setting for the nCPAP device used for this study. An automated CPAP device that optimizes airway pressure to patient needs may have provided superior clinical effects.

In summary, this pilot study demonstrated that deep sedation of TKA patients, in combination with FNB and SAB, resulted in moderate hypercarbia (mean and median $Paco_2$ = 55 mm Hg). The application of nCPAP in the nCPAP group reduced $Paco_2$ versus control group patients who received standard airway management, but the range of such reduction ranged widely, from 1.4 to 12.6 mm Hg. In the absence of nCPAP treatment, the baseline $Paco_2$ among deeply sedated patients who received an airway was not different from that of patients who did not receive an airway. Finally, among control group patients, the initial $Paco_2$ during deep sedation was similar to the $Paco_2$ when measured after an additional 30-minute period of deep sedation. ▪

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