CHEST

Postoperative Oxygen Therapy in Patients With OSA

A Randomized Controlled Trial

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BACKGROUND: Surgical patients with OSA are at increased risk for perioperative complications. Postoperative supplemental oxygen is commonly used, but it may contribute to respiratory depression in patients with OSA receiving opioids. The objective of the study is to investigate the effect of postoperative supplemental oxygen on arterial oxygen saturation (Sa_{O_2}), sleep respiratory events, and CO_2 level in patients with untreated OSA.

METHODS: Consented patients with an apnea hypopnea index (AHI) > 5 events per hour on a preoperative polysomnography were randomized (1:1) to oxygen (O_2 group) or no oxygen (control group). The O_2 group received oxygen at 3 L/min via nasal prongs for three postoperative nights. The primary outcomes were polysomnographic parameters measuring Sa_{O_2}, sleep respiratory events, and P_{CO_2} measured by transcutaneous CO_2 monitor ($P_{tc}CO_2$) on nights 1 through 3. The intention-to-treat and per protocol analysis were completed.

RESULTS: There were 123 patients randomized (O_2 group: n = 62; control group: n = 61). On night 3, the O_2 vs control group had a higher average Sa_{O_2} (95.2% ± 3% vs 91.4% ± 4%, respectively; $P < .001$) and lower oxygen desaturation index (median, 2.3; 25th-75th percentile, 0.2-13.8 vs median, 18.5; 25th-75th percentile, 8.2-45.9 events per hour, respectively; $P < .0001$). The O_2 group had a decreased AHI (median, 8.0; 25th-75th percentile, 2.1-19.9 vs median, 15.6; 25th-75th percentile, 9.5-45.8, respectively; $P = .016$), hypopnea index ($P < .001$), and central apnea index ($P = .026$) and a shortened longest apnea hypopnea duration ($P = .002$). Although time percentage with $P_{tc}CO_2 \geq 55$ mm Hg ≥ 10% on postoperative night 1, 2, or 3 was found in 11.4% patients, there was no difference in $P_{tc}CO_2$ between the groups.

CONCLUSIONS: Postoperative supplemental oxygen was found to improve oxygenation and decrease the AHI without increasing the duration of apnea-hypopnea event or $P_{tc}CO_2$ level. A small number of patients had significant CO_2 retention while receiving supplemental oxygen.

TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT01552304; URL: www.clinicaltrials.gov

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KEY WORDS: hypoventilation; oxygen; sleep apnea; surgery

ABBREVIATIONS: AHI = apnea hypopnea index; CT90 = cumulative time percentage with $Sa_{O_2} < 90\%$; NREM = nonrapid eye movement (sleep); ODI = oxygen desaturation index; OHS = obesity hypoventilation syndrome; PSG = polysomnography; $P_{tc}CO_2$ = P_{CO_2} measured by transcutaneous CO_2 monitor; $P_{tc}CO_2$-CT55 = time percentage with $P_{tc}CO_2 \geq 55$ mm Hg; RCT = randomized controlled trial; REM = rapid eye movement (sleep); Sa_{O_2} = arterial oxygen saturation; SDB = sleep-disordered breathing

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OSA is the most common type of sleep-disordered breathing (SDB). In surgical patients, the prevalence of OSA by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes or polysomnography (PSG) is 7% to 10%,[1,2] with a large proportion remaining undiagnosed.[3] Patients with OSA may have an increased sensitivity to anesthetics or opioids,[4-6] greater upper airway collapsibility,[7,8] and increased risk of postoperative complications.[2,9,10] CPAP therapy is the mainstay treatment for patients with moderate-to-severe OSA, but its adherence remains a challenge.[11-13] For patients with newly diagnosed untreated OSA or suspected OSA, surgical timing may not allow adequate time to establish diagnosis and initiate treatment.[14]

For surgical patients with OSA, supplemental oxygen may be more acceptable than CPAP therapy, but three clinical concerns exist. First, hypoxemia may play a critical role in respiratory arousal in surgical patients with OSA. When supplemental oxygen abolishes hypoxemia, the apnea duration may increase,[15-17] causing hypoventilation as evidenced by hypercarbia, leading to possible life-threatening respiratory depression. Second, postoperative opioids may depress respiration centrally and impair the arousal threshold causing arousal failure, possibly leading to sporadic case of death.[18] The third concern is that supplemental oxygen may mask the ability of oximetry to detect abnormalities in the level of ventilation.[19,20]

To date, no published study has investigated the effect of postoperative supplemental oxygen on patients with newly diagnosed untreated OSA. The objective of this randomized controlled trial (RCT) was to investigate the effect of postoperative supplemental oxygen on Sa_{O_2}, sleep respiratory events, and CO_2 level in patients with untreated OSA. We hypothesize that postoperative supplemental oxygen would improve oxygenation in patients with OSA, without significantly increasing the duration of sleep apneic episodes and arterial CO_2 tension.

Materials and Methods

Trial Design

This prospective RCT was registered at ClinicalTrials.gov (No. NCT01552304). The study was completed at Toronto Western Hospital, University Health Network, Toronto, Ontario, Canada, from February 2012 to December 2015, with Institutional Review Board approval (No. UHN 11-0302-AE). Supplemental oxygen at 3 L/min via nasal prongs was the trial intervention. The primary outcomes were PSG parameters measuring arterial oxygen saturation (Sa_{O_2}), sleep respiratory events (frequency and duration), and P_{CO_2} measured by transcutaneous CO_2 monitor ($P_{tc}CO_2$) on postoperative night 3. Approximately 60% and 7% of patients at our institution receive supplemental oxygen on postoperative nights 1 and 3, respectively.[21] To minimize the cross contamination of the control group, we chose night 3 as the time point for outcome measurement.

Eligibility and Trial Procedures

The inclusion criteria were as follows: (1) elective surgery with $\geq$ 3 nights stay, (2) age 18 to 80 years, and (3) patients at high risk of OSA (STOP-Bang questionnaire score $\geq$ 3)[22] or with diagnosed untreated OSA. Patients with any of the following conditions were excluded: (1) unable to give informed consent; (2) diagnosed OSA with treatment; (3) possible postoperative ventilation; and (4) serum bicarbonate (HCO_3^-) > 30 mml/L, indicating potential hypoventilation, such as obesity hypoventilation syndrome (OHS).

Eligible surgical patients attending preoperative clinic were consented (Fig 1). Recruited patients completed a preoperative PSG at home with a level II 10-channel portable device (Embletta x100; Embla) as previously described.[23] The PSG recording montage consisted of two electroenephalographic channels (C3 and C4), left or right electroculogram, chin muscle electromyograms, nasal cannula (pressure), thoracic and abdominal respiratory effort bands, body position sensor, and pulse oximetry. This montage allows us to measure the parameters on sleep architecture, sleep respiratory events, arousal events, sleep positon, oxygen desaturation, and heart rate. The PSG recordings were manually scored by a PSG technologist according to the American Academy of Sleep Medicine 2007 criteria.[24] Apnea was defined as $\geq$ 90% drop in air flow from baseline for $\geq$ 10 seconds. Apneic episodes were further classified as obstructive, central, or mixed apneas. Hypopnea was defined as $\geq$ 50% reduction in air flow for $\geq$ 10 seconds and $\geq$ 3% decrease in Sa_{O_2} or associated with arousal. Oxygen desaturation index (ODI) is the average number of episodes of desaturation $\geq$ 4% and lasting $\geq$ 10 seconds per hour of sleep.

Patients with an apnea hypopnea index (AHI) $\geq$ 5 events per hour were equally randomized into the oxygen (O_2) group or control group. Allocation was made via a computerized block randomization by a research analyst not involved in the study implementation. The research coordinator, the PSG technologist, and the chart reviewers were blinded to the group allocation. Patients in the control group were managed by anesthesiologists and surgeons as per routine practice, including supplemental oxygen or CPAP therapy as clinically indicated. In the O_2 group, patients received 3 L/min nasal supplemental oxygen for 3 postoperative nights (nights 1-3) in addition to the routine care. Postoperative night 1 was defined as the night of surgery.

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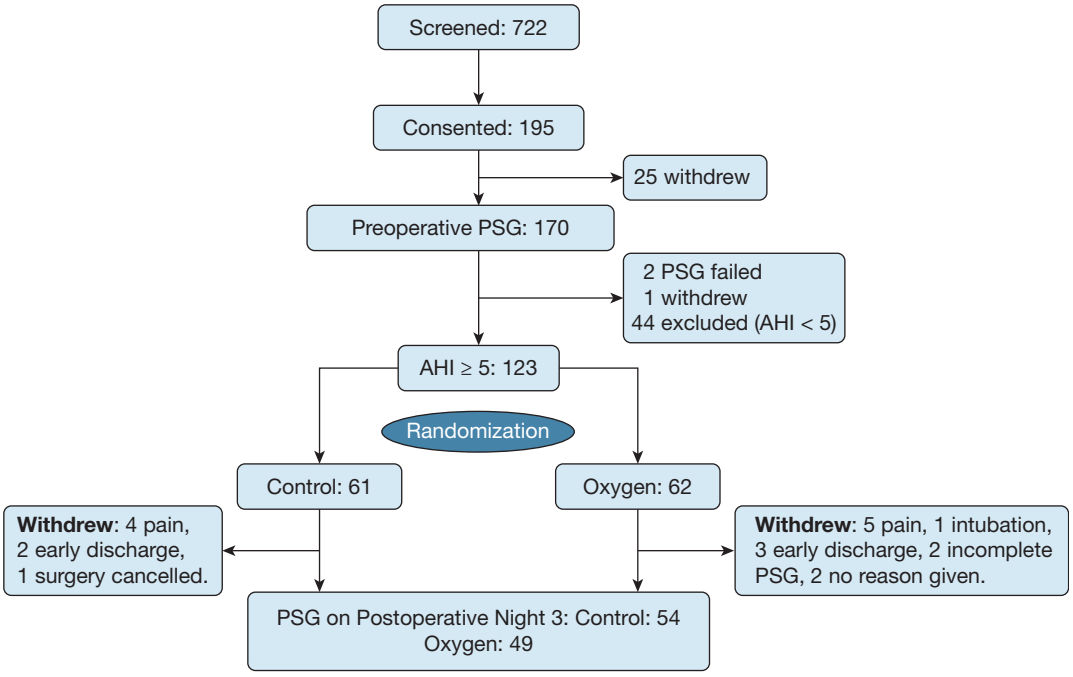

Figure 1 – *Flowchart of patient recruitment and follow-up. AHI = apnea hypopnea index; PSG = polysomnography.*

The study patients completed PSG on night 3. $P_{tc}CO_2$ was monitored with a CO_2 monitor (TCM400; Radiometer Medical ApS) via a probe attached to the inner side of the patient's arm on nights 1 to 3. A related model capable of monitoring both $P_{tc}CO_2$ and Sa_{O_2} (TOSCA 500 instrument; Radiometer Medical ApS) has demonstrated a stable long-term (6 hours) measurement of $P_{tc}CO_2$ without relevant drift.[25] Repeated calibration against gas with a known CO_2 concentration, autocalibration, and membrane replacement was performed according to the manufacturer's recommendations. A total of 255 CO_2 monitorings were done, and 18 (7.6%) failed (recording < 2 hours).

Recording between 9 PM and 6 AM was selected. Unreliable data with extremely low readings ($P_{tc}CO_2$ < 20 mm Hg) were removed. The parameters of mean, median, highest $P_{tc}CO_2$, and time percent with $P_{tc}CO_2$ > 45 and 55 mm Hg were extracted from $P_{tc}CO_2$ recordings. Patients were visited daily by a research coordinator for assistance with the devices and data collection.

Statistical Analysis

Because, to our knowledge, there are no published studies with a similar design, the sample size estimation was based on two studies comparing supplemental oxygen and CPAP in nonsurgical patients with OSA that used cumulative time percentage with Sa_{O_2} < 90% (CT90).[26,27] Based on the average CT90 of these two studies (1.8% in O_2 group vs 4.8% in control group) and the larger SD (4.5%), assuming a two-tailed two-sample *t* test, α error = 0.025, power = 0.85, and equal allocation into two groups, the estimated total sample size was 100. Accounting for a 20% dropout rate, the number of patients randomized would be 100 × 1.20 = 120 patients (60 per group).

Data were entered into a specifically designed Microsoft Access database (Microsoft) and checked for possible errors. SAS 9.3 for Windows (SAS Institute) was used for data analysis. Descriptive statistics were completed on the clinical data and the SDB parameters on the preoperative baseline PSG. An intention-to-treat analysis was first carried out according to randomization (O_2 group vs control group). Missing PSG data (control group: n = 7; O_2 group: n = 13) on night 3 were imputed with preoperative value (last observation carried forward). Because oxygen is often prescribed after surgery, supplementary analyses were carried out according to the dropout and actual use of oxygen (per protocol). In per protocol analyses, regardless of randomization, patients receiving oxygen on night 3 were grouped into the Oxygen group, and those not receiving oxygen were grouped into the No-Oxygen group.

Continuous variables with normal distribution are presented as mean ± SD, and comparison between groups was assessed using an independent two-sample *t* test. Variables with skewed distribution are presented as median (25th-75th percentile), and comparison between groups was performed with the nonparametric Mann-Whitney *U* test. Categorical data are presented as frequency and percentage, and χ^2 test was used for statistical assessment. The *P* values for multiple comparisons were adjusted using the Holm-Bonferroni method. The potential risk factors for postoperative hypercapnia were evaluated by univariate logistic regression.

Results

Study Population and Baseline Data

The recruitment and follow-up of patients are shown in Figure 1. There were 123 patients with AHI ≥ 5 events per hour randomized to the O_2 group (n = 62) or control group (n = 61). The demographic data, average AHI, American Society of Anesthesiologists physical status, comorbidities, postoperative 72-hour opioids requirement, and type of surgery and anesthesia were similar between the groups (Table 1). Excluding the dropouts, 49 (O_2 group) and 54 (control group) patients

TABLE 1] Clinical Data

Variables	Control Group (n = 61)	O_2 Group (n = 62)
Sex, F/M	18 (30)/43 (70)	26 (42)/36 (58)
Age, y	62 ± 12	62 ± 10
BMI, kg/m^2	33 ± 8	33 ± 8
Neck circumference, cm	42 ± 6	40 ± 6
Preoperative AHI	16.1 (9.5-32.8)	16.9 (8.5-29.5)
Mild OSA (AHI: 5-15)	29 (47.6)	26 (41.9)
Moderate OSA (AHI: 15-30)	15 (24.6)	21 (33.9)
Severe OSA (AHI: > 30)	17 (27.9)	15 (24.2)
ASA physical status		
I	0 (0)	1 (1.8)
II	22 (35.9)	17 (26.8)
III	37 (60.4)	42 (67.7)
IV	2 (3.8)	2 (3.6)
Comorbidities		
Hypertension	33 (54)	27 (44)
Diabetes	12 (20)	16 (26)
Gastroesophageal reflux	15 (25)	17 (27)
Smoker	13 (21)	9 (15)
Asthma	8 (13)	5 (8)
COPD	2 (3)	2 (3)
Coronary artery disease	2 (3)	3 (5)
Myocardial infarction	0 (0)	1 (2)
Stroke	0 (0)	1 (2)
Hypothyroidism	6 (10)	4 (7)
72-h opioid requirement, mg[a]	35.4 (17.2-95.7)	46.0 (20.0-82.7)
Type of surgery		
Orthopedic	20 (33)	10 (16)
General	8 (13)	11 (18)
Spine	32 (52)	41 (66)
Urology	1 (2)	0 (0)
Type of anesthesia		
General/regional	48 (79)/13 (21)	55 (87)/8 (13)

Data are presented as frequency (%), median (25th-75th percentile), or mean ± SD. AHI = apnea hypopnea index; ASA = American Society of Anesthesiologists; F = female; M = male.
[a]Opioid requirement was presented as equivalent morphine dose in milligrams.

completed PSG on night 3, respectively (Fig 1). In the O_2 group, one patient with a history of emphysema was excluded because of intubation as a result of hypercarbia and desaturation. The patient was extubated in the ICU 4 hours later. In patients receiving general surgery, four (6.5%) patients in the O_2 group underwent upper abdominal procedures (gastric bypass: n = 3; gastrectomy: n = 1), and three (4.9%) patients in the control group received upper abdominal procedures (gastric bypass: n =2; gastroplasty: n = 1).

Oxygen Therapy

In the control group, despite randomization to no supplemental oxygen, 11 (20%) of the patients received 3 L/min supplemental oxygen with nasal prongs on night 3, as ordered by the health-care teams. In the control group, more patients with severe OSA received supplemental oxygen on postoperative night 3: mild SDB: 10.3% (3/29); moderate SDB: 13.3% (2/15); and severe SDB: 35.3% (6/17). The difference was not significant (P = .090).

Nine patients in the control group also received supplemental oxygen during the daytime. Of them, 7 patients experienced desaturation because of bronchospasm (n = 2), atelectasis (n = 1), and undefined reasons (n = 4); other patients experienced hypotension, hypertension, inadequate pain control, and somnolence. In the O_2 group, all patients received 3 L/min supplemental oxygen on night 3. No patient received CPAP therapy.

Effect of Oxygen on Sao_2

There was no difference in the baseline variables regarding oxygen saturation (average Sao_2, lowest Sao_2, CT90, and ODI) on the preoperative PSG either based on the intention-to-treat (Fig 2A, Table 2) or per protocol (as treated) analysis (Fig 2C, Table 3). On night 3, supplemental oxygen significantly improved oxygen saturation per intention-to-treat (Fig 2B, Table 2) and per protocol analyses (Fig 2D, Table 3).

Effect of Oxygen on SDB

The baseline parameters on the preoperative PSG were similar between the O_2 and control groups (intention-to-treat) (Fig 3A, Table 2) or between the Oxygen and No-Oxygen groups (per protocol analysis) (Table 3). On night 3, based on the intention-to-treat analysis

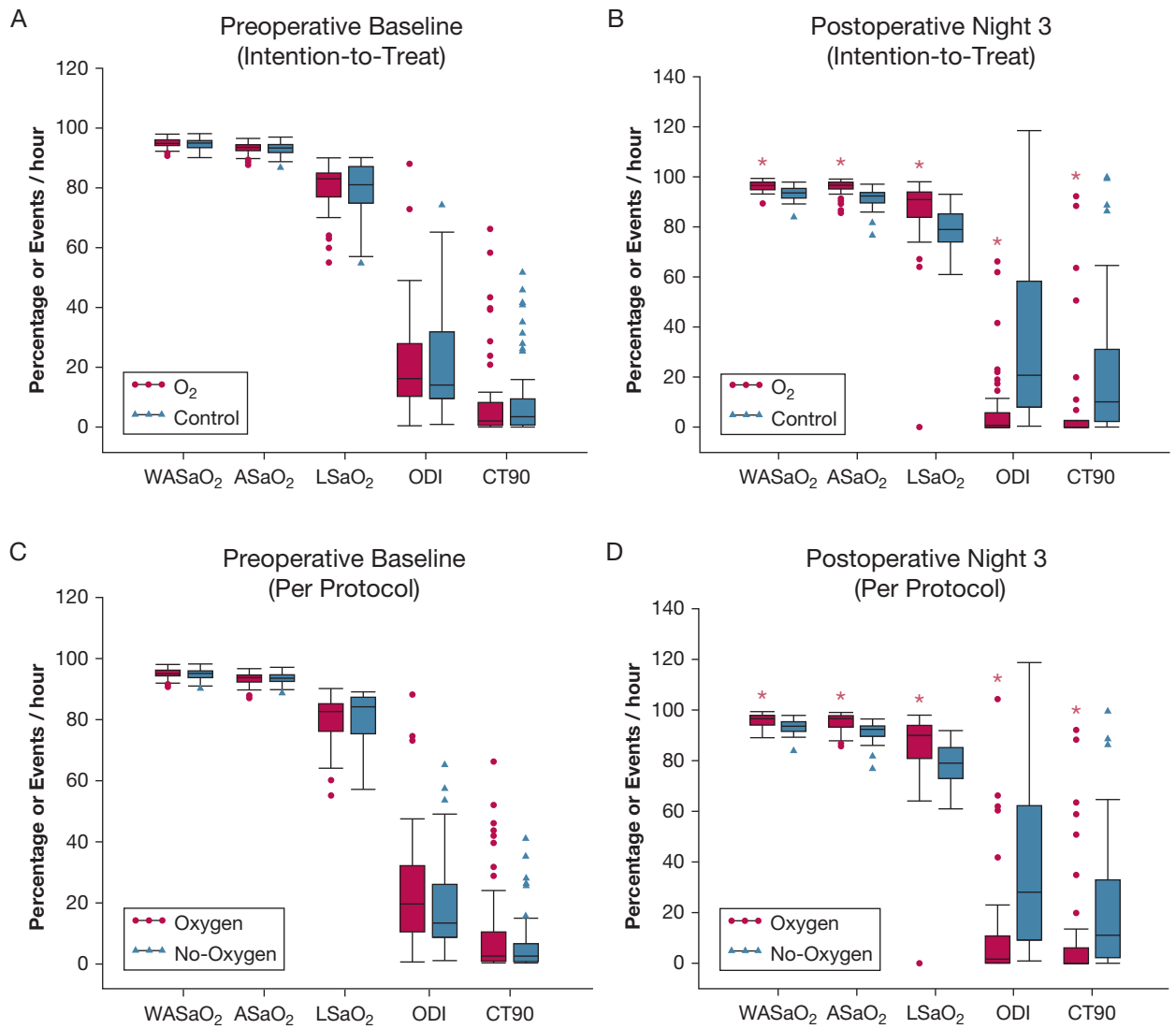

Figure 2 – *A-D, Boxplot depicting changes in parameters measuring oxygen saturation. A, Preoperative, intention-to-treat analysis. B, Postoperative night 3, intention-to-treat analysis. C, Preoperative, per protocol analysis. D, Postoperative night 3, per protocol analysis. The box represents the interquartile range (IQR), the line inside the box represents the median, the upper whisker is drawn from the upper edge of the box to the largest value within 1.5× IQR, the lower whisker is drawn from the lower edge of box to the smallest value within 1.5× IQR, and colorful dot and triangles indicate the values outside 1.5× IQR. ASaO2 = average pulse oxygen saturation (%); CT90 = cumulative time percentage with SaO_2 < 90% (%); LSaO2 = lowest pulse oxygen saturation (%); ODI = oxygen desaturation index (events/h); WASaO2 = wake average pulse oxygen saturation (%). *Adjusted P < .05 vs control or nonoxygen group.*

TABLE 2] Polysomnography Data (Intention-to-Treat)

Variables	Preoperative Baseline				Postoperative Night 3			
	Control Group (n = 61)	O_2 Group (n = 62)	Raw *P* Value	Adjusted *P* Value	Control Group (n = 61)	O_2 Group (n = 62)	Raw *P* Value	Adjusted *P* Value
AHI, events/h	16.1 (9.5-32.8)	16.9 (8.5-29.5)	.869	> .999	15.6 (9.5-45.8)	8.0 (2.1-19.9)	.002	.016
REM-AHI, events/h	36.7 (19.1-50.9)	37.5 (18.6-54.8)	.834	> .999	36.0 (11.0-53.3)	19.0 (0-49.0)	.062	.186
NREM-AHI, events/h	12.4 (5.7-30.5)	14.9 (5.2-17.0)	.882	> .999	13.0 (5.1-44.0)	4.7 (1.6-18.3)	.006	.033
Obstructive apnea index	8.1 (2.4-19.1)	7.0 (2.5-17.0)	.716	> .999	4.8 (1.2-17.5)	3.3 (0.8-14.3)	.421	.421
Central apnea index	0 (0-0.8)	0 (0-0.6)	.570	> .999	0 (0-2.2)	0 (0-0.2)	.015	.078
Mixed apnea index	0 (0-0)	0 (0-0.1)	.490	> .999	0 (0-0)	0 (0-0)	.144	.287
Hypopnea index	7.0 (4.0-11.4)	6.9 (5.0-10.5)	.730	> .999	5.8 (2.4-14.8)	0.4 (0-5.7)	< .0001	< .0001
Respiratory arousal index	5.1 (2.4-9.9)	3.7 (1.6-10.8)	.314	> .999	3.4 (1.0-5.6)	1.1 (0.2-5.6)	.028	.112
RERA index	0.8 (0.3-1.6)	0.8 (0.3-1.9)	.324	> .999	0.3 (0-14.2)	0.3 (0-0.9)	.7004	> .999
Total arousal index	11.4 (7.2-17.2)	11.2 (7.2-16.5)	.517	> .999	8.6 (5.0-13.9)	8.3 (3.9-13.3)	.696	> .999
Mean event duration, s	23.1 (19.8-25.6)	23.2 (18.8-27.5)	.955	> .999	18.6 (16.3-22.1)	18.7 (15.4-23.8)	.746	.746
Longest event duration, s	59.1 (46.0-73.7)	56.2 (44.6-70.8)	.621	> .999	46.5 (30.7-59.7)	39.2 (24.3-51.0)	.053	.105
Oxygen desaturation index	14.1 (9.5-31.8)	16.1 (10.3-27.8)	.828	> .999	18.5 (8.2-45.9)	2.3 (0.2-13.8)	< .0001	< .0001
Lowest Sao_2	79.6 ± 8.5	80.5 ± 7.4	.862	> .999	78.6 ± 7.9	85.3 ± 13.9	< .0001	< .0001
CT90	3.4 (0.6-9.2)	1.9 (0.5-8.0)	.532	> .999	9.4 (1.6-30.5)	1.0 (0-7.9)	< .0001	< .0001
Average Sao_2	93.1 ± 1.9	93.3 ± 1.9	.417	> .999	91.4 ± 3.5	95.2 ± 3.2	< .0001	< .0001
Wake Sao_2	94.6 ± 1.6	95.0 ± 1.5	.363	> .999	93.5 ± 2.8	95.8 ± 2.2	< .0001	< .0001

Data are presented as median (25th-75th percentile), mean ± SD, or as otherwise indicated. Central apnea index = average hourly number of central apnea episodes; CT90 = cumulative time percentage with Sao_2 < 90%; Hypopnea index = average hourly number of hypopnea episodes; Mixed apnea index = average hourly number of apnea episodes with characteristics of both obstructive or central apnea; NREM-AHI = apnea hypopnea index during non-rapid eye movement sleep; Obstructive apnea index = average hourly number of obstructive apnea episodes; REM-AHI = apnea hypopnea index during rapid eye movement sleep; RERA index = respiratory-related arousal index; Respiratory arousal index = average hourly sleep arousals because of respiratory events; Sao_2 = arterial oxygen saturation; Wake Sao_2 = average Sao_2 while patient awake during polysomnography. See Table 1 legend for expansion of other abbreviation.

TABLE 3] Polysomnography Data (Per Protocol, 2 Polysomnographies)

Variables	Preoperative Baseline				Postoperative Night 3			
	No-Oxygen Group (n = 44)	Oxygen Group (n = 59)	Raw *P* Value	Adjusted *P* Value	No-Oxygen Group (n = 44)	Oxygen Group (n = 59)	Raw *P* Value	Adjusted *P* Value
AHI, events/h	13.8 (9.1-28.1)	17.9 (8.8-32.8)	.484	> .999	17.1 (10.2-58.4)	4.4 (1.3-19.4)	.0002	.002
REM-AHI, events/h	28.9 (18.1-47.2)	37.7 (17.1-54.8)	.665	> .999	38.4 (19.6-54.7)	6.9 (0-36.0)	.0009	.005
NREM-AHI, events/h	12.1 (5.5-26.7)	16.2 (5.7-36.3)	.432	> .999	14.90 (6.5-55.2)	3.6 (1.1-17.6)	.0009	.005
Obstructive apnea index	6.5 (2.3-12.2)	7.6 (2.9-21.0)	.362	> .999	4.8 (1.2-18.8)	2.4 (0.8-14.3)	.181	.242
Central apnea index	0.2 (0-0.8)	0 (0-0.6)	.474	> .999	0.3 (0-3.7)	0 (0-0.2)	.007	.026
Mixed apnea index	0 (0-0)	0 (0-0.1)	.486	> .999	0 (0-0.2)	0 (0-0)	.086	.240
Hypopnea index	6.5 (4.0-10.9)	7.4 (5.0-11.2)	.353	> .999	8.3 (3.7-20.5)	0.1 (0-3.2)	< .0001	< .0001
Respiratory arousal index	4.5 (2.2-10.1)	5.6 (1.9-11.2)	.484	> .999	3.3 (0.9-5.4)	1.0 (0.2-5.7)	.081	.242
RERA index	0.7 (0.3-1.4)	0.9 (0.3-2.1)	.141	0.846	0.3 (0-1.3)	0.3 (0-0.7)	.529	> .999
Total arousal index	10.6 (7.0-16.4)	12.2 (9.3-18.0)	.183	0.916	7.8 (3.8-14.0)	9.4 (5.2-13.9)	.416	> .999
Mean event duration, s	23.5 (19.8-26.0)	23.4 (18.9-27.6)	.941	> .999	18.7 (16.2-22.6)	17.1 (15.1-21.2)	.147	.147
Longest event duration, s	57.6 (45.9-75.2)	61.3 (46.0-74.8)	.665	> .999	49.6 (33.6-66.6)	33.8 (21.3-47.0)	.001	.002
Oxygen desaturation index	13.2 (8.7-25.9)	19.5 (10.3-31.8)	.245	> .999	28.1 (9.1-62.0)	1.5 (0.2-10.6)	< .0001	< .0001
Lowest Sao_2	80.5 ± 8.2	79.9 ± 8.0	.417	> .999	78.0 ± 18.0	85.9 ± 14.0	< .0001	< .0001
CT90	2.2 (0.5-6.2)	2.3 (0.5-10.1)	.435	> .999	11.0 (2.3-32.9)	0.2 (0-5.9)	< .0001	< .0001
Average Sao_2	93.4 ± 1.8	93.0 ± 2.0	.385	> .999	91.5 ± 3.7	95.3 ± 3.3	< .0001	< .0001
Wake Sao_2	94.8 ± 1.7	94.8 ± 1.6	.946	> .999	93.2 ± 3.0	95.9 ± 2.3	< .0001	< .0001

Data are presented as median (25th-75th percentile), mean ± SD, or as otherwise indicated. See Table 1 and 2 legends for expansion of abbreviations.

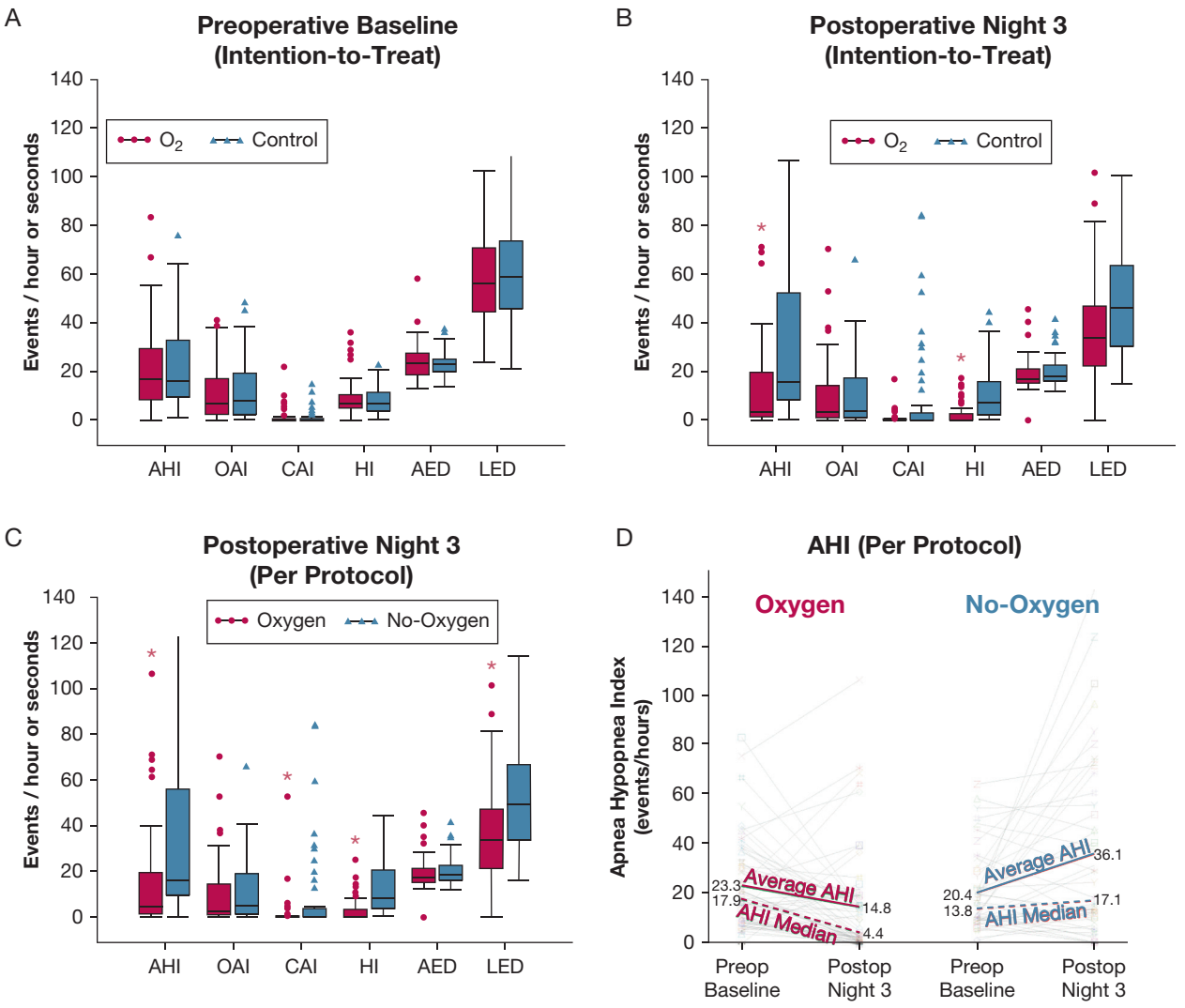

Figure 3 – *A-D, Impact of oxygen therapy on frequency and duration of sleep-disordered breathing events. The boxplots represent the difference between the two groups in preoperative measurement, intention-to-treat analysis (A), postoperative night 3, intention-to treat analysis (B), and per protocol analysis (C). Panel D shows AHI change from preoperative to postoperative night 3 in two groups, per protocol analysis. AED = average event duration (s); CAI = central apnea index (events/h); HI = hypopnea index (events/h); LED = longest event (apnea-hypopnea) duration (s); OAI = obstructive apnea index (events/h); Postop = postoperative; Preop = preoperative. See Figure 1 legend for expansion of other abbreviation. *Adjusted P < .05 vs control or No-Oxygen group.*

(Fig 3B, Table 2), the O_2 group had a lower AHI, nonrapid eye movement (sleep) (NREM)-AHI, and hypopnea index. Based on per protocol analysis (Fig 3C, 3D, Table 3), the O_2 group also demonstrated a lower AHI, NREM-AHI, rapid eye movement (sleep) (REM)-AHI, central apnea index, and hypopnea index. The longest apnea-hypopnea event duration was shortened. In the O_2 group, AHI was significantly reduced from preoperative baseline to night 3 (median, 17.9; 25th-75th percentile, 8.8-32.8 to median, 4.4; 25th-75th percentile, 1.3-19.4 events per hour; $P < .001$) (Fig 3D). In the No-Oxygen group, AHI increased from a median 13.8 (25th-75th percentile, 9.1-28.1) preoperatively to 17.1 (25th-75th percentile, 10.2-58.4) events per hour on night 3 ($P = .132$) (Fig 3D). In all patients receiving oxygen supplementation on postoperative night 3, patients with severe SDB vs mild SDB had significantly more AHI reduction (median, −31.0; 25th-75th percentile, −41.4 to −11.1 vs median, −5.3; 25th-75th percentile, −7.8 to 5.7 events per hour, respectively; $P < .05$).

No difference occurred in the sleep architecture between groups on preoperative baseline or night 3, either based on intention-to-treat or per protocol analysis (data not shown).

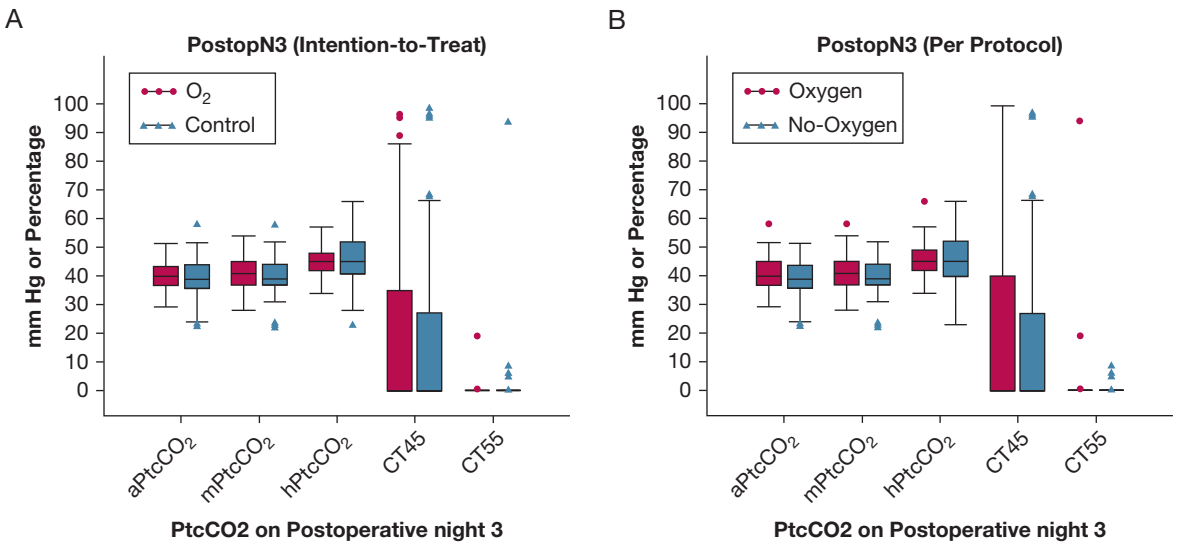

Figure 4 – *A, B, Boxplot to show the impact of oxygen therapy on CO_2 level of postoperative night 3. A, Intention-to-treat analysis. B, Per protocol analysis. aPtcCO2 = average P_{CO_2} measured by transcutaneous CO_2 monitor (mm Hg); CT45 = cumulative time percentage with P_{CO_2} measured by transcutaneous CO_2 monitor > 45 mm Hg (%); CT55 = cumulative time percentage with P_{CO_2} measured by transcutaneous CO_2 monitor > 55 mm Hg (%); hPtcCO2 = highest P_{CO_2} measured by transcutaneous CO_2 monitor (mm Hg); mPtcCO2 = median P_{CO_2} measured by transcutaneous CO_2 monitor (mm Hg); PostopN3 = postoperative night 3.*

Effect of Oxygen on $P_{tc}CO_2$

The $P_{tc}CO_2$ data on nights 1 through 3, based on intention-to-treat analysis, were summarized in Figure 4A and Table 4. No difference was found between the control and O_2 groups in the average $P_{tc}CO_2$, median $P_{tc}CO_2$, number of patients with $P_{tc}CO_2$ > 45 mm Hg or $P_{tc}CO_2$ > 55 mm Hg, and the overnight cumulated time percentage with $P_{tc}CO_2$ > 45 mm Hg or time percentage with $P_{tc}Co_2 \geq$ 55 mm Hg ($P_{tc}CO_2$-CT55). The per protocol analysis did not show a difference either (Fig 4B). However, a significant increase in $P_{tc}CO_2$ was found in a small number of patients. A total of 14 (11.4%) patients had $P_{tc}CO_2$-CT55 ≥ 10% on postoperative night 1, 2, or 3 (Table 5). Most (93%; 13/14) were receiving oxygen therapy at the time of elevated CO_2 levels (control group: n = 7; O_2 group: n = 6). A large number (9/14) experienced the highest $P_{tc}CO_2$ on night 1. Only one patient had the comorbidity of COPD. Two patients experienced prolonged overnight desaturation (Sa_{O_2} < 90%). No patient had life-threatening complications.

To explore the potential risk factors for postoperative hypercapnia, we used $P_{tc}CO_2$-CT55 ≥ 10% as the dependent variable to individually evaluate its association with oxygen supplementation, age, sex, BMI, neck circumference, type of surgery and anesthesia, comorbidities (COPD, asthma, diabetes, and smoker), American Society of Anesthesiologists physical status, preoperative HCO_3^-, average Sa_{O_2}, lowest Sa_{O_2}, CT90, or ODI. None of these factors was found significantly associated with postoperative hypercapnia, with CT90 and lowest Sa_{O_2} having a *P* value < 0.1 (*P* = .061 and *P* = .096, respectively).

Discussion

To date, this is the first RCT on postoperative supplemental oxygen in surgical patients with newly diagnosed untreated OSA. Postoperative supplemental oxygen was found to improve oxygenation and decreased AHI without significantly increasing the apnea-hypopnea event duration or $P_{tc}CO_2$ level. Eleven percent of patients had significant CO_2 retention while receiving supplemental oxygen.

Hypoxemia is an immediate consequence of apneic and hypopnea events. OSA-related complications could be induced by hypoxemia.[28] Our data from the intention-to-treat analysis show that supplemental oxygen significantly decreased AHI, NREM-AHI, and hypopnea index. The results from the per protocol (as treated) analysis show that supplemental oxygen not only decreased AHI, NREM-AHI, and hypopnea index but also decreased REM-AHI, central apnea index, and longest apnea-hypopnea event duration. Because 20% of patients in the control group received supplemental oxygen, results from the per protocol analysis would better reflect the effects of supplemental oxygen on sleep respiratory events.

TABLE 4] Transcutaneous P_{CO_2} ($PtcCO_2$) on First Three Postoperative Nights (Intention-to-Treat)

Variables	Group	Postoperative Night 1	Postoperative Night 2	Postoperative Night 3
No., control group/O_2 group		40/36	38/42	42/39
Time monitored, h	Control	8.4 (7.7-9.0)	8.1 (6.4-9.0)	7.8 (3.8-8.5)
	O_2	8.3 (7.2-9.0)	8.1 (7.2-9.0)	8.5 (7.4-9.0)
	P	.460	.896	.009
Average $P_{tc}CO_2$, mm Hg	Control	41.0 ± 9.5	40.9 ± 6.6	39.4 ± 7.8
	O_2	39.4 ± 7.9	40.3 ± 5.5	40.5 ± 5.6
	P	.382	.455	.947
Median $P_{tc}CO_2$, mm Hg	Control	41.1 ± 9.6	41.1 ± 6.8	39.9 ± 8.2
	O_2	39.4 ± 8.3	40.5 ± 5.8	40.8 ± 5.9
	P	.362	.460	.923
Highest $P_{tc}CO_2$, mm Hg	Control	47.4 ± 11.9	46.3 ± 8.4	45.8 ± 8.5
	O_2	44.8 ± 8.1	44.5 ± 6.6	44.7 ± 6.1
	P	.234	.195	.146
$P_{tc}CO_2 > 45$ mm Hg	Control	16 (44.4)	16 (42.1)	18 (42.9)
	Oxygen	18 (45.0)	17 (40.5)	16 (41.0)
	P	.961	.883	.868
Time percent $P_{tc}CO_2 > 45$ mm Hg	Control	0 (0-48.6)	0 (0-27.6)	0 (0-27.0)
	O_2	0 (0-14.1)	0 (0-23.8)	0 (0-39.9)
	P	.950	.970	.838
$P_{tc}CO_2 > 55$ mm Hg	Control	8 (20.0)	4 (10.5)	5 (11.9)
	O_2	5 (13.9)	3 (7.1)	3 (7.7)
	P	.480	.593	.714
Time percent $P_{tc}CO_2 > 55$ mm Hg	Control	0 (0-0)	0 (0-0)	0 (0-0)
	O_2	0 (0-0)	0 (0-0)	0 (0-0)
	P	.478	.590	.519

Data are presented as No. (%), median (25th-75th percentile), mean ± SD, or as otherwise indicated. $P_{tc}CO_2$ = P_{CO_2} measured by transcutaneous CO_2 monitor.

In previous studies of nonsurgical patients with OSA, the effect of supplemental oxygen on sleep respiratory events was inconsistent. Compared with breathing room air, breathing oxygen reduced the frequency of apnea, which may be related to increased Pa_{CO_2}, stimulating ventilation during sleep.[15] In contrast, other studies found that the length of apnea was increased by breathing oxygen,[29] and AHI was not decreased.[17,30] In peritoneal dialysis patients with OSA, nocturnal oxygen therapy decreased hypopnea and central apnea.[31] Oxygen effectively reduced central sleep apnea in patients with eucapnia, but obstructive and mixed apneas were unaffected by oxygen.[32] In this study, the decrease in AHI was mainly caused by a drop in hypopnea index and, to a minor degree, central apnea. Because hypopnea index was not separated into central or obstructive hypopnea component, the contributing role of each cannot be determined. Another possible mechanism for the reduction of hypopnea events is caused by improvement of oxygenation by supplemental oxygen, rendering less events meeting hypopnea criterion (Tables 2, 3).

The discrepancy in the effect of supplemental oxygen on sleep respiratory events both between subjects and between studies may be caused by the various pathophysiologic mechanisms causing OSA.[33] The mechanisms include the following: (1) an anatomically collapsible upper airway characterized by a high passive critical closing pressure[34]; (2) inadequate response of the upper airway dilator muscles during sleep characterized by minimal increase in electromyographic activity in response to progressive negative pharyngeal pressure[35,36]; (3) waking up prematurely to airway narrowing characterized by a low respiratory arousal threshold[37,38]; and (4) an oversensitive ventilatory

TABLE 5] Detailed Information of Patients With Time Percentage of $P_{tc}CO2 \geq 55$ mm Hg $\geq 10\%$ on Postoperative Night 1, 2, or 3

Patient No.	Age, y	Sex	BMI, kg/m^2	Neck, cm	ASA Class	Preoperative AHI	Oxygen	Night With Highest $P_{tc}CO_2$	72-h Opioids in Morphine Equivalent, mg	Mean $P_{tc}CO_2$	Highest $P_{tc}CO_2$	$P_{tc}CO_2$-CT55	Sa_{O_2} CT90	Comorbidities	Postoperative Complications[a]
1	58	M	37.6	41	3	10.1	Yes	1	544.5	76.5	96.0	95.6	8.1	None	Inadequate pain control
2	51	F	30.9	37	3	16.4	Yes	1	113.3	57.8	62.0	86.3	0	Smoker	Incision leaking
3	80	M	24.3	42	3	18.7	Yes	1	32.5	56.5	67.0	63.9	1.4	Arrhythmia	None
4	65	M	28.4	43	3	47.6	Yes	1	105.0	54.2	58.0	25.9	19.8	HTN, DM, arrhythmia	Hypertension, hypotension, somnolence
5	54	F	44.4	43	2	64.4	Yes	1	17.7	53.2	59.0	29.0	0.2	DM, smoker	None
6	77	F	44.9	41	3	28.8	Yes	1	30.8	53.2	59.0	29.0	98.0	GERD, DM, arthritis	Desaturation
7	76	F	37.4	41.5	3	45.6	Yes	1	30.0	52.7	68.0	29.0	0.5	GERD, DM	Hypotension, desaturation, somnolence
8	55	M	26.9	40	3	30.8	Yes	1	75.7	51.8	60.0	13.9	55.0	None	Desaturation, hypotension
9	64	M	46.4	53	3	21.7	Yes	1	30.0	43.5	61.0	17.4	23.9	HTN, DM, hypothyroidism	Hypertension, hypotension, desaturation, inadequate pain control
10	46	F	25.8	41	2	9.5	Yes	2	7.5	58.3	63.0	83.5	0.0	GERD, DM, smoker	Confusion, desaturation
11	63	F	43.6	42	4	39.8	Yes	2	49.8	54.9	58.0	52.7	12.0	None	Inadequate pain control, desaturation
12	60	F	32.6	38	3	7.4	Yes	3	0	58.4	66.0	93.8	0.0	HTN, GERD, smoker, COPD	Hypertension, bronchospasm, inadequate pain control

(Continued)

TABLE 5] (Continued)

Patient No.	Age, y	Sex	BMI, kg/m^2	Neck, cm	ASA Class	Preoperative AHI	Oxygen	Night With Highest $P_{tc}CO_2$	72-h Opioids in Morphine Equivalent, mg	Mean $P_{tc}CO_2$	Highest $P_{tc}CO_2$	$P_{tc}CO_2$-CT55	Sao_2 CT90	Comorbidities	Postoperative Complications[a]
13	62	M	27.8	42	3	16.3	Yes	3	241.0	51.3	57.0	19.0	9.1	GERD	Hypotension, desaturation, inadequate pain control, motor deficit
14	44	M	30.4	42	2	10	No	2	154.0	53.3	63.0	29.1	94.6	None	None

DM = diabetes mellitus; GERD = gastroesophageal reflux disease; HTN = hypertension; $P_{tc}CO_2$-CT55 = time percentage with $P_{tc}CO_2 \geq 55$ mm Hg. See Table 1, 2, and 4 legends for expansion of other abbreviations.
[a]Postoperative complications include bronchospasm (expiratory wheezing), desaturation ($Sao_2 < 90\%$ and/or cyanosis and/or $Pao_2 < 60$ mm Hg requiring supplemental oxygen therapy), hypertension (systolic BP > 200 mm Hg for > 15 min), hypotension (systolic BP < 80 mm Hg for > 15 min), inadequate pain control (pain cannot be controlled by regular dose of narcotics), motor deficit (unexpected inability to lift the upper or lower extremity for > 1 h, excluding spinal or epidural anesthesia), and somnolence (state of feeling drowsy).

control system characterized by high loop gain.[38] With the different pathophysiologic mechanisms, strategies to target treatment would be more effective.

Supplemental oxygen was shown to decrease AHI in patients with high loop gain, but not in patients with low loop gain.[39] The high loop gain in patients with OSA is induced by intermittent hypoxia and can be reversed by preventing hypoxia with supplemental oxygen or CPAP therapy.[40,41] Supplemental oxygen increases ventilatory stability in patients with ventilatory instability (high loop gain).[39] Further work is needed to determine whether patients with OSA caused by other pathophysiologic processes would benefit from supplemental oxygen.

One concern for surgical patients with OSA is that supplemental oxygen could lead to longer apneas events with associated hypercapnia and sustained hypoventilation. In previous studies, the duration of apnea was found increased by supplemental oxygen.[16,29] In a study of 28 asymptomatic men with heavy snoring, the frequency of apneas was not decreased, but the length of apnea was increased by supplemental oxygen.[29] In another study of 20 obese men with sleep apnea and COPD, mean event duration and end apneic P_{CO_2} were increased by supplemental oxygen (4 L/min).[16] In this study, we found that the duration of the longest apnea-hypopnea events was shortened by supplemental oxygen. There are two possible reasons for our finding of shortening of longest apnea-hypopnea event duration. The first reason is because of the difference in study populations. In our study, only 3% of patients had COPD, whereas in the Alford et al study,[16] all patients had COPD. We also excluded patients with possible OHS by not recruiting patients with $HCO_3 \geq 30$ mEq/L. Patients with COPD and OHS are more likely to suffer from respiratory suppression and CO_2 retention with supplemental oxygen.[42] The second reason is the definition of event duration. In our study, the duration was calculated based on both apnea and hypopnea events. Supplemental oxygen eliminated some of the hypopnea events by making them not meeting hypopnea criteria because of improved oxygen saturation, possibly leading to shortened duration of apnea-hypopnea events.

OHS is present in 10% to 20% of patients with OSA.[43] Supplemental oxygen may worsen hypercapnia in patients with OHS.[42] To avoid recruiting patients with OHS, patients with serum HCO_3^- levels > 30 mmol/L were excluded. A low flow (3 L/min) of oxygen was

used. These factors may contribute to no overall difference in $P_{tc}CO_2$ metrics between groups on nights 1 through 3, either on intention-to-treat or per protocol analysis. A small number (11.4%) of patients experienced substantial CO_2 retention, especially those receiving oxygen on night 1. When opioids or hypnotics are used, administration of oxygen may cause significant CO_2 retention in a small number of patients.[20] To define the risk factors for postoperative hypercapnia, we need a study with a larger sample size.

Increased inspired oxygen may result in greater opioid-induced respiratory depression.[20] When supplemental oxygen is given, it may mask the ability of oximetry to detect abnormalities in the level of ventilation.[19,20] Additional methods for detecting hypoventilation, such as continuous measurement of respiratory rate and end-tidal CO_2 monitoring, may be needed.

A limitation of this study is cross contamination. To ensure the safety of the participants, the perioperative care team could order oxygen or CPAP if deemed clinically necessary. Although no CPAP therapy was prescribed, a high percentage of patients in the control group received postoperative supplemental oxygen. This may interfere with the interpretation of the results. To minimize the effect of cross contamination, outcomes were measured on night 3 with less patients in the control group receiving oxygen, and data were subjected to per protocol (as treated) analysis to delineate the true effect of oxygen therapy. Another limitation is that the amplitude of postoperative change in $P_{tc}CO_2$ could not be determined because of the lack of preoperative baseline data of $P_{tc}CO_2$. This may have led to an underestimation of the true $P_{tc}CO_2$ changes with oxygen. Finally, the results are not generalizable to patients with OHS because of the exclusion of patients with serum $HCO_3^- > 30$ mmol/L.

In conclusion, postoperative supplemental oxygen improved oxygenation in surgical patients with OSA. Supplemental oxygen decreased AHI, hypopnea index, and central apnea index and shortened the longest apnea-hypopnea event duration. Although no overall difference was found between groups in $P_{tc}CO_2$ level, a significant increase of $P_{tc}CO_2$ was found in 11.4% of patients, especially those receiving oxygen on postoperative night 1. Postoperative supplemental oxygen could be used as an alternative therapy for patients with OSA not adherent to CPAP, newly diagnosed patients without adequate time to initiate CPAP therapy, or patients with suspected OSA. Additional monitoring of respiratory rate or $P_{tc}CO_2$, especially on postoperative night 1, is recommended. Further work is needed to identify OSA phenotypes which would benefit from postoperative supplemental oxygen and to identify which patients should be monitored for hypoventilation with respiratory rate or $P_{tc}CO_2$.

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