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Review Article

Death or near-death in patients with obstructive sleep apnoea: a compendium of case reports of critical complications

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Abstract

The care of surgical patients with obstructive sleep apnoea (OSA) invokes concerns with safety and liability because of the risk that exists for perioperative death or near-death. The purpose of this review is to analyse the available literature to identify risk factors for perioperative critical complications in patients with OSA. Literature reports were screened for life threatening complications and deaths in surgical patients with OSA. The critical complications were sub-grouped as death/near-death events (death and anoxic brain damage) *vs* critical respiratory events (CRE)/other events and analysed for various risk factors. Both univariate and multivariate analyses were conducted to identify the potential risk factors.
In total, 15 case reports and two medico-legal reports, comprising of 60 total patients with OSA were included in our analysis. Overall, there were 43 deaths or near-death events and 12 critical respiratory events and five other life threatening events. Ten patients (17%) with OSA were undiagnosed before surgery. Only 31% (11/35) were on preoperative continuous positive airway pressure (CPAP), with 36% (4/11) of them continuing CPAP in the postoperative period. The majority of them received a morphine equivalent daily dose less than 10 mg. Eighty percent of the events occurred in the first 24 h and 67% occurred on the general hospital ward.
Patients with OSA are at risk of critical complications including death during the initial 24 h after surgery. Morbid obesity, male sex, undiagnosed OSA, partially treated/untreated OSA, opioids, sedatives, and lack of monitoring are risk factors for death or near-death events.

Key words: death; obstructive sleep apnoea; postoperative complications; screening; surgery

Obstructive sleep apnoea (OSA) is a highly prevalent sleep breathing disorder which may be associated with an increased risk of cardiopulmonary complications for patients undergoing surgical procedures.[1–3] Studies using screening questionnaires found that 20 to 40% of elective surgical patients were at high risk for OSA.[4 5] These patients may have undiagnosed OSA at the time of their surgery.[6 7] The effects of anaesthetics, sedatives and opioids on ventilatory responsiveness, arousal mechanisms and upper airway muscle tone have been implicated in potentially aggravating OSA in the postoperative period leading to life threatening hypoxia and hypercapnia, particularly in patients with untreated OSA.

Respiratory depression may occur in patients with OSA who receive opioids in the postoperative period. Patients with OSA may be at a higher risk of respiratory arrest when they are given analgesics to treat postoperative pain, especially in an unmonitored environment. Recent literature has shown that patients with OSA can develop critical complications in the postoperative period.[1 3 8] A closed malpractice claims of 12 surgical patients with OSA who were found 'dead-in-bed' was recently reported.[9] Identifying risk factors for these postoperative deaths in patients with OSA constitutes a significant step in advancing perioperative patient safety. As deaths or near-deaths are rare events, prospective studies are often unable to provide sufficient information for these critical complications. To overcome this knowledge gap, case reports have a unique value in providing crucial insight on rare clinical outcomes.[10] The objective of this review is to identify the perioperative pattern and risk factors for major mortality and morbidity in patients with OSA by evaluating the medical literature and assessing the available case reports, case series and medico-legal reports in the perioperative period.

Methods

We screened case reports, case series and medico-legal reports to analyse life threatening complications and deaths in adult patients (≥18 yr) with OSA in the perioperative period. The literature search was performed with the help of an expert librarian. We searched the Medline database during the period of 1946 - June 2016. Our search was restricted to English language articles only.

The search used the Medical Subject Heading (MeSH) free-text and index terms "perioperative," "complications," "adverse events," "anaesthesia," "anesthesia," "obstructive sleep apnea," "obstructive sleep apnea syndrome," "obstructive sleep apnoea," "obstructive sleep apnoea syndrome," "sleep disordered breathing," "obesity hypoventilation syndrome," "apnea or apnoea," "hypopnea or hypopnoea." To supplement our database searches, a citation search of references from primary or review articles was also performed.

Study population

The inclusion criteria were as follows: (1) case reports, case series reports or medico-legal reports with information available on OSA; (2) patients who underwent a surgical procedure that was associated with a life threatening adverse event or death that was attributable to the presence of OSA, which was either suspected or diagnosed preoperatively.

Studies were selected independently by two reviewers (Y.S. and M.N.) who screened the titles and abstracts to determine whether the studies met the eligibility criteria. Both reviewers independently considered all materials for possible inclusion. In the preliminary phase of the review, irrelevant articles were excluded based on the title of the article. In the later stage, the abstract and/or full-text articles were evaluated to determine suitability for inclusion. The number of excluded articles and the rationale for exclusion were recorded. Any disagreements were resolved by consensus or by consulting the senior author (F.C.).

Data extraction

The following information was collected from each study: author, yr of publication, age, sex, BMI, mode of diagnosis, severity (AHI events h^{-1}) of OSA, data on continuous positive airway pressure (CPAP) therapy, type of surgery and anaesthesia, administration (and routes) of opioids and sedatives, serious postoperative outcomes and timing and location of the outcomes.

Outcome data

Cases were categorized by outcomes: death, anoxic brain injury, critical respiratory events (CREs) and other life threatening events attributable to OSA. A CRE was defined as an unresponsive and hypoxic or apneic patient needing rescue by medical therapy or resuscitation. Other life threatening complications included cardiac complications such as heart block or cardiac arrest with successful resuscitation of the patient.

Statistical analysis

Our main objective was to analyse all the critical perioperative outcomes associated with OSA in relation to the diagnosis, severity and treatment of OSA, opioid/sedative administration, timing and location of the events.

Frequency statistics were presented about perioperative patterns (e.g. timing and location) for major mortality and morbidity in patients with OSA. Critical complications were sub-divided into two groups based on the severity of complications - death/near-death events (death and anoxic brain damage) *vs* CREs/other events to analyse various risk factors such as the diagnosis and severity of OSA, preoperative and postoperative CPAP use and opioid use (mode and dose). Both non-parametric (χ^2) and parametric statistics (univariate and multivariate logistic regressions) were conducted to identify the potential risk factors by pooling together individual patient data (IPD) across all studies. Age (≥41 yr *vs*<41 yr), sex, BMI category (≥35 kg/m^2 *vs*<35 kg/m^2), and presence or absence of comorbidities served as the covariates in the logistic model. We used Stata version 14 for data analysis.[11]

Results

Our initial electronic search identified 935 case reports or case series and 73 medico-legal reports. After the initial screening, 920 case reports or case series and 71 medico-legal reports were excluded because they did not satisfy the predetermined eligibility criteria. Only reports of mortality and near-deaths associated with patients with suspected or diagnosed OSA undergoing surgery were included. In total, 15 case reports and two medico-legal reports were included in our analysis (Fig. 1). Seventy percent of the reports are from the USA, 18% from Canada and 12% from Europe.

The descriptive data of the population included in the selected case-reports are summarized in Table 1. Details of the critical postoperative events in patients with OSA are listed in Table 2.

In our analysis of 15 case reports and two medico-legal reports, a total of sixty patients with OSA suffered critical complications. Overall, there were 26 deaths, 17 anoxic brain injuries, 12 CREs and five other life-threatening complications including two patients who were successfully resuscitated from cardiac arrests, and three patients with heart blocks. Sixty-two percent were males and 38% were females. The mean age of males was 49(9) yr (mean SD), and the mean age of females was 46(8) yr. The BMI was 42(13) kg m^{-2}. Among the sixty patients, 12 underwent orthopaedic surgery, 12 general surgery, 10 bariatric surgery, 10 upper airway surgeries, three ear, nose, and throat procedures, four cardiac surgery and the remaining nine various procedures such as genitourinary surgery. Table 3 presents the summary of characteristics of risk factors associated with

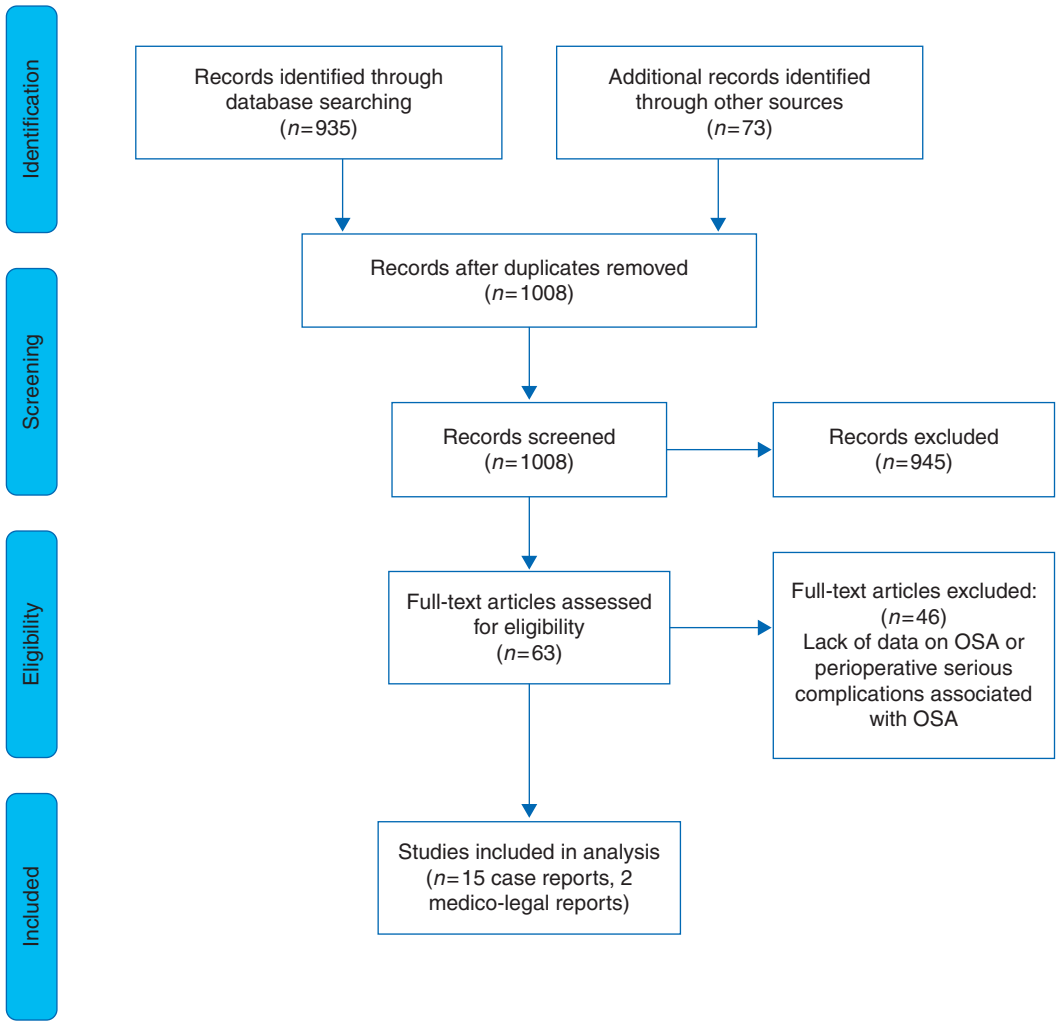

Fig 1 Flow chart of study selection process. *n*, Number; OSA, Obstructive Sleep Apnoea.

death/near-death and CRE/other events. Table 4 presents the analysis of the various risk factors in relation to death/near-death and CRE/other events.

Diagnosis of OSA

Among 60 patients with death or near-death complications, 83% (50/60) of patients had a preoperative diagnosis of OSA. In the remaining 17% (10/60) of patients with undiagnosed OSA, eight had a postoperative CRE, one suffered a heart block during sleep and the other suffered anoxic brain injury. OSA was diagnosed postoperatively in these 10 patients; three by polysomnography, two by postoperative oximetry, three by history analysis, one with computer-assisted monitoring of respiration and one had no details on diagnosis.

After the near-death events, three patients underwent polysomnography and OSA was diagnosed postoperatively at varying times after surgery.[12 23 24] Of two patients who had oximetry-diagnosed OSA, one developed a heart block in the postoperative period and underwent oximetry which revealed nocturnal desaturations to 86%, the pulmonologist suggested a diagnosis of OSA and recommended CPAP.[19] The other patient with recurrent severe airway obstruction after extubation had overnight oximetry monitoring, the standard test in the reported hospital, which revealed mild OSA.[17]

Three patients had a diagnosis of OSA based on a history of heavy snoring, daytime somnolence and poor concentration.[13 15 19] One was reported to have undergone computer-assisted respiratory monitoring after developing severe respiratory obstruction with 134 obstructive events over the first four h on the first postoperative day. Obstruction improved with CPAP.[14] The details about the postoperative diagnosis of OSA were not described for one patient.[27]

Only 3/60 patients had data reported on preoperative apnoea hypopnoea index (AHI) and one had data on postoperative AHI. One patient with a preoperative AHI of 55 events h^{-1} died; two with a preoperative AHI of 16 and 17.5 events h^{-1} and one with a postoperative AHI of 81 events h^{-1} developed CREs, respectively.

Table 1 Descriptive data of population, apnoea hypopnoea index and perioperative CPAP usage. OSA, Obstructive sleep apnoea; CPAP, Continuous positive airway pressure; cm of H_2O, cm of water; Diagnosis:dx; M, Male; F, Female; NA, Not available; PSG, Polysomnography; GERD, Gastro-esophageal reflux disease; TIA, Transient ischemic attack; CAD, Coronary artery disease; MI, Myocardial infarction; MO, Morbid obesity; ODI, Oxygen desaturation index; CT 90, Cumulative time of desaturation<90%

Study ID	Sex	Age (Yr)	BMI (kg m^{-2})	Comorbidities	OSA: diagnosed & suspected (*n*) AHI events h^{-1}	Preoperative CPAP (cm H_2O)	Postoperative CPAP (cm of H_2O)
Samuels and colleagues[12] 1986	M	38	22.6	None	Undiagnosed OSA	No	Postoperative PSG + CPAP
Lamarche and colleagues[13] 1986	M	65	28	NA	Undiagnosed OSA	No	Postoperative OSA dx
Reeder and colleagues[14] 1991	M	74	31	None	Undiagnosed OSA, preoperative oximetry revealed an ODI=36; CT90=14 min	No	Postoperative respiratory study 134 obstructive events, over 1st 4h postoperatively, 5 cm H_2O nasal CPAP
Etches and colleagues[15] 1994	M	56	NA	None	Undiagnosed OSA	No	Postoperative OSA dx
Rennotte and colleagues[16] 1995	M	62	32	OSA	Untreated OSA, Preoperative AI: 55	No	No
Rennotte and colleagues[16] 1995	M	64	35	OSA	Untreated OSA, Preoperative AHI;16	No	Nasal CPAP
Vidhani and colleagues[17] 1997	M	38	28	OSA	Undiagnosed OSA	No	Postoperative OSA dx 5 cm H_2O CPAP
Ostermeier and colleagues[18] 1997	F	41	36.9	Juvenile rheumatoid arthritis	Untreated OSA	No	No
Ostermeier and colleagues[18] 1997	M	66	36.3	Hypertension	Untreated OSA	No	No
Ostermeier and colleagues[18] 1997	F	44	27.5	None	Untreated OSA	No	No
Block and colleagues[19] 2001	F	59	44	MO	Undiagnosed OSA,	No	Refused CPAP
Block and colleagues[19] 2001	F	38	74	Hypertension, MO	Undiagnosed OSA	No	Postoperative OSA dx
Block and colleagues[19] 2001	M	49	52	Diabetes, CAD, Previous MI, MO	Untreated OSA	Non-compliant with CPAP	CPAP on postoperative day 1, Effective vs pauses in heart rate
Cullen and colleagues[20] 2001	M	42	NA	NA	Untreated OSA	No	No
Lofsky and colleagues[21] 2002	M	45	45	OSA, MO	Diagnosed, treated OSA	Preoperative CPAP	Postoperative CPAP
Lofsky and colleagues[21] 2002	M	32	NA	OSA	Diagnosed, treated OSA	Preoperative CPAP	Postoperative CPAP
Bolden and colleagues[22] 2007	NA	NA	NA	NA	2 patients with untreated OSA	No	NA
Bolden and colleagues[23] 2009	M	45	41	MO	Diagnosed, untreated OSA	No	No
Bolden and colleagues[23] 2009	F	38	64	MO	Undiagnosed OSA	No	Postoperative PSG after 6 months: severe OSA; desaturations 70–80%; CPAP 12 cm H_20.
Bolden and colleagues[23] 2009	F	37	63	Asthma, Hypertension, Depression, GERD, MO	Diagnosed OSA, on CPAP	CPAP 8 cm H_2O preoperative AHI 17.5 events h^{-1}	CPAP 8 cm H_2O

Yegneswaran and colleagues[24] 2009	F	66	45.3	Hypertension, asthma, smoking, MO TIA	Undiagnosed OSA	No	Postoperative dx by PSG, AHI 81 events h^{-1}
Gallagher and colleagues[25] 2010	F	NA	76	MO	Diagnosed and untreated OSA	NA	No
Garcia and colleagues[26] 2014	M	50	51	GERD, OSA, MO, gout, type 2 DM, polyarthritis and depression	Diagnosed, untreated OSA	No	No
Benumof and colleagues[9] 2016	M F	50–60	24–54	NA	9 - Severe OSA 1 - Moderate OSA 2 - Suspected OSA. 11 obesity related 1 retrognathia, 8 males and 4 females 7 on CPAP	Yes, 7 patients	Not on oxygen or CPAP
Fouladpour and colleagues[27] 2016	M-15 F-9	mean 41.7	NA	NA	23 Diagnosed OSA, 1 undiagnosed	NA	NA

CPAP therapy

In most case reports, details regarding CPAP therapy and compliance were not available. Among the 60 patients with OSA that had critical complications, only 18.3% (11/60) were identified with certainty as receiving CPAP therapy preoperatively, one of which was non-compliant. Eight did not receive CPAP therapy in spite of diagnosed OSA and 10 were not on CPAP as a result of undiagnosed OSA. Details on CPAP therapy were not reported in 25 patients.

Of 11 patients who were on preoperative CPAP therapy, 63.6% (7/11) did not receive CPAP postoperatively. They either died or developed anoxic brain damage after being discharged to an unmonitored bed. Of the four patients who continued to receive postoperative CPAP; one died, the second patient sustained anoxic brain damage, the third patient developed CREs and the fourth patient sustained heart block, both of which were later treated. H of CPAP usage were not available for all four patients, and monitoring with audible pulse oximetry was lacking for two patients.

Of eight patients who had known OSA and had not received preoperative CPAP therapy, six received CPAP treatment postoperatively, two died, one developed anoxic brain damage and five had life threatening CREs. As a result of the lack of adequate information on CPAP therapy in these case reports, the therapeutic effect of CPAP on outcomes could not be established.

Subgroup comparison between patients with death/near-death and CRE/other events showed that 43% of the patients with death/near-death events were using CPAP preoperatively compared with 14% with CREs/other events (χ^2=9.4, P=0.009; OR = 4.5). Patients who did not use CPAP postoperatively had a strong likelihood of having death/near-death events *vs* CREs (33.3 fold risk, OR = 1/0.03) (Table 4).

Comorbidities associated with critical complications

Morbid obesity was associated with eight deaths, five anoxic brain injuries and four life-threatening CREs, making it the most common comorbidity. Hypertension was associated with one death and two CREs. A patient with OSA and diabetes mellitus and coronary artery disease presented with postoperative heart block. Our subgroup analysis between patients with death/near-death and CRE/other complications showed a higher proportion of comorbidities present in the death/near-death group compared with CREs (88% *vs* 75%, χ^2=15.4, P<0.001) (Table 4).

Association of OSA, opioids, sedatives and critical complications

The route of administration of opioids varied among the patients. Seventeen patients received i.v. opioids, eight i.v. patient controlled analgesia (IV PCA) opioids, three i.m. opioids, four epidural opioids, and two oral opioids. The route of administration was not reported in 11 patients. Seventy-five percent (45/60) of the patients with life threatening adverse outcomes received opioids. The dose of opioids administered was not reported in 64% (29/45) of patients. Eighty-one percent (13/16) of the patients with reported opioid doses were found to receive relatively small doses of opioids with a morphine equivalent daily dose (MEDD) less than 10 mg (i.v.); only 20% (3/16) received a relatively higher dosage of opioids (Table 3). Three patients[21 23] received an i.v. MED of 25 mg (over six h), 29 mg (over eight h) and 60 mg (over 18 h), respectively. Twenty-five percent of

Table 2 Data on surgery, anaesthesia and postoperative outcomes. OSA, Obstructive sleep apnoea; CPAP, Continuous positive airway pressure; NA, Not available; Sp_{O_2}, Oxygen saturation of haemoglobin; GA, General Anaesthesia; PACU, Post anaesthesia care unit; ICU, Intensive care unit; ACLS, Advanced cardiac life support; DIB, Death in bed; ABG, Arterial blood gas; pH, Partial pressure of hydrogen in artery; Pa_{O_2}, Partial pressure of oxygen in artery; $P_{A_{CO_2}}$, Partial pressure of carbon dioxide in artery; PSG, Polysomnogram; POD, Postoperative day; ENT, Ear nose throat surgery; MAC,; Monitored anaesthesia care; PCA, Patient controlled analgesia; REM, Rapid eye movement; TKR, Total knee arthroplasty; AHI, Apnoea hypopnoea index; Cx, Complications

Study ID	Type of surgery and anaesthesia	Dose of opioids/ sedatives	Postoperative Cx	Timing of complication	Interventions	Comments
Samuels and colleagues[12] 1986	Reduction of tibial fracture SA and sedation	i.m. Meperidine 50 mg, promethazine 25 mg for premedication.	Respiratory obstruction and coma after premedication	Intraoperative & postoperative period. Patient awake in the evening.	Naloxone 0.4 mg IV x3 Physostigmine 1 mg IV. Discharged after elective tracheostomy	Unarousable to painful stimuli during surgery, $Sp_{O_2} < 70\%$. No response to interventions. Postoperative PSG: OSA with multiple episodes of O_2 desaturation bradycardia and VPB
Lamarche and colleagues[13] 1986	Radical prostatectomy GA	5 mg epidural morphine	Respiratory depression	8 h after surgery	Antagonism with naloxone	
Reeder and colleagues[14] 1991	Aortic reconstructive surgery GA	Morphine 7 mg i.v. (1 mg boluses over 4h)	Severe respiratory obstruction 3 events of Sp_{O_2}<85% Large fluctuations in SBP & DBP	4 h post-extubation	CPAP, O_2 therapy	
Etches and colleagues[15] 1994	Bilateral TKA GA	PCA morphine 16 mg over 12 h	Respiratory depression	POD 1 unarousable, obstructed	Antagonism with naloxone	Probable OSA
Rennotte and colleagues[16] 1995	CABG GA	Postoperative i.v. morphine, diazepam	Respiratory arrest, death	POD 8	CPAP, intubation and mechanical ventilation	
Rennotte and colleagues[16] 1995	CABG GA	Postoperative i.v. fentanyl, morphine, midazolam	Severe hypoxemia, ventricular arrhythmia, external defibrillations	POD 4	Intubation, mechanical ventilation, CPAP	
Vidhaniand colleagues[17] 1997	Emergency mastoidectomy GA	i.v. morphine 10 mg	Upper airway obstruction upon extubation	Post-extubation	Re-intubation, but had recurrent episodes of upper airway obstruction	
Ostermeier and colleagues[18] 1997	Total hip arthroplasty GA + epidural block	Epidural analgesia 0.06% bupivacaine+fentanyl (10 ug mL^{-1}), 7 ml h^{-1}	Cardiorespiratory arrest and death	POD 2	Repeated bolus of naloxone, controlled ventilation and defibrillation.	Increase in intensity of REM sleep after POD 1,
Ostermeier and colleagues[18] 1997	Bilateral TKR Epidural anaesthesia Ventral hernia repair	Epidural 0.06% bupivacaine+fentanyl (10 ug mL^{-1}) infusion increased from 7 ml h^{-1} to 9 ml h^{-1}	Cardiorespiratory arrest and death	POD 3	Resuscitation Resuscitation	Epidural opioids can lead to late respiratory depression

Ostermeier and colleagues[18] 1997	Epidural anaesthesia	Epidural 0.1% bupivacaine + fentanyl (10 ug mL^{-1}), 8 ml h^{-1}	Cardiorespiratory arrest and death	POD 2 (>29 h after initiation of the epidural)		Sensitivity to opioids, epidural opioids not titrated to pain.
Block and colleagues[19] 2001	Bariatric surgery GA	i.v. meperidine	Heart block, desaturation in nocturnal oximetry	POD 14		OSA induced heart block
Block and colleagues[19] 2001	Bariatric surgery GA	i.v. PCA morphine	Heart block during sleep, sinus bradycardia + high-grade 2nd degree AV block +VPB	POD 15		OSA induced heart block
Block and colleagues[19] 2001	Bariatric surgery GA	Oral hydrocodone	Episodes of sinus arrest during sleep	POD 1	Postoperative CPAP	OSA induced heart block
Cullen and colleagues[20] 2001	Ear surgery GA + fibreoptic intubation	4 mg i.m. morphine	Cardiac arrest and death	ward, 4 h after surgery	Tracheostomy	Unmonitored patient
Lofsky and colleagues[21] 2002	Rotator cuff repair GA	i.m. meperidine 100 mg + phenergan 25 mg repeated after 3h	Cardiac arrest and death	9 h after surgery	Could not be resuscitated	
Lofsky and colleagues[21] 2002	ORIF arm fracture GA	i.v. PCA fentanyl 25 mcg bolus, 12 min lock out and 25 mcg every h.	Respiratory arrest	1st postop night	Resuscitated, Anoxic brain damage	
Bolden and colleagues[22] 2007	Inpatient and ambulatory surgeries	i.v. and oral opioids, dose: NA	2 cardiac arrests, no deaths	POD 2	None	Postoperative hypoxemias despite CPAP. One cardiac arrest in patient managed off protocol, 2nd patient on postoperative oral opioids had cardiac arrest one day after discharge
Bolden and colleagues[23] 2009	Repair of tibial fracture GA	16 mg morphine i.v. over 2.5h in PACU, 10 mg morphine i.v. 10 mg oral oxycodone over 5h in the ward	Cardiac arrest and death	Within 24 h after surgery	CPR and defibrillation	Several apnoeic episodes in PACU and 1 apneic episode in ward. Large doses of opioids in an unmonitored environment, ABG after arrest: pH 6.97, $P_{A_{CO_2}}$ > 100 mmHg
Bolden and colleagues[23] 2009	Uterine artery embolization i.v sedation	Hydromorphone PCA 20 mg over 18 h	Patient unarousable and apneic, treated for aspiration pneumonia in ICU	Within 24 h after surgery	Intubation	Initial Sp_{O_2} during the Code: 60%. ABG after tracheal intubation: pH 6.93, $P_{A_{CO_2}}$ 103 mm Hg, Pa_{O_2} 102 mmHg..
Bolden and colleagues[23] 2009	Gastric bypass GA	PCA morphine basal rate of 1 mg h^{-1}, 1.0 mg bolus, lockout 6 min, every h maximum 10 mg	8 episodes of Sp_{O_2} < 90% despite CPAP	Occurring over 72 h	postoperatively	Patient awakened and instructed to breathe deeply. Sp_{O_2} >94%

Continued

Table 2 Continued

Study ID	Type of surgery and anaesthesia	Dose of opioids/ sedatives	Postoperative Cx	Timing of complication	Interventions	Comments
Yegneswaran and colleagues[24] 2009	ORIF wrist RA	PCA morphine 1.5 mg bolus, lockout 10 min.	Respiratory arrest	12 h after surgery	Resuscitated with naloxone ICU transfer	PSG on POD 2: severe OSA (AHI = 81), mean Sp_{O_2} 87%, minimum Sp_{O_2} 78%.
Gallagher and colleagues[25] 2010	Gastric bypass GA	i.v. Dexmedetomidine for preoperative sedation, 350 μg of fentanyl	Postoperative hypoventilation, pH 7.08, $P_{A_{CO_2}}$ 122 mm Hg, Pa_{O_2} 71 mm Hg, Sp_{O_2} of 88%	PACU	Mechanical ventilation 3h	Opioid induced respiratory depression
Garcia and colleagues[26] 2014	Bariatric surgery GA	NA	Cardiopulmonary arrest after extubation in supine position	Multiple episodes of asystole in OR and ICU. Asystole and death in ICU	Multiple attempts of resuscitation with CPR	Possible obesity supine death syndrome
Benumof and colleagues[9] 2016	3 orthopaedic, 6 abdominal (3 open, 3 laparoscopic), 3 upper airway, 12 GA and 1 fibreoptic intubation	Morphine PCA with basal infusion, 8 received small doses of opioids	12 cardiac arrests, (7 deaths, 5 anoxic brain injury)	2 in PACU, 10 in ward, all within 29 h	5 - ACLS successful but hypoxic encephalopathy 3 - no ACLS. 4 - ACLS failed	2 - PACU arrests 3 - autopsy consistent with -ve pressure pulmonary edema. No OSA–DIB in patients with mild OSA. 2 PACU arrests - 1 small doses of narcotics over 1h, 1 received 2.5 mg hydromorphone over 90 min
Fouladpour and colleagues[27] 2016	33.3% general surgery, 37.5% ENT procedures for treatment of OSA, 29.1% miscellaneous, 20 GA, 4 MAC	8/22 patients who died or had anoxic brain injury received opioids	11 deaths. 11 anoxic brain injury; 2 airway Cx 1 tracheostomy, 1 post-extubation pulmonary edema	Intraop Cv 21% (5), PACU, b% (8) 46% (11) in ward	NA	Intraop and PACU cardiac arrests >50% Related to difficulty with airway Mx and/or premature extubation Unmonitored arrests in ward mostly led to deaths

Table 3 Summary of characteristics of risk factors associated with critical complications. Cx, Complications; NA, Not available; OSA, Obstructive sleep apnoea; CRE, Critical respiratory events; AHI, Apnoea hypopnoea index; CPAP, Continuous positive airway pressure; D, Death; PACU, Post anaesthesia care unit

Parameters	Data
Age [Mean(SD)], sex	60 patients. 62% males [49(9) yr] and 38% females [46(8) yr]
Body habitus (Mean SD)	Overall BMI: 4 ± (13) kg m^{-2}
Outcomes reported (n=60)	26 deaths, 17 anoxic brain injury, 12 CRE, 5 other serious complications (2 cardiac arrest: resuscitated, 3 heart block)
AHI data (events h^{-1}) (n=4)	Mean preoperative AHI 30: 2 CRE, 1 death Postoperative AHI 81: 1 CRE
CPAP use (n=50)	OSA diagnosed preoperatively: 50 CPAP treatment: 11 Did not receive CPAP/treatment or information NA: 39
Timing of critical complications (n=60) %	92 (45/49)–1st 72h, 80 (39/49)–1st 24h, 12 (6/49)–24–72h, 8 (4/49)–>72h, Complication timing: NA (n=11)
Location of critical complications (n=60) %	OR: 13 (8/60) PACU: 18 (11/60) Ward: 67 (40/60)
Opioid use: % Opioids given: 45 Opioids not given: 15	75 (45/60) OSA patients with death or near-death received opioids, 81 received relatively small doses of opioids
Route of opioid administration	i.v. opioids: 17 i.m. opioids: 3 Epidural opioids: 4 i.v. PCA opioids: 8 Oral opioids: 2 No opioid: 15 Route of administration NA: 11

patients (15/60) did not receive any opioids, but received either general anaesthetics or sedatives (Table 3).

The subgroup comparison analysis between patients with death/near-death and CRE/other complications showed a higher effect for parenteral/epidural as the route of administration of opioids among CREs group (71% *vs* 19%). Further analysis on the dosage of i.v. opioids showed a clear dose-response pattern on death/near-death group (i.e. increased odds of death/near-death with increasing opioid doses) (ORs of 1.0, 1.5 and 3.0 at opioid doses of < 10 mg, 10-25 mg and >25 mg; P for trend<0.005).

Timing and location of the critical complications

The timing of the critical complications was reported in 81.7% (49/60) of cases. Ninety-two percent (45/49) of the critical complications occurred within the first 72 h after surgery (Fig. 2). Importantly, 80% occurred in the initial 24 h, with 12% occurring between 24-72 h. Overall, 67% of complications occurred on the surgical wards, 13% in the operating rooms, 18% in the post-anaesthesia care units (PACU) and the remaining 2% in the patients' home after discharge (Fig. 3).

Discussion

To our knowledge, this is the largest comprehensive collection of perioperative critical complications including deaths in patients with OSA. Sixty critical complications after surgery attributable to OSA are reported in this analysis of the medical literature. Eighty-three percent of patients with OSA had a preoperative diagnosis and 17% were undiagnosed before surgery. Thirty-one percent of patients (11/35) with OSA were reported to be using CPAP preoperatively. Only four of these patients continued utilizing CPAP therapy postoperatively. Seventy-five percent of patients with OSA who suffered severe life threatening complications received opioids, and these events occurred with relatively small doses of opioids of MEDD<10 mg in 81% of the patients, regardless of the route of administration. Eighty percent of deaths or near-deaths occurred in the first 24 h and nearly 67% took place on the general hospital ward. In this review, morbid obesity, male sex, undiagnosed/untreated OSA, suboptimal use of postoperative CPAP, need for opioid analgesia, and lack of appropriate postoperative monitoring were the risk factors identified to predispose an OSA patient to critical complications.

There are conflicting reports about the association of OSA with perioperative mortality. Two nationwide studies on patients undergoing general, orthopaedic, cardiac and bariatric surgeries found a decreased mortality in OSA patients.[28 29] The authors have postulated this to be as a result of the better monitoring and management of diagnosed OSA patients, protective effect of ischaemic preconditioning and obesity paradox in OSA patients.[30] On the contrary, a nationwide inpatient study on 258,455 patients who underwent revision total hip or total knee arthroplasty found that OSA was associated with a two-fold increase in-hospital mortality (OSA *vs* non-OSA 0.4% *vs* 0.2%; P=0.002).[31] The most recent meta-analysis on OSA patients

Table 4 Sub-group analysis of risk factors in relation to death/near-death and CRE/Other events. No data were available to calculate OR; [a]Multivariate logistic regression adjusted for age, sex, BMI and comorbidities; [b]no reference data was available to calculate OR for the group; [†]Parametric and non-parametric statistics were computed using 'unknown' data as an additional category in the cross-tabulation; [‡]As a result of high collinearity with a covariate ("presence of comorbidities"), multivariate logistic regression did not adjust this confounder. CRE, Critical respiratory events, OSA, Obstructive sleep apnoea, CPAP, Continuous positive airway pressure, OR, Odds ratio, SE, Standard error

Risk factors	CRE & others (N = 17)		Death/ Near-death (N = 43)		$\chi^{2\dagger}$ (P-value)	Unadjusted OR (SE)	Adjusted OR[a] (SE)
Sex		%		%			
Men	7	41	30	70	7.7 (0.054)	2.6 (1.6)	4.0 (3.4)
Women	8	47	13	30		1	1
Age Category							
≤40 yr	5	29	1	2	9.9 (0.002)	1	1
≥41 yr	12	71	42	98		17.5 (20.0)	4.2 (5.6)
BMI category							
<35 Kg/m^2	4	33	2	11	6.3 (0.044)	1	1
≥35 Kg/m^2	8	67	17	89		4.3 (4.1)	2.6 (3.8)
Presence of comorbidities							
No	3	25	1	13	15.4 (<0.001)	1	1
Yes	9	75	7	88		2.3 (2.9)	2.2 (3.7)
Diagnosis of OSA							
OSA diagnosed	3	23	26	100	30.8 (<0.001)	1	1
OSA undiagnosed	10	77	0	0		.	.
Treatment of OSA							
OSA treated	0	0	2	22	1.2 (0.563)	.[b]	.
OSA untreated	4	100	7	78		.	.
Presence of severe OSA							
No	0	0	3	23	2.5 (0.280)	.[b]	.
Yes	2	100	10	77		.	.
Preoperative CPAP							
No	12	86	12	57	9.4 (0.009)	1	1
Yes	2	14	9	43		4.5 (3.9)	2.0 (2.8)
Postoperative CPAP							
No	2	20	19	90	17.1 (<0.001)	1	1
Yes	8	80	2	10		0.03 (0.03)	0.1 (0.1)
Route of opiate use[‡]							
Parenteral/epidural	12	71	8	19	14.8 (<0.001)	0.1 (0.1)	0.2(0.2)
No-opioids or unknown	5	29	35	81		1	1
Dosage of IV use							
Up to 10 mg	3	50	1	33	8.1 (0.045)	1	1
11–25 mg	2	33	1	33		1.5 (2.5)	1.9 (4.6)
26+ mg	1	17	1	33		3.0 (5.5)	14.6 (39.9)

undergoing cardiac surgery had higher death rates compared with non-OSA patients (3.8% *vs* 1.4%).[32]

A retrospective review of orthopaedic patients from the National Surgical Sample showed that OSA patients are 1.86 (95% CI 1.65; 2.09) times more likely to have pulmonary and 1.59 (95% CI 1.48; 1.71) times more likely to have cardiac complications compared with the general population.[33] A meta-analysis of 13 studies found that OSA was associated with higher odds for any postoperative cardiac event [odds ratio (OR) 2.07; P=0.007] and respiratory events (OR 2.43; P=0.003).[2] The most recent Bayesian meta-analysis involving 23,609 patients suggested that HR-OSA is related with higher risk of postoperative adverse events (OR 3.93, 95% Credible Interval 1.85 to 7.77, P=0.003) and longer length of hospital stay (mean difference 2.01; 95% Credible Interval 0.77 to 3.24; P=0.005) when compared with LR-OSA patients.[8] Recent evidence showed that the presence of OSA was associated with a risk of postoperative respiratory depression requiring naloxone antagonism (OR = 2.45; P=0.008).[34] A recent study of insurance claims of postoperative respiratory depression resulting in brain damage or death identified diagnosed OSA in 15% and suspected OSA in 9% of these patients.[35]

Morbid obesity

We found that morbid obesity is a risk factor as patients with death or near-death events were morbidly obese with BMI 42(13) kg m^{-2}. Obesity was five times more prevalent among OSA patients compared with those without the disease, predisposing them to postoperative pulmonary complications.[36] Obesity is the most common and well-recognized risk factor for OSA. In addition, patients with obesity hypoventilation syndrome may be at higher risk of perioperative complication than patients with OSA.[37] Patients with severe OSA and obesity

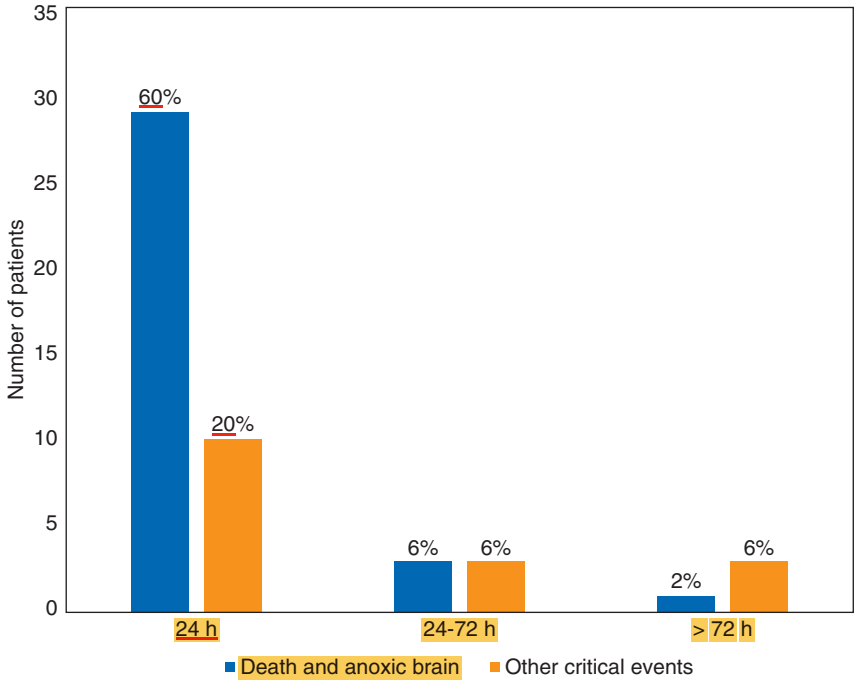

Fig 2 Timing of postoperative critical complications in patients with obstructive sleep apnoea. The 1st 24 h after surgery is a high-risk period for critical complications. Data suggest that 80% of the critical complications occur in the 1st 24 h after surgery.

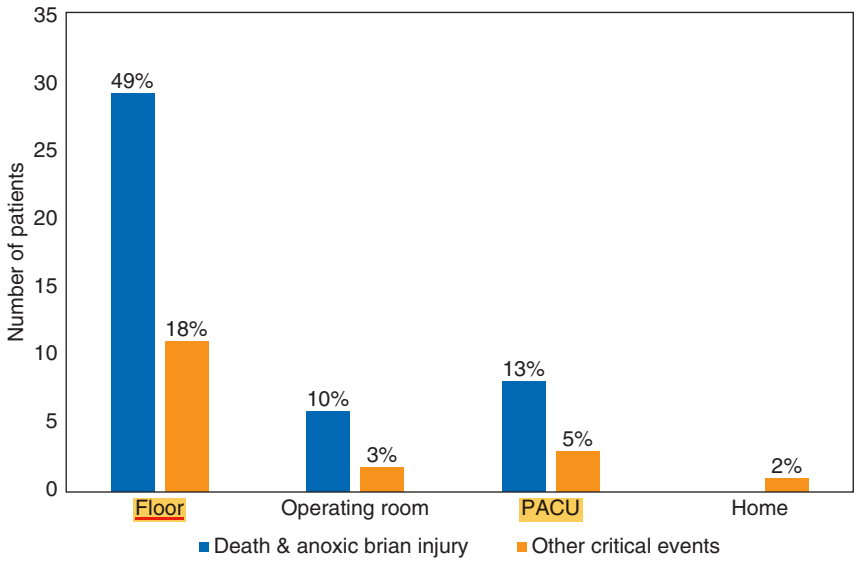

Fig 3 Location of postoperative critical complications in patients with obstructive sleep apnoea. PACU, Post-anaesthesia care unit. Sixty-seven percent of the critical complications occur on the ward, with 31% occurring in the perioperative environment (operating room and PACU).

hypoventilation syndrome are likely to experience recurrent episodes of apnoea/hypopnoea during sleep, leading to hypoventilation and significant nocturnal hypercapnia.[38] This causes an increase in serum bicarbonate levels indicating compensatory renal retention in response to chronic respiratory acidosis.[39] Testing for serum bicarbonate in addition to the STOP-Bang questionnaire may increase specificity to identify severe OSA and possibly obesity hypoventilation syndrome.[40 41]

Male sex

Male OSA patients have been shown to have a two-fold higher AHI postoperatively than female OSA patients.[42] We have found that 62% of the critical complications occurred in males. Males are two to three times more likely to have OSA than females[43] with longer periods of apnoea and more significant oxygen desaturations, despite a lower BMI.[44 45]

Undiagnosed OSA

Undiagnosed OSA may play a role in the occurrence of death or near-death events. Seventeen percent of the OSA patients in our analysis were undiagnosed. A large proportion (80-90%) of surgical patients with moderate-to-severe OSA could be undiagnosed and untreated at the time of surgery.[7] It has been shown that patients with undiagnosed OSA may have higher cardiopulmonary complications than patients with diagnosed OSA and CPAP prescription.[46]

Severity of OSA

Severity of OSA is a major risk factor for consideration in those with critical complications. Mutter and colleagues[46] demonstrated significant trends of increased risk with increasing OSA severity and pulmonary complications in OSA patients (diagnosed or undiagnosed) and with cardiac complications in undiagnosed OSA patients. Similarly, Chung and colleagues[47] showed that preoperative severity of OSA was shown to be associated with postoperative adverse events. Unfortunately, a limited number of patients with reported AHI were available in the case reports, but no deaths or near-deaths were reported in patients with mild OSA (AHI<15 events h^{-1}).

CPAP therapy

A possible contributing factor to the critical complications is that the majority of patients with OSA may have been partially treated or untreated before surgery. We found that only 31% were on preoperative CPAP, of which one was non-compliant. Our findings are consistent with the literature that CPAP compliance in the perioperative setting was relatively low at 45%.[48] Forty-three percent of patients on preoperative CPAP died or sustained anoxic brain damage *vs* 14% who developed CRE's/other events. This increased death/near-death in patients on preoperative CPAP could be attributed to having more severe OSA and only 10% of these patients continued CPAP in the postoperative period. Postoperative CPAP utilization has been reported to be suboptimal even in patients with an established diagnosis of OSA who were using CPAP preoperatively. Only 63% of the patients on preoperative home CPAP received it postoperatively.[49] Twenty-seven percent of OSA patients not using home CPAP were found to require CPAP postoperatively and these patients had the highest incidence of postoperative complications.[49]

Although the current evidence for the efficacy of CPAP in the perioperative period is limited, two recent retrospective large database studies showed that CPAP may have beneficial effects on postoperative outcomes.[46 50] Preoperative use of home CPAP was associated with a reduced risk of serious complications and a shorter hospital stay.[51] A recent meta-analysis reported that the use of CPAP may reduce AHI and length of stay in the postoperative period.[52]

In order to ensure optimization of patients with OSA, intensive education of health-care professionals and patients is needed to ensure that patients are instructed to bring their CPAP device to the hospital and to use CPAP therapy during the vulnerable postoperative period. The Society of Anesthesia and Sleep Medicine has made recent recommendations on preoperative preparation of OSA patients in order to minimize risk and ensure optimal perioperative management.[53]

Effects of anaesthesia, sedatives and opioids

The dose-dependent depression of the upper airway muscle activity by general anaesthesia is well established.[54] Opioids interfere with the chemical, behavioral and motor control of respiration,[55–57] and can lead to severe hypoxia, alveolar hypoventilation and death. We found that one patient died and another developed anoxic brain damage, despite receiving perioperative CPAP. Both received opioids in an unmonitored environment, highlighting the particular susceptibility of patients with OSA to anaesthetic agents, sedatives, and opioids and the need for continuous monitoring.

In this review, patients with OSA developed critical complications regardless of the dose and route of administration of opioids. Seventy-five percent of patients received opioids and 81% of these patients received typical or less than typical doses of opioids. Nineteen percent received a relatively higher dose of opioids, which is consistent with a closed claims analysis of postoperative opioid-induced respiratory depression in which 16% of patients were identified as having received excessive doses of opiods.[35] Another study found that the majority of patients received a MEDD less than 1.5 mg kg^{-1} day^{-1}.[58] The low overall opioid dose and high pain scores preceding the events suggest increased opioid sensitivity as a possible mechanism.[59 60]

It is important to note that OSA is a complex multifactorial disease with distinct phenotypes which may contribute to critical complications.[61] Some patients with OSA have a high threshold for arousal, whereas others with a low arousal threshold wake up frequently to minimal oxygen desaturation. It has been postulated that a delay in arousal caused by opioids or other sedative medications can precipitate an arousal arrest (complete arousal failure) leading to sudden unexpected death as a result of respiratory failure.[62] These patients are in a state of "arousal dependent survival". At present, there is no conventional way to identify patients with a high arousal threshold preoperatively.

Lack of monitoring

We found that 80% of complications occurred within the first 24 h, confirming findings of previous studies.[51 62] This may be because of the combined effects of anaesthetic agents, sedatives, and narcotics. Twelve percent of deaths or near-deaths occurred on postoperative days two and three. This may be as a result of decreased pain, less surveillance and increased rapid eye movement (REM) sleep causing loss of upper airway tone

during this period. REM sleep is associated with a greater number of apneic episodes than non-REM sleep.[63 64]

Sixty-seven percent of death or near-death events occurred on the hospital wards. As described previously, OSA patients with a high arousal threshold are particularly susceptible to opioid induced respiratory depression and respiratory arrest in an unmonitored environment, especially when they experience complete pain relief postoperatively. Lapses in monitoring are often implicated in the majority of these preventable deaths. Current monitoring in the ward is often limited to isolated spot checks that include physiologic parameters such as the patients' heart rate, respiratory rate, and temperature, typically every four h, which leaves patients unmonitored for ninety-six percent of the time.[65] It is important to note that three patients who were on CPAP postoperatively were found to have critical complications. It may be useful to use a sedation scale to assess patients on opioid therapy both before and after administration of opioids.[66] The Anaesthesia Patient Safety Foundation has recommended continuous electronic monitoring of postoperative patients on opioids with high resolution pulse oximetry and possibly capnography to detect early desaturation and initiate treatment.[62 67] Continuous monitoring of patients with OSA, recurrent PACU respiratory events and those who require narcotic analgesics for pain are recommended.[68–70] At present, deciding on the optimal level and duration of monitoring for patients with OSA requires further research.

Limitations

Our review has some limitations as a result of the small number and the quality of reports available in the literature. Although we have analysed the published data on perioperative critical complications associated with OSA to-date, the actual number of these outcomes could be underestimated. Secondly, we excluded case reports that were not published in English. Third, our results from the multivariate analysis should be interpreted with caution because of the small sample size and wider confidence intervals (or large standard errors). Finally, many of the case reports did not provide information such as the severity of OSA and CPAP usage, which may have given us further insight into the causes of these critical complications.

Conclusion

OSA patients are at risk for critical complications, including deaths, after surgery. Morbid obesity, male sex, undiagnosed OSA patients, partially treated/untreated OSA, perioperative suboptimal use of CPAP, opioids, sedatives, and lack of monitoring are risk factors for these complications. In North America, the Society of Anesthesia and Sleep Medicine and the American Society of Anesthesiologists are collecting data on perioperative complication in an OSA Death and Near Miss Registry. Data obtained from the OSA Death and Near Miss Registry will help to further understand the risk factors leading to these events. Education of health care professionals and patients regarding these risk factors are keys to ensuring that OSA patients are optimized before and after surgery. Continuous postoperative monitoring in the first 24 h, and improved compliance with CPAP may mitigate the risk for death or near-death events in patients with suspected or untreated OSA.

Authors' contributions

Study design/planning: Y.S., F.C.
Data analysis: J.P.
Study conduct: Y.S., M.N., F.C.
Writing paper: Y.S., M.N., J.W., F.C.
Revising paper: all authors

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