Review Article

A systematic review of the effects of sedatives and anesthetics in patients with obstructive sleep apnea

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Abstract

The objective of this review is to determine the effects of perioperative sedatives and anesthetics in surgical patients with obstructive sleep apnea (OSA) on respiratory events, medication requirements, hemodynamics, pain, emergence, and hospital stay. We searched The Cochrane CENTRAL Register of Controlled Trials, Medline, Embase, and Cochrane Database of Systematic Reviews from 1950 to June 2010 for relevant articles. All prospective and retrospective studies were eligible for inclusion if the effects of perioperative administration of sedation and anesthetics on medication requirements, pain, emergence, hemodynamics, respiratory events, and length of hospital stay in OSA patients were reported. The search strategy yielded 18 studies of 1467 patients. Of these, 456 patients were documented as having OSA. Few adverse respiratory effects were reported. Eight out of 700 (1.14%) patients undergoing middle ear surgery with midazolam and fentanyl had impaired upper airway patency and were retrospectively diagnosed as having OSA by polysomnography. Also, intraoperative snoring causing uvular edema in the postoperative period was described in an OSA patient undergoing upper limb surgery when propofol was administered with midazolam and fentanyl for sedation. A decrease in oxygen saturation in the postoperative period was described with propofol and isoflurane in 21 OSA patients undergoing uvulo-palato-pharyngoplasty and tonsillectomy surgery ($P<0.05$). Perioperative alpha 2 agonists were shown to decrease the use of anesthetics ($P<0.05$), analgesics ($P=0.008$) and anti-hypertensives ($P<0.001$) in OSA patients. Contradictory reports regarding emergence occurred with intraoperative dexmedetomidine. Intraoperative opioids decreased the analgesic consumption ($P=0.03$) and pain scores ($P<0.05$) in the postoperative period. There was limited data on the length of hospital stay. There were few adverse effects reported when patients with known OSA underwent elective surgery with the currently available sedatives and anesthetics. Adverse events were reported with midazolam. However, the quality and number of patients in the studies were limited. There is a need for further trials with large numbers and uniform reporting of outcomes.

Key words: Anesthetics, effects, obstructive sleep apnea, sedative

Introduction

Obstructive sleep apnea (OSA) is the most prevalent sleep-associated breathing disorder, caused by repetitive partial or complete obstruction of the upper airway. It is characterized by episodes of apnea during sleep lasting for more than 10 s.

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The prevalence of sleep disordered breathing, as described in a sleep laboratory, is 24% in men and 9% in women,[1] whereas the prevalence of overt OSA is 4% in men and 2% in women.[2] Moderately severe OSA (AHI > 15) is present in 11.4% of men and 4.7% of women, respectively, in the general population.[3,4]

The deposition of fat in the upper airway in these patients at the lateral pharyngeal walls decreases pharyngeal caliber and increases upper airway resistance and negative intra-thoracic pressure.[5-7] The combination of these factors predispose OSA patients to upper airway collapse during sleep and anesthesia.[8,9]

To date, various studies described an increase in postoperative complications in OSA patients as compared to control. Higher rates of postoperative complications in OSA patients (39%) versus control (18%) were described in patients undergoing hip or knee replacement surgeries. Serious complications were

described in 24% of OSA patients versus 9% of the non-OSA patients.[10] Significant postoperative oxygen desaturation was reported in the OSA patients (17%) versus non-OSA patients (8%) undergoing elective surgery.[11]

The administration of sedatives, anesthetics, and analgesics in OSA patients worsen obstruction of the pharynx.[12-15] In OSA patients under general anesthesia, there is greater depression of the upper airway muscles than the diaphragm. Thus, breathing efforts continue while upper airway muscle activity is markedly reduced predisposing these patients to upper airway collapse during inspiration.[16] This is due to the depression of central respiratory output to the upper airway dilator muscles and the upper airway reflexes.[17-20] In addition, general anesthesia directly inhibits laryngeal respiratory modulated mechanoreceptors, and therefore, upper airway reflexes, and thus depresses arousal responses.[21,22]

With the increase in obesity and the consequent rise in prevalence of OSA, clinicians need evidence-based guidelines regarding the perioperative management of OSA to minimize adverse events related to the administration of anesthetic agents. Preoperative screening for OSA and perioperative management strategies have been suggested in previous reviews.[23-25] The American Society of Anesthesiologists published a guideline for anesthesiologists in the perioperative management of OSA patients.[26] These guidelines apply to both inpatients and outpatients diagnosed with OSA, procedures performed in an operating room, and in other locations where sedation or anesthesia is administered. However, the guidelines do not describe the effect of sedatives and anesthetics in patients with OSA in the perioperative period.

Knowledge of the effects of sedative medications will help inform anesthesiologists about the choice of sedatives in OSA patients. The objective of this systematic review is to determine the effect of perioperative sedatives and anesthetics in surgical patients with OSA on medication requirements, hemodynamics, respiratory events, pain, emergence, and hospital stay in order to make recommendations regarding the use of perioperative sedatives and anesthetics in OSA patients based on the best-available evidence.

Materials and Methods

We searched The Cochrane CENTRAL Register of Controlled Trials (Quarter 2010), Medline (R) (1950-June 2010), Embase (1980-2010), and Cochrane Database of Systematic Reviews (2005-May 2010) for relevant articles. The following key words were used for the literature search: "sedatives," "hypnotics," "OSA," and "anesthesia." The medical subject heading index terms on Medline were "sleep disordered breathing," "sedatives," "hypnotics," and "anesthetics". We also used "sedatives," "sleep," and "anesthetics" as index terms to capture data relating to themes of "sedatives," "hypnotics," "OSA" and "anesthetics." Other search areas included "sedatives" combined with "sleep" or "upper airway," "anesthesia," and "analgesia." We reviewed the abstracts of the following meetings: Canadian Anesthesiologists' Society (2000-009), American Society of Anesthesiologists (2000-2009), Sleep Medicine meeting abstracts (2000-2010), and International Anesthesia Research Society (2000-2010). We also manually searched reference lists from the already retrieved articles to identify further trials. The Medline search strategy is available as a web appendix.

Selection criteria

Two reviewers (SA and JW) independently assessed titles, abstracts, and/or the full-text papers retrieved from the electronic database and manual searches for possible inclusion according to the predefined selection criteria. Disagreements between the authors were resolved by the third author (FC). In the first phase of the review, obviously irrelevant articles were excluded by reviewing the title of the search results. In the next phase, the abstract and/or full-text articles were evaluated to determine if they met the eligibility criteria.

All randomized controlled trials (RCTs), prospective studies, and retrospective studies were eligible for inclusion if they reported the effects of perioperative administration of sedation and anesthetics on medication requirements, pain, emergence, hemodynamics, respiratory events, and hospital stay in OSA patients. As adverse effects of sedatives are rare, case reports and correspondence were also included when they met one of the study criteria. Moreover, the included studies must have met these criteria: Human studies, adults and published in English. Obese patients without OSA, studies in animals, studies in the pediatric population, and not reporting one of our outcomes were excluded.

Quality assessment of the studies

All the papers were classified according to the Oxford Centre for Evidence based Medicine Levels of evidence. The appraisal process focused on the strength of the study design. The classification was as follows: Level 1: 1a: Systemic Review (SR) (with homogeneity) of RCTs; 1b: Individual RCT (with narrow Confidence Interval); 1c: All or none (met when all patients died before the treatment became available, but some now survive on it; or when some patients died before the treatment became available, but none now die on it). Level 2: 2a: SR (with homogeneity) of cohort studies; 2b: Individual cohort study (including low quality RCT); 2c:

"outcomes" research; ecological studies. Level 3: 3a: SR (with homogeneity) of case-control studies; 3b: Individual Case-Control Study; Level 4: Case-series (poor quality cohort and case-control studies); Level 5: Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles."

Whenever possible, Levels 1 and 2 papers were preferentially used; however, Levels 3- papers were used whenever Levels 1 and 2 papers were unavailable. The methodological quality of the records was assessed from the available studies. For RCTs, the methodological quality was assessed on the basis of the quality of randomization, allocation concealment procedure, degree of blinding, and postoperative patient follow-up. If randomization was determined through a computer related means, a table of random numbers or another similar process, it was considered "adequate." Allocation was considered "adequate" if it was carried out by staff members unrelated to the study and used methods such as serially numbered opaque-sealed envelopes. If caregivers and outcome assessors were blinded to the patient allocated groups, blinding was considered "adequate." If dropouts and withdrawals were specified, patient follow-up was considered "adequate." This was independently evaluated by the first author (SA). If there was any doubt, the second author (JW) was consulted.

Data extraction was performed by two reviewers (SA and JW) and validated by the senior author (FC). The following data were extracted from the study: Type of study, sample size, method of diagnosis of OSA, type of procedure, drug interventions, medication requirements, pain, emergence, hemodynamics, respiratory events, and hospital stay.

Results

The search strategy resulted in 2959 articles. The irrelevant papers by title review and abstracts (2736) were excluded leaving 223 articles. Eighteen articles were selected for further analysis including 1 RCT, 3 prospective studies, 4 retrospective chart reviews, 2 cases series, 7 case reports, and a correspondence meeting our criteria [Figure 1]. The remaining 205 articles were excluded due to the following reasons: Irrelevant abstracts or full-text review (160 articles), duplicate records (15 articles), reviews (15 articles), studies on obese patients without OSA (8 articles), studies on pediatric population (4 articles), and studies on nonsurgical population (3 articles). The characteristics of all the included studies are shown in Tables 1 and 2. Polysomnography was mentioned as a diagnostic tool in 8 articles; previous history of OSA was described in 10 articles. Based on the level of evidence, we had 1 Level 1b study, 3 level 2b studies; 4 level 2c studies, and 10 level 4 studies.

An adequate method of randomization was described in the RCT.[27] The allocations were equal between the control and the intervention groups. The method of blind assessment was adequate and there were no drop outs.

Effects of sedatives and anesthetics on respiratory events in OSA patients

13 of 18 (72.2%) articles assessed respiratory events with the administration of sedatives and anesthetics in OSA patients. These articles had 149 OSA patients out of 1175 patients. There were three prospective studies describing the use of propofol and fentanyl in general anesthesia[28-30] and two case reports describing the use of propofol for sedation.[31,32] The use of propofol with an inhalational anesthetic agent showed variable effects. Decreased oxygen saturation ($P < 0.05$) was described in the immediate postoperative period when propofol was administered with isoflurane.[29,30] However, no difference in oxygen desaturation index between OSA and non-OSA groups was noted in a randomized prospective study with propofol, desflurane, and remifentanil.[28] With the administration of propofol alone for sedation, no adverse respiratory effects were reported.[31] In summary, the administration of propofol alone or with desflurane and remifentanil was not associated with any adverse respiratory effects. However, decreased oxygen saturation occurred in the immediate postoperative period when propofol was administered with isoflurane.

The use of midazolam and fentanyl for sedation caused a few adverse respiratory events [Table 1] in two case reports.[32,33] Temporary interruption of middle ear surgery with sedation using midazolam and fentanyl was described in eight OSA patients due to difficulty in maintaining upper airway patency.[33] These patients were retrospectively diagnosed as having OSA by polysomnography. Loud snoring leading to uvular edema was described with midazolam, fentanyl, and propofol sedation in an OSA patient undergoing left upper limb procedure with brachial plexus block.[32] However, uneventful office-based laser uvulo-palato-pharyngoplasty was reported with sedation using midazolam and fentanyl.[34]

There was only one randomized prospective placebo-controlled trial describing the role of alpha 2 agonists (clonidine and dexmedetomidine) in OSA patients [Table 2]. This study of 30 OSA patients described less perioperative desaturation ($P<0.05$) with clonidine premedication versus non-OSA patients.[27]

There were four case reports [Table 2] on the intraoperative use of dexmedetomidine with no adverse respiratory events.[35-38] Most published data reported its use in the perioperative

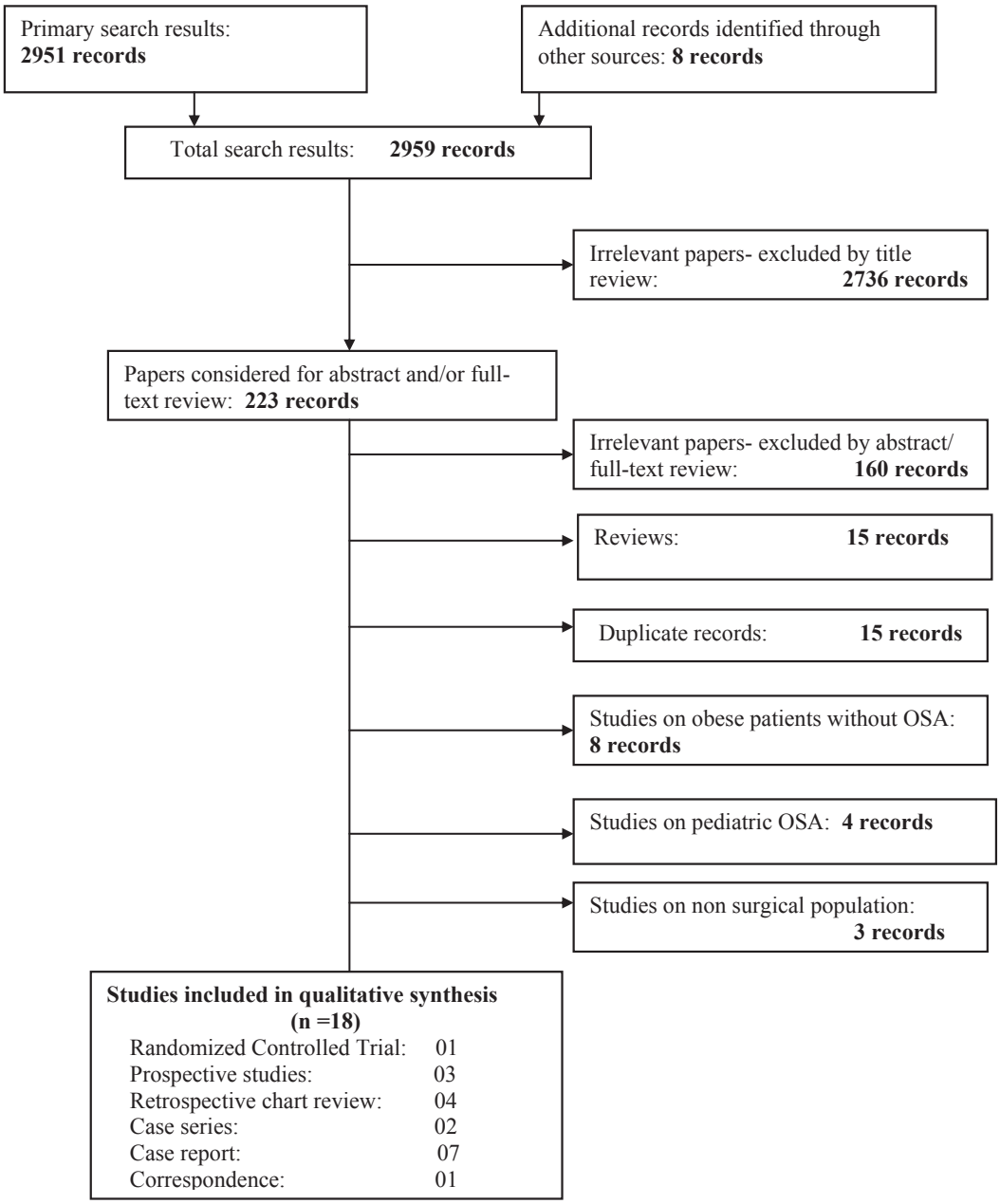

Figure 1: Flow diagram showing screened, excluded, and analyzed papers

setting as a bolus (0.1 mcg/kg) followed by an infusion ranging from 0.1 to 0.7 mcg/kg/hr. The use of a higher infusion rate of dexmedetomidine at 10 mcg/kg/h as a sole anesthetic agent in an OSA patient undergoing tracheal resection maintained intraoperative saturation above 95% without any breathing difficulties.[37] However, there were no prospective studies other than these case reports.

Effects of sedatives and anesthetics on the requirement of perioperative medications in OSA patients

Nine of 18 (50%) articles described the effect of sedatives and anesthetics on the requirement of medications (inhalational anesthetic agents, analgesics, rescue medications). There were 331 patients with OSA out of 366 patients studied. Sedation with propofol [Table 1] as a bolus and infusion along with local anesthetic infiltration eliminated the need for additional sedatives/analgesics during the intraoperative period in an OSA patient undergoing vasectomy.[31] Similar findings were documented in an OSA patient with sedation using a combination of intravenous midazolam, fentanyl, and ketamine for upper limb surgery.[32] The use of intravenous ketamine for sedation [Table 1] did not necessitate further anesthetic/sedative medications in an OSA patient undergoing tracheostomy.[39]

The use of alpha 2 agonists in OSA patients reduces the

Table 1: Effect of sedatives and anesthetics in obstructive sleep apnea patients

Authors	Study design	Level of evidence	Diagnosis	Type of surgery	Number of patients	Intervention type	Medications requirement	Pain and emergence	Hemodynamics	Respiratory events	Hospital stay
Ahmad[28] 2008	Randomized prospective study	2b	PSG	Laparoscopic bariatric	41 pts OSA: 31 Non-OSA: 9	Standard GA using propofol, desflurane and remifentanil infusion	NA	No difference in pain scores and morphine requirement between OSA and non-OSA groups	Hemodynamics maintained within 20% of preop level in both groups	No difference in oxygen desaturation index, total hypoxemic episodes between OSA and non-OSA groups	No difference in discharge between two groups
Hendolin[29] 1994	Randomized prospective study	2b	PSG	UPPP and bilateral tonsillectomy	41 pts Propofol (20) OSA: 12 Non-OSA: 8 Thiopentone (21) OSA: 12 Non- OSA: 9	Propofol bolus and infusion (20 pts) Thiopentone and isoflurane (21 pts) Fentanyl 100 mcg	No significant difference	↓ Pain score in propofol group ($P<0.05$); Smooth emergence in both groups	Hemodynamics maintained within 25% of awake measurements in both groups	↓ spontaneous breathing and O_2 saturation in isoflurane group ($P<0.05$)	NA
Eikermann[30] 2010	Prospective descriptive study	2b	Previous h/o OSA	Bariatric	100 pts (36 OSA pts)	GA using fentanyl/ propofol, desflurane or isoflurane, remifentanil	NA	NA	NA	↓ SpO_2 before and during induction of anesthesia ($P<0.05$). Nadir SpO_2 was ↓ in non-OSA group ($P<0.05$)	NA
Cillo JE[34] 2005	Chart review[$]	2c	PSG	UPPP	15 OSA pts	Fentanyl 50-100 ug Midazolam 1-5 mg	NA	NA	NA	No airway obstruction or respiratory distress	NA
Ezri T[41] 2004	Chart review[$]	2c	PSG	Laproscopic bariatric (167) Open bariatric (67)	234 Laproscopic: 8/167 OSA Open: 4/67 OSA	GA using thiopentone/ propofol, fentanyl	NA	↓ Meperidine/ morphine/ diclofenac in open bariatric group ($P=0.03$)	Stable hemodynamics in both groups	No adverse events	Shorter hospital stay in laproscopic group ($P=0.01$)
Brown D[39] 1986	Case report	4	Previous h/o OSA	Tracheostomy	1	Ketamine 100 mg bolus and infusion at 30 mg/h	Does not require further sedation/ bronchodilators	↓ agitation	NA	↓ wheeze and airway pressure during mechanical ventilation	Discharged home on 6th POD
Iwama H[31] 2003	Case report	4	Previous h/o OSA	Vasectomy	1	Propofol bolus followed by Infusion; Local anaesthetic infiltration	NA	Smooth emergence; Less pain at surgical site	NA	No adverse events	Discharged home after 2 hours

(Table 1 Contd...)

(Table 1: Contd..)

Authors	Study design	Level of evidence	Diagnosis	Type of surgery	Number of patients	Intervention type	Medications requirement	Pain and emergence	Hemodynamics	Respiratory events	Hospital stay
Miller[32] 2006	Case report	4	PSG	Upper limb procedure	1	Midazolam (2 mg) Fentanyl (100 ug) Ketamine (90 mg) Propofol (30 mg) Brachial plexus block	NA	NA	NA	Intraoperative snoring without apnoeic episodes	Uvular edema on 2nd POD
Agro F[33] 2004	Corres*	4	PSG	Middle ear	700 (8 OSA pts)	Midazolam 0.03 mg/kg Fentanyl 1.4-1.5 ug/kg	NA	NA	NA	Temporary interruption of surgery in 8/700 patients (1.14%)	NA

$: Retrospective; Corres: Correspondence; UPPP: UvuloPalato Pharyngoplasty; PSG: Polysomnography; OSA: Obstructive sleep apnea; Dex: Dexmedetomidine; NA: Not available; O_2: Oxygen; SpO_2: Oxygen saturation; GA: General Anesthesia; h/o: History of; POD: Post-Operative Day; pts: Patients*

requirement of perioperative anesthetics, analgesics, and anti-hypertensives [Table 2]. In a randomized prospective trial, preoperative oral clonidine reduced the propofol requirement ($P<0.05$) and the use of antihypertensive drugs ($P<0.001$).[27] In a retrospective chart review of 268 patients undergoing airway reconstruction surgery, the use of dexmedetomidine intraoperatively as a bolus and infusion decreased the use of anti-hypertensives ($P=0.005$).[40]

Effect of sedatives and anesthetics on intraoperative hemodynamics in OSA patients

Ten of 18 (55.6%) articles described hemodynamic changes with administration of sedatives and anesthetics. Of 645 patients studied, 375 patients had OSA. Currently used sedatives and anesthetics did not have any adverse effects on intraoperative hemodynamics with the exception of clonidine [Table 1]. Standard general anesthesia using propofol, fentanyl, remifentanil, isoflurane, or desflurane maintained stable hemodynamics in these patients.[28,29,41]

The use of alpha 2 agonists was shown to alter hemodynamic parameters perioperatively [Table 2]. Oral clonidine premedication was associated with a significant reduction of mean arterial pressure and heart rate ($P < 0.05$) during surgery and emergence.[27]

In a retrospective chart review of 268 OSA patients undergoing airway reconstruction surgery, the use of dexmedetomidine maintained stable hemodynamics.[40] Similar findings were described in a retrospective cohort involving 22 OSA patients undergoing laparoscopic bariatric surgery.[42] There were case reports of stable hemodynamics [Table 2] with the use of dexmedetomidine for patients undergoing laparoscopic adrenal resection and awake thyroidectomy.[35,38] However, transient hypotension [Table 2] was described in case reports of patients undergoing tracheal resection and tracheostomy.[37,43] Essentially, intraoperative dexmedetomidine was mostly associated with stable hemodynamics and oral clonidine premedications was associated with lowering of blood pressure and heart rate.

Effect of sedatives and anesthetics on pain and emergence in postoperative period

14 of 18 (77.8%) articles described postoperative pain and emergence with the administration of sedatives and anesthetics in OSA patients. Out of 649 patients studied, 379 patients had OSA. Emergence was smooth with the currently used sedatives and anesthetics [Table 1]. Smooth emergence was described when propofol was administered as a bolus and infusion for an OSA patient undergoing vasectomy.[31] In a prospective randomized study of 41 patients undergoing uvulo-palato-pharyngoplasty [Table 1], there was no difference in

Table 2: Effect of clonidine and dexmedetomidine in OSA patients

Authors	Study design	LOE	Diagnosis	Type of surgery	Pts N	Intervention	Medication requirement	Pain and emergence	Hemodynamics	Respiratory events	Hospital stay
Pawlik[27] 2005	RCT	1b	PSG	Septoplasty ± UPPP	30	Oral clonidine 2 ug/kg the evening before and 2 h before induction	↓ Propofol (P <0.05). ↓ Antihypertensives (P <0.001)	↓ mean VAS in PACU and 24h (P <0.001) in clonidine group; faster eye opening on command in clonidine group (P <0.05)	↓ MAP and HR during surgery and emergence in clonidine group (P <0.001)	↓ desaturation indices in perioperative period vs baseline values in both groups (P <0.05)	NA
Chawla [40] 2010	Chart review$	2c	Previous h/o OSA	Airway re-construction	Dex 125 Control 143	Dex 1 ug/kg and infusion of 0.1-0.2 ug/kg/hr	↓ Hydralazine (P <0.001) ↓ GTN (P = 0.005) ↓ Clonidine (P <0.001) ↓ Beta blockers (P <0.001)	↓ Morphine (P = 0.008)	Stable MAP	NA	NA
Olumuyiwa[42] 2009	Cohort$	2c	PSG	Laparoscopic bariatric	22 OSA pts	Dex 1 ug/kg and infusion at 0.4 ug/kg/hr	No intraoperative opioid needed	↓ Pain score in PACU; No postoperative opioid needed	Stable hemodynamics	NA	NA
Dhar[38] 2003	Case series	4	Previous h/o OSA	Laparoscopy; colostomy	2	Dex 1 ug/kg and infusion at 0.2 ug/kg/hr	NA	Smooth emergence	Stable hemodynamics	No adverse events	NA
Basem[43] 2007	Case series	4	Previous h/o OSA	Tracheos-tomy	5:2 OSA pts	Dex 1 ug/kg and infusion at 0.6 ug/kg/hr	NA	Patients comfortable	Transient ↓ BP	No adverse events	NA
Plunkett[35] 2009	Case report	4	Previous h/o OSA	Awake Thy-roidectomy	1	Dex 1 ug/kg and infusion at 0.2-1.0 ug/kg/hr	↓ Fentanyl	↓ Pain score in PACU	Stable intraop vital signs	No adverse events	NA
Ramsay[37] 2006	Case report	4	Previous h/o OSA	Tracheal resection	1	Dex 1ug/kg and infusion at 0.7-10 ug/kg/hr	No intraop or postop opioid	No pain Smooth emergence	↓ BP	SpO_2 >95% throughout the procedure	2 days
Hofer[44] 2004	Case report	4	Previous h/o OSA	Roux-en-Y gastric bypass	1	Dex 1.4 ug/kg and infusion at 0.7 ug/kg/hr	NA	↓ Morphine	NA	NA	NA
Huncke[36] 2008	Case report	4	Previous h/o OSA	Awake craniotomy	1	Dex 0.4ug/kg and infusion at 0.1-0.2 ug/kg/hr	Remifentanil infusion	Minimal pain; Mildly sedated; Verbally responded	NA	No adverse events	NA

RCT: Randomized double-blinded placebo-controlled trial; LOE: Level of evidence; Pts N: Number of patients; $: Retrospective; UVPP: Uvulo palato pharyngoplasty; PSG: Polysomnography; OSA: Obstructive sleep apnea; Dex: Dexmedetomidine; PACU: Post anesthesia care unit; NA: Not available; SpO_2: Oxygen saturation; VAS: Visual analog scale; MAP: Mean arterial pressure; HR: Heart rate

emergence between propofol and the thiopentone groups.[29] Ketamine was found to decrease agitation in a patient undergoing tracheostomy who was refractory to sedation with lorazepam.[39]

Emergence from anesthesia was rapid with clonidine involving 30 OSA patients versus the control group.[27] Contradictory reports regarding emergence occurred with intraoperative dexmedetomidine [Table 2]. Smooth emergence was described in an OSA patient undergoing tracheal resection.[37] However, mild sedation responding to verbal commands was described in an OSA patient who had undergone awake craniotomy with dexmedetomidine.[36] Emergence was smooth with the use of propofol and/or clonidine, but there is one case report of mild sedation with dexmedetomidine.[27,29,36]

There was no difference in pain scores with the anesthetic techniques described in the studies [Table 1]. Intraoperative opioids decrease both analgesic consumption and pain scores in the postoperative period. In a randomized prospective study involving 53 OSA patients undergoing laparoscopic bariatric surgery, the use of fentanyl and remifentanil was found to decrease pain ($P < 0.05$) in the immediate postoperative period.[28,29] In a retrospective chart review involving 12 OSA patients undergoing laparoscopic bariatric surgery, intraoperative use of fentanyl was found to decrease the analgesic consumption ($P = 0.03$) in the postoperative period.[41]

The use of alpha 2 agonists in OSA patients during the perioperative period decreased the opioid requirement and pain scores and contributed to smooth emergence from anesthesia [Table 2]. A randomized double-blinded placebo-controlled trial of 30 patients reported a lower mean visual analog score ($P < 0.001$) in the post-anesthetic care unit and the first 24 h with the use of oral clonidine premedication versus placebo.[27]

In a retrospective chart review of 268 patients undergoing airway reconstructive surgery [Table 2], intraoperative dexmedetomidine was found to reduce morphine requirements ($P = 0.008$) in the postoperative period.[40] There were case reports of opioid sparing action with dexmedetomidine [Table 2] in gastric bypass surgery[44] and in awake thyroidectomy.[35] Intraoperative use of fentanyl or dexmedetomidine lowered pain scores and reduced postoperative morphine requirements.

Effect of sedatives and anesthetics on the hospital stay

The length of hospital stay following administration of sedatives and anesthetics was described in less than half of the studies, 6/18 (33.3%). These studies had 48 OSA patients out of 280 patients studied. There was no difference in the hospital stay with the currently used sedatives and anesthetics [Table 1]. OSA patients receiving propofol for conscious sedation met the discharge criteria within 2 h.[31] Shorter hospital stay ($P = 0.01$) was described with the use of propofol and fentanyl in 12 OSA patients undergoing laparoscopic bariatric surgery over open restrictive bariatric surgery [Table 1].[41] This could be due to the short acting anesthetic agents and early return of bowel function with laparoscopic surgery. However, there was no difference in discharge from hospital in 31 OSA patients who underwent laparoscopic bariatric surgery with standard anesthetic technique.[28] There was limited data on the hospital stay with the use of dexmedetomidine in OSA patients.

Discussion

Our systematic review yielded 18 articles describing the effects of sedatives and anesthetics on perioperative respiratory events, medication requirements, hemodynamics, postoperative pain, emergence, and hospital stay in patients with OSA. Few adverse effects were reported when patients with known OSA underwent elective surgery with the currently available sedatives and anesthetics. These reports were limited by the number of patients, their level of evidence, and the uniformity of reporting of outcomes.

Benzodiazepines depress central nervous system (CNS) activity and increase the level of inspiratory effort required to cause arousal after sleep in OSA patients. Studies *in vivo* and *in vitro* have described gamma amino butyric acid (GABA) A and *N*-methyl-D-aspartate (NMDA) receptors in the cortex, thalamus, brain stem, and striatum as important targets of hypnotic drugs.[45,46] The administration of midazolam markedly increases supraglottic upper airway resistance and induces central apnea followed by obstructive apneic events.[47] Benzodiazepines decrease the arousal response to hypoxia and hypercarbia and thereby increase the duration of apnea.[48] Even a small dose of triazolam (0.25 mg), a benzodiazepine, has been shown to increase apneic duration and worsen oxygen saturation in patients with severe OSA.[49] Similarly, the administration of pentobarbital, a barbiturate in healthy volunteers increases upper airway resistance and end-tidal CO_2 concentration when compared to placebo.[50]

Eight patients with undiagnosed OSA undergoing middle ear surgery with midazolam and fentanyl had impaired upper airway patency.[33] These patients were retrospectively diagnosed as having OSA by polysomnography. Also, intraoperative snoring causing uvular edema in the postoperative period was reported when propofol was administered with midazolam and fentanyl for sedation.[32] This edema could be due to synergistic respiratory depression caused by midazolam in conjunction with a preexisting dysfunctional airway in OSA

patients. Every effort should be made to minimize the use of sedatives in OSA patients to minimize adverse events. With its sedative properties and elimination half-life of 2 h, midazolam should be avoided or only small doses should be used in OSA patients. Preoperative screening of patients with the STOP-Bang questionnaire may have alerted the anesthesiologists to the possibility of OSA and direct the appropriate perioperative management.[23]

In a retrospective study of elective non-cardiac surgical procedures, respiratory complications were more frequent in patients with OSA (44%) versus those without OSA (28%).[11] Of these respiratory complications, oxygen desaturation was the major adverse event.[11] In another retrospective study of patients undergoing hip or knee replacement surgery, significantly higher postoperative complications occurred in OSA patients versus non-OSA patients.[10] A recent retrospective cohort study of 65,774 OSA patients undergoing orthopedic procedures and 51,509 OSA patients undergoing general surgical procedures found that OSA patients had significantly higher pulmonary complications like aspiration pneumonia, acute respiratory distress syndrome, and intubation/mechanical ventilation.[51] Due to the small patient numbers, our systematic review in OSA patients showed only eight cases of temporary interruption of middle ear surgery and one case of uvular edema with intraoperative snoring with the use of sedatives.

Inhalational anesthetic agents have shown variable responses during emergence in OSA patients. In a randomized prospective study involving 24 OSA patients, the use of propofol and isoflurane in upper airway surgery delayed recovery of respiration with a drop in oxygen saturation.[29] This may be due to the quantified effects of sub-anesthetic concentrations of inhalational anesthetics on the human ventilatory response to hypoxia.[52] However, further studies evaluating its effects on respiratory events are warranted. Faster emergence after bariatric surgery was described with sevoflurane over isoflurane.[53] Similar effects were noticed with desflurane over isoflurane or propofol.[54]

The administration of propofol in healthy volunteers has been shown to produce a sleep-like state with slow waves on electroencephalogram (EEG) and decreased consciousness even in the presence of high gamma activity.[55,56] However, there is no data on the effects of propofol and EEG changes with known OSA patients.

Ketamine anesthesia abolishes the coupling between loss of consciousness and upper dilator muscle dysfunction and thereby protects upper airway patency in OSA patients.[30] Ketamine was used as an effective sedating agent for a tracheostomy procedure in an OSA patient who was refractory to lorazepam sedation. Concentration-dependant relaxation of the trachealis muscle has been described in animal studies,[57,58] but its effect on OSA patients needs to be evaluated. Ketamine may offer advantages of maintaining upper airway patency in OSA patients and further studies are warranted.

Clonidine decreases perioperative anesthetic and analgesic requirements in OSA patients. It increases the slow-wave activity (delta) and attenuates the physiological alpha fluctuations and thereby causes sedation and lower bispectral index scores (BIS).[59] Administration of clonidine preoperatively has been shown to potentiate the effects of anesthetics[60] and decrease the requirement of propofol.[61]

Studies on the analgesic potency of clonidine did not show consistent results, ranging from minor analgesic effects to significant opioid sparing effect.[62,63] However, superior analgesia with significant opioid sparing effect has been described in OSA patients with preoperative clonidine.[27] The reduced opioid requirement with clonidine in OSA patients could be due to upregulation of mu opioid receptors in the brainstem caused by continuous hypoxemia as described in a hypoxic animal model.[64] The use of clonidine in OSA patients has shown less oxygen desaturation in the postoperative period. The combination of REM sleep suppression and reduced use of opioids with clonidine may have reduced oxygen desaturation indices.[27,65]

There may be a theoretical advantage of using dexmedetomidine in OSA patients. The use of dexmedetomidine stimulates receptors in the locus coeruleus causing sedation and analgesia by stimulating spinal cord receptors.[66] Dexmedetomidine infusion causes a mild decrease in minute ventilation and an increase in $PaCO_2$; however, these effects are much less pronounced than with opioids and are similar to those seen during profound sleep.[67] The use of dexmedetomidine reduces the propofol and morphine requirements during bispectral index-guided sedation[68] and reduces the requirement of midazolam by 80% and morphine by 50% when compared to placebo.[69] There are no RCTs with the use of dexmedetomidine in OSA patients. Most of the published data are from case reports and retrospective chart review.[35-38,40,42-44] Though dexmedetomidine was shown to be advantageous over currently used sedatives and anesthetics in case reports, well-designed studies involving large numbers of OSA patients are warranted.

There is limited data on the length of hospital stay in OSA patients with the currently used sedatives and anesthetics. However, a significantly prolonged hospital stay has been described in OSA patients compared with patients

without OSA after non-cardiac, hip, or knee replacement surgeries.[10,70]

The results of our review must be interpreted with caution due to several limitations. There was a lack of studies that clearly had the objective of determining the effects of sedatives and anesthetics on respiratory events, hemodynamic changes, medication requirements, pain, emergence, and hospital stay. Thus, we included the case reports and case series. In these studies, there was also a lack of reported adverse effects from sedatives or anesthetics may result from the limited number of patients. As well, there was a lack of uniformity in the outcomes assessed. However, it is difficult to perform large prospective studies in the OSA patient population because there may be increased vigilance by clinicians to avoid adverse events. The rarity of adverse events may necessitate reporting of adverse events with patient registry, events through case series or outcomes databases from multiple centers with detailed reporting of patient characteristics, drug doses, and other contributory factors.

In conclusion, based on the results of our systematic review, there were adverse effects reported when patients with known OSA underwent elective surgery with the currently available sedatives and anesthetics. Impaired airway patency in eight undiagnosed OSA patients, and uvular edema with intraoperative snoring in a known OSA patient with sedation using midazolam, have been described. Caution is suggested with the use of benzodiazepines. However, these reports are limited by the number of patients, their level of reported evidence, and the uniformity of reporting of outcomes. There is a need for further trials with large numbers and uniform reporting of outcomes.

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