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Negative pressure pulmonary edema causing postoperative hypoxemia: is there a relationship with the administration of sugammadex?

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Keypoints

1. Post-obstructive pulmonary edema or negative pressure pulmonary edema (NPPE) is an uncommon, but well-described cause of hypoxemia following anesthetic care.
2. NPPE results from the generation of negative intrathoracic pressure due to forceful inhalation against an obstructed airway, most commonly laryngospasm.
3. The pathophysiology is characterized by non-cardiogenic pulmonary edema, which is clinically manifested by postoperative hypoxemia, tachypnea, a cough with the production of pink, frothy sputum, increased work of breathing, and respiratory insufficiency.
4. Once a diagnosis of NPPE is made and other causes of postoperative hypoxemia ruled out, treatment includes the administration of supplemental oxygen, diuresis, and inhaled β-adrenergic agonists. If hypoxemia persists, non-invasive respiratory support with CPAP or BiPAP is indicated followed by endotracheal intubation in severe cases.
5. Although no definitive relationship or mechanism has been proven, anecdotal reports note the association of reversal of neuromuscular blockade with sugammadex and the occurrence of NPPE.

Abstract

Negative pressure pulmonary edema is an uncommon cause of postoperative hypoxemia. Following upper airway obstruction, negative pressure pulmonary edema occurs due to the generation of negative intrathoracic pressure by forceful inhalation against an obstructed upper airway. This complication has previously been described in the context of laryngospasm during anesthetic care as well as a variety of other clinical scenarios including strangulation, foreign body aspiration, and obstructive sleep apnea. In the postoperative patient, management of this complication requires recognition and differentiation from other etiologies of hypoxemia. We present a 17-year-old adolescent who developed hypoxemia in the post-anesthesia care unit due to negative pressure pulmonary edema following laryngospasm during emergence from anesthesia and tracheal extubation. The differential diagnosis of postoperative hypoxemia in an otherwise healthy patient is presented, investigative work-up reviewed, and treatment options discussed. Additionally, the anecdotal association of sugammadex with NPPE is outlined.

Keywords

Negative pressure pulmonary edema; non-cardiogenic pulmonary edema; hypoxemia; laryngospasm; sugammadex

Introduction

Post-obstructive pulmonary edema or negative pressure pulmonary edema (NPPE) is an uncommon, but well-described cause of hypoxemia following anesthetic care. While the exact pathophysiology of this complication is not completely understood, it results from the generation of negative intrathoracic pressure due to forceful inhalation against an obstructed airway.[1-3] The negative intrapulmonary pressure results in fluid movement across the alveolar membrane and non-cardiogenic pulmonary edema. NPPE has been separated into type 1, which occurs when there is forced inspiration with acute upper airway obstruction, while type 2 occurs after releasing a chronic airway obstruction (tonsillectomy).[4] The most commonly identified etiology is laryngospasm during emergence from anesthesia. It generally occurs as a brief, isolated event in an otherwise young, healthy, and muscular patient with the ability and strength to generate high negative intrathoracic pressures. It may also occur in patients with associated comorbid conditions or specific physical phenotypes including obesity, obstructive sleep apnea, and following upper airway surgery. A large study of 85,561 patients reported an incidence of 0.019% following anesthetic care.[5]

Studies of the alveolar fluid in NPPE demonstrate a low ratio of alveolar/serum protein, demonstrating that the process is primarily transudative, but in some cases the negative pressure may lead to rupture of alveolar capillaries and damage to the alveolar membrane, leading to an exudative alveolar/serum protein ratio. These pathophysiologic changes manifest as postoperative hypoxemia, respiratory insufficiency, increased work of breathing (WOB), and cough with the production of a frothy pink sputum.[6,7] We present a 17-year-old adolescent who developed hypoxemia following a laparoscopic appendectomy which was subsequently determined to be the result of negative pressure pulmonary edema. The potential etiologies of postoperative hypoxemia are reviewed, the pathogenesis of post-obstructive pulmonary edema discussed, and a treatment algorithm presented. Additionally, the anecdotal association of sugammadex with NPPE is outlined.

Case report

Presentation of this case report was in accordance with the guidelines of the Institutional Review Board of Nationwide Children's Hospital (Columbus, Ohio). The patient was a 17-year-old male who presented to the emergency department for evaluation of right lower quadrant abdominal pain, nausea, and anorexia. Abdominal ultrasound revealed acute appendicitis without abscess and the patient was admitted for laparoscopic appendectomy under general anesthesia. At the time of admission, the patient's history and physical exam were unremarkable and he had no comorbid diseases. Past surgical history included adenotonsillectomy and tympanostomy. His weight was 65.4 kilograms, height was 169.4 centimeters with a body mass index of 27.2 kg/m^2. Preoperative vital signs included temperature 36.6 °C, pulse: 98 beats/minute, respirations 16 breaths/minute, blood pressure 112/54 mmHg, and room air oxygen saturation 95%. His physical examination was unremarkable with a normal airway examination and a Mallampati grade 1 view. The patient was transported to the operating room and routine American Society of Anesthesiologists' monitors were placed. Midazolam (2 mg) was administered intravenously and after pre-oxygenation with 100% oxygen, a rapid sequence induction was performed with propofol (200 mg) and fentanyl (100 µg). Neuromuscular blockade was achieved with rocuronium (100 mg) and his trachea intubated. Anesthesia was maintained with sevoflurane in air and oxygen. Dexamethasone (4 mg) and ondansetron (4 mg) were administered to prevent postoperative nausea and vomiting. Hydromorphone (0.5 mg) and acetaminophen (1 gram) were administered for postoperative analgesia. Dexmedetomidine (20 µg) was administered to prevent emergence delirium. There were no

intraoperative complications. Intraoperative fluids included 1000 mL of lactated Ringer's and there was minimal blood loss. At the completion of the surgical procedure which lasted approximately 75 minutes, residual neuromuscular blockade was reversed with sugammadex (300 mg) and when the patient was awake, his trachea was extubated. Following extubation, there was breath holding/laryngospasm which was treated with the application of continuous positive airway pressure (CPAP). Spontaneous respirations resumed and the patient was transported to the post-anesthesia care unit (PACU). Twenty minutes after arrival in the PACU, the patient had pink, frothy secretions, hypoxemia (oxygen saturation 80-85%) despite the application of supplemental oxygen via nasal cannula, and increased work of breathing (WOB) with tachypnea. Physical examination revealed bilateral rales. There was no improvement with the administration of albuterol (2.5 mg) via high flow nebulization. CPAP was applied by a facemask at 8 cmH_2O with inspired oxygen at 50%. This resulted in decreased WOB and resolution of the tachypnea. Furosemide (10 mg) was administered intravenously. A single dose of lorazepam (2 mg) was administered to provide anxiolysis and facilitate tolerance of the mask during the use of CPAP. Over the ensuing 5 hours, the CPAP was weaned off and nasal canula oxygen (3 liters/minute) placed to provide supplemental oxygen and maintain the oxygen saturation greater than 95%. The patient was transferred to the inpatient surgical ward and the oxygen was weaned off over the next 12 hours. The remainder of his postoperative course was unremarkable, and he was discharged home on postoperative day 1.

Discussion

In general, hypoxemia may be caused by one of five potential etiologies including a low inspired oxygen concentration, true shunt as is seen in patients with congenital heart disease, diffusion abnormalities of the alveolar basement membrane, hypoventilation, and ventilation-perfusion inequalities.[8-10] During postoperative care, the latter two categories predominate as explanations for new onset hypoxemia. Hypoventilation is generally easy to identify given its association with a low respiratory rate, upper airway obstruction, and hypercarbia. In the absence of residual respiratory depression from various anesthetic agents including opioids, postoperative hypoxemia primarily results from ventilation-perfusion inequalities. These may be caused by atelectasis, pneumonia, acid-aspiration, or NPPE as was seen in our patient. In this scenario, alveolar space disease results in the perfusion of inadequately ventilated alveoli leading to poorly oxygenated pulmonary venous blood and resultant systemic desaturation.

The diagnosis of NPPE in the postoperative patient is primarily clinical and is dependent on recognition of the associated event, generally laryngospasm. Other causes of cardiogenic or non-cardiogenic pulmonary edema such as tachyarrhythmias, acute heart failure, anaphylaxis, and volume overload should be ruled out. This is followed by identification of the specific signs and symptoms including hypoxemia, increased work of breathing, tachypnea, and a cough with the production of frothy pink sputum. As noted in our patient, the episode of upper airway obstruction may be brief and seemingly clinically insignificant, requiring only repositioning of the airway and the application of CPAP. Although radiologic imaging may demonstrate alveolar space disease, which is diagnostic of non-cardiogenic pulmonary edema and supports the diagnosis of NPPE, it is generally not needed unless used to exclude other causes of hypoxemia.[10,11]

During the perioperative period, laryngospasm remains the most common etiologic event leading to NPPE.[5] Due to various developmental and anatomical reasons, laryngospasm occurs more commonly in pediatric-aged patients. One retrospective study noted an incidence of 8.7 per 1000 procedures in adults, with a rate of 17.4 per 1000 procedures in pediatric patients.[12] Laryngospasm is a primitive protective reflex resulting from stimulation of the airway with fluid or secretions. It results in glottic closure, thereby preventing aspiration. During the perioperative period, precipitating factors include a light plane of

anesthesia, secretions, airway instrumentation including laryngoscopy, airway stimulation during surgery, and tracheal extubation.[13-15] This problem is particularly common in children who have recently suffered a respiratory tract infection, which increases airway irritability, or in patients exposed to tobacco smoke.[16] However, the incidence of NPPE following laryngospasm is low and does not appear to be related to the severity or duration of the obstruction. As noted in our patient, NPPE can occur following a brief, easily treated episode of upper airway obstruction. Outside of the perioperative period, NPPE has also been reported in a wide range of conditions including strangulation, hanging, foreign body aspiration, and following tonsillectomy in patients with obstructive sleep apnea.[1-5,17-20]

Recent case reports and retrospective studies have brought attention to a possible association between NPPE and the use of sugammadex for reversal of neuromuscular blockade. Sugammadex is a cyclodextrin compound which encapsulates and tightly binds steroidal-based neuromuscular blocking agents, thereby removing them from the neuromuscular junction and reversing neuromuscular blockade.[21] Sugammadex has become widely used due to its ability to reverse neuromuscular blockade without the undesirable cholinergic adverse effects of acetylcholinesterase inhibitors such as neostigmine.[21] However, there have been anecdotal reports of the potential association of sugammadex with laryngospasm and NPPE.[22-26] In a retrospective review of anesthetic care for 27,498 patients, sugammadex was administered to 2164. NPPE was identified in two patients that received sugammadex (2 of 2164 or 0.09%) and none of the 25,334 patients who did not receive sugammadex.[27] The authors acknowledged the obvious issues with a retrospective chart review study and concluded that their pilot audit study demonstrated that the use of sugammadex might be a significant risk factor for NPPE in anesthetized patients if acute airway obstruction occurred unanticipatedly. They suggested further large-scale studies should to support their findings. Further discussion, comments, and a conflicting opinion were provided by Drs. Brull and Prielipp in a letter to the editor with their comments regarding the study of Kao et al.[28] While an exact mechanism to account for the association of sugammadex with laryngospasm and NPPE has not been proposed or accepted, future observations and studies are needed to further define this relationship. Whether the use of sugammadex had any impact on the occurrence of laryngospasm and NPPE in our patient is speculative.

Treatment of suspected NPPE begins with a review of the events leading up to the clinical deterioration and identification of an obstructive event involving the upper airway. As noted in our patient, the event may be brief and with a limited initial clinical impact only to have the patient develop hypoxemia in the PACU. A chest radiograph is indicated if the etiology is unclear, as other causes of hypoxemia (aspiration, atelectasis) may present with similar clinical findings (tachypnea, increased WOB, hypoxemia). Treatment paradigms are tailored based on the patient's clinical status (Table 1).

Table 1: Treatment algorithm for negative pressure pulmonary edema

1. Establish diagnosis
    a. Clinical history of upper airway event
    b. Presence of hypoxemia
    c. Clinical signs and symptoms
        i. Tachypnea, increased work of breathing, cough with pink frothy sputum
    d. Rule out other causes of cardiogenic or non-cardiogenic pulmonary edema
2. Chest radiograph if diagnosis is in doubt
3. Supplemental oxygen with standard nasal cannula
4. Tracheal intubation and resuscitation for respiratory failure or hemodynamic instability
5. Respiratory techniques to re-establish functional residual capacity
    a. High flow nasal cannula
    b. Continuous positive airway pressure (CPAP)
    c. Bilevel positive airway pressure (BiPAP)
6. Pharmacologic therapy
    a. Diuretics
    b. Inhaled β-adrenergic agonists

Patients with impending respiratory failure or hemodynamic compromise may require tracheal reintubation and resuscitation. In most cases, symptomatic treatment initially includes the administration of supplemental oxygen. In mild cases, this may include standard nasal cannula. In most severe cases, techniques to re-establish

functional residual capacity (FRC) may be required including high-flow nasal cannula or application of CPAP or BiPAP (bilevel positive airway pressure). Non-invasive respiratory support including CPAP to treat postoperative hypoxemia has been shown to decrease the need for tracheal reintubation following abdominal surgery.[26] As the pathogenesis of NPPE involves non-cardiogenic pulmonary edema, pharmacologic therapy with diuretics or inhaled β-adrenergic agonists may be used to hasten the resolution of pulmonary edema and improve oxygenation. In addition to these measures, continued observation in the PACU or intensive care unit (ICU) is warranted. As noted in our patient, clinical improvement may be seen in a few hours thereby allowing care in the PACU and then admission to the inpatient ward rather than the ICU once clinical symptomatology has improved. As with our patient, uncomplicated cases without residual pulmonary edema or supplemental oxygen requirement can be safely discharged within 24 hours.

References

1. Lemyze M, Mallat J. Understanding negative pressure pulmonary edema. Intensive Care Med. 2014;40:1140-1143.
2. Krodel DJ, Bittner EA, Abdulnour R, Brown R, Eikermann M. Case scenario: acute postoperative negative pressure pulmonary edema. Anesthesiology. 2010;113:200-207.
3. Fremont RD, Kallet RH, Matthay MA, Ware LB. Post-obstructive pulmonary edema: a case for hydrostatic mechanisms. Chest. 2007;131:1742-1746.
4. Bhattacharya M, Kallet RH, Ware LB, Matthay MA. Negative-pressure pulmonary edema. Chest 2016;150:927-933.
5. Tsai PH, Wang JH, Huang SC, Lin YK, Lam CF. Characterizing post-extubation negative pressure pulmonary edema in the operating room-a retrospective matched case-control study. Perioper Med. 2018;7:28.
6. Scarbrough FE, Wittenberg JM, Smith BR, Adcock DK. Pulmonary edema following postoperative laryngospasm: case reports and review of the literature. Anesth Prog. 1997;44:110-116.
7. Halow KD, Ford EG. Pulmonary edema following post-operative laryngospasm: a case report and review of the literature. Am Surg. 1993;59:443-447.
8. Morton CP, Drummond GB. Change in chest wall dimensions on induction of anaesthesia: a reappraisal. Br J Anaesth. 1994;73:135-139.
9. Wahba RW. Perioperative functional residual capacity. Can J Anaesth. 1991;38:384-400.
10. Karcz M, Papadakos PJ. Respiratory complications in the post-anesthesia care unit: A review of pathophysiological mechanisms. Can J Respir Ther. 2013;49:21-29.Bhaskar B, Fraser JF. Negative pressure pulmonary edema revisited: Pathophysiology and review of management. Saudi J Anaesth. 2011;5:308-313.
11. Cascade PN, Alexander GD, Mackie DS. Negative-pressure pulmonary edema after endotracheal intubation. Radiology. 1993;186:671-675.
12. Olsson GL, Hallen B. Laryngospasm during anaesthesia. A computer-aided incidence study in 136,929 patients. Acta Anaesthesiol Scand. 1984;28:567-575.
13. Tait AR, Malviya S, Voepel-Lewis T, et al. Risk factors for perioperative adverse respiratory events in children with upper respiratory tract infections. Anesthesiology. 2001;95:299-306.
14. Van der Walt J. Anesthesia in children with viral respiratory tract infections. Paediatr Anaesth. 1995;5:257-261.
15. Schreiner MS, O'Hara I, Markakis DA, et al. Do children who experience laryngospasm have an increased risk of upper respiratory tract infection? Anesthesiology. 1996;85:475-479.
16. Lakshmipathy N, Bokesch PM, Cowen DE, Lisman SR, Schmid CH. Environmental tobacco smoke: a risk factor for pediatric laryngospasm. Anesth Analg. 1996;82:724-727.

17. Raj V, Bhatnagar V. Post Obstructive pulmonary edema following attempted suicide by hanging. Med J Armed Forces India. 2009;65:184-185.
18. Derks L, Plash W, Powell E, Tilney PV. 16-year-old female near hanging with negative pressure pulmonary edema. Air Med J. 2017;36:5-7.
19. Toukan Y, Gur M, Bentur L. Negative pressure pulmonary edema following choking on a cookie. Pediatr Pulmonol. 2016;51:E25-E27.
20. Chaudhary BA, Nadimi M, Chaudhary TK, Speir WA. Pulmonary edema due to obstructive sleep apnea. South Med J. 1984;77:499-501.
21. Tobias JD. Current evidence for the use of sugammadex in children. Paediatr Anaesth 2017;27:118-125.
22. Choi WK, Lee JM, Kim JB, et al. Diffuse alveolar hemorrhage following sugammadex and remifentanil administration: a case report. Medicine. 2019;98:e14626.
23. Ikeda-Miyagawa Y, Kihara T, Matsuda R. Case of negative pressure pulmonary edema after administration of sugammadex under general anesthesia with laryngeal mask airway. Jpn J Anesthesiol. 2014;63:1362-1365.
24. Lee JH, Lee JH, Lee MH, Cho HO, Park SE. Postoperative negative pressure pulmonary edema following repetitive laryngospasm even after reversal of neuromuscular blockade by sugammadex: a case report. Korean J Anesthesiol. 2017;70:95.
25. Han IS, Han BM, Jung SY, Yoon JR, Chung EY. Negative pressure pulmonary hemorrhage after laryngospasm during the postoperative period. Acute Crit Care. 2018;33:191-195.
26. McGuire B, Dalton AJ. Sugammadex, airway obstruction, and drifting across the ethical divide: a personal account. Anaesthesia. 2016;71:487-492.
27. Kao CL, Kuo CY, Su YK, Hung KC. Incidence of negative-pressure pulmonary edema following sugammadex administration during anesthesia emergence: A pilot audit of 27,498 general anesthesia patients and literature review. J Clin Anesth. 2020;62:109728.
28. Brull SJ, Prielipp RC. Sugammadex and negative pressure pulmonary edema: what you see is not what you get. J Clin Anesth. (in press).
29. Jaber S, Lescot T, Futier E, et al. Effect of noninvasive ventilation on tracheal reintubation among patients with hypoxemic respiratory failure following abdominal surgery: a randomized clinical trial. JAMA. 2016;315:1345-1353.