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Postoperative Acute Respiratory Distress Syndrome in Patients With Previous Exposure to Bleomycin

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Abstract

Objective: To determine the incidence and risk factors for postoperative acute respiratory distress syndrome (ARDS) in a large cohort of bleomycin-exposed patients undergoing surgery with general endotracheal anesthesia.

Patients and Methods: From a Mayo Clinic cancer registry, we identified patients who had received systemic bleomycin and then underwent a major surgical procedure that required more than 1 hour of general anesthesia from January 1, 2000, through August 30, 2012. Heart, lung, and liver transplantations were excluded. Postoperative ARDS (within 7 days after surgery) was defined according to the Berlin criteria.

Results: We identified 316 patients who underwent 541 major surgical procedures. Only 7 patients met the criteria for postoperative ARDS; all were white men, and 6 were current or former smokers. On univariate analysis, we observed an increased risk of postoperative ARDS in patients who were current or former smokers. Furthermore, significantly greater crystalloid and colloid administration was found in patients with postoperative ARDS. We also observed a trend toward longer surgical duration and red blood cell transfusion in patients with postoperative ARDS, although this finding was not significant. Intraoperative fraction of inspired oxygen was not associated with postoperative ARDS. In bleomycin-exposed patients, the incidence of postoperative ARDS after major surgery with general anesthesia is approximately 1.3% (95% CI, 0.6%-2.6%). For first major procedures after bleomycin therapy, the incidence is 1.9% (95% CI, 0.9%-4.1%).

Conclusion: The risk of postoperative ARDS in patients exposed to systemic bleomycin appears to be lower than expected. Smoking status may be an important factor that modifies the risk of postoperative ARDS in these patients.

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Bleomycin is an antitumor antibiotic highly effective in the treatment of testicular carcinomas, lymphomas, squamous cell carcinomas, and Kaposi sarcoma.[1] It was originally isolated from the yeast *Streptomyces verticillus* in 1966, and it works by breaking the DNA double helix through production of free radicals.[2] Since the early days of bleomycin use, acute pulmonary toxic effects have been identified as the most serious adverse events of bleomycin therapy, manifesting acutely in 10% to 40% of patients with nonspecific symptoms, such as dyspnea, tachypnea, and nonproductive cough.[3] Typical bleomycin regimens used for cancer therapy may lead to pneumonitis,[4] pulmonary fibrosis,[5,6] and impairment of pulmonary function.[7,8] The overall mortality of bleomycin-associated pulmonary toxic effects is estimated to range from 1% to 2%.[9-12]

In this context, perioperative management of patients with previous exposure to bleomycin can be challenging because of the compounded risk of postoperative pulmonary complications.[13,14] More than 3 decades of human and animal investigations have sought strategies to mitigate this risk. Such strategies include conservative crystalloid administration and ventilator assistance, including limitation of the administered fraction of inspired oxygen (Fio_2). Evidence supporting this practice originated in a study by Goldiner et al[14] in the late 1970s that described 5 bleomycin-exposed patients who received a mean intraoperative Fio_2 of 0.39 during surgery and subsequently

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developed fatal postoperative acute respiratory distress syndrome (ARDS). The same report described a subsequent cohort of 12 patients for whom the mean intraoperative Fio_2 was limited to 0.24, and fluid administration favored a greater proportion of colloid rather than crystalloid solutions. Within this group, no postoperative pulmonary complications occurred and all patients survived. Ensuing case reports extended the concern of perioperative oxygen toxic effects in surgical patients.[15,16]

In the early 1980s, several animal studies determined that interstitial fibrosis was the major pathologic manifestation of oxygen toxic effects after bleomycin exposure.[17-20] Taken together, the human and animal studies led to the long-standing recommendation that anesthesiologists administer intraoperative Fio_2 as low as tolerated for bleomycin-exposed patients. Similarly, fluid replacement strategies on the basis of colloids over crystalloids have been routinely favored in these patients.[13]

Although it is generally accepted that oxygen toxic effects are a risk in bleomycin-exposed surgical patients, not all studies have supported the practice of limiting Fio_2 administration in the perioperative period.[13,21] Along these lines, it is reasonable to postulate that there are risks with severe Fio_2 restriction in all surgical patients (ie, infection and wound healing[22]) but especially in patients with preexisting interstitial lung disease, who are at greater risk of perioperative hypoxemia. With this information as background, the objective of this study was to determine the incidence of postoperative ARDS in a large cohort of patients with previous systemic bleomycin exposure undergoing major surgery requiring more than 1 hour of general anesthesia. Furthermore, we aimed to identify preoperative, intraoperative, and postoperative risk factors associated with postoperative ARDS.

PATIENTS AND METHODS

Institutional review board approval was obtained through the Mayo Clinic Health System. Minnesota state law requires a general authorization to review medical records for research. Patients who receive care at Mayo Clinic can opt out of this authorization if they desire. For the present investigation, all included participants had authorized the use of their medical records for research.

Data were collected from 3 primary sources: (1) the Perioperative DataMart, (2) Mayo Clinic Life Science Services and the Data Discovery Query Builder (MCLSS/DDQB), and (3) The Mayo Clinic Cancer Registry. A detailed description of the data extraction capabilities of DataMart and the MCLSS/DDQB can be found in previous reports by this institution.[23-25] Specific variables extracted from the Perioperative DataMart included the following: height, weight, age, date of birth, sex, and body mass index. Body mass index, a measure of weight in kilograms divided by the square of height in meters, was calculated from the most recent height and weight documented before the surgical procedure. All details related to the surgical procedure, anesthesia start and stop times, surgery start and stop times, and American Society of Anesthesiologists patient classification score were also collected from the Perioperative DataMart.[24,25] For the present investigation, categories of data collected from this resource included baseline comorbidities, preoperative laboratory values, and medications being taken at the time of the surgical procedure.

The overall data collection strategy is depicted in the Figure. An extensive search of all Mayo Clinic patients with a history of systemic (ie, nontopical) bleomycin exposure was conducted using the Mayo Clinic Cancer Registry and the MCLSS, identifying 1120 unique patients. The MCLSS/DDQB was then used to identify which of these patients underwent surgical procedures from January 1, 2000 (advent of the electronic intraoperative anesthesia record), through August 30, 2012. Procedures were required to occur after the final dose of bleomycin. Within this cohort of bleomycin-exposed patients, 960 procedures were performed. Minor procedures that lasted less than 1 hour and those that did not require endotracheal intubation were subsequently excluded (n=411). All heart, lung, and liver transplantations were also excluded (n=3). These transplantation procedures were excluded because of presumed left atrial hypertension in cardiac transplant patients, the confounding variable of pulmonary reimplantation response in lung transplant surgery,[26] and the historically high risk of ARDS with liver transplantation.[27,28] Minor, noninvasive procedures were excluded because it has been reported that postoperative ARDS in bleomycin-exposed patients is

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