Clinical Study

No Perioperative Pulmonary Complications after Restricted Oxygen Exposition in Bleomycin-Treated Patients: A Short Report

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Hyperoxic exposure during general anaesthesia after receiving bleomycin treatment is purported to potentiate bleomycin-induced pulmonary toxicity. The aim of this study was to retrospectively assess perioperative pulmonary complications after general anaesthesia for retroperitoneal lymphadenectomy in patients who underwent bleomycin treatment <6 months earlier. A consecutive series of 47 patients who underwent surgery after bleomycin treatment were reviewed. Anaesthesia was induced with an inspired fraction of oxygen (FiO₂) of 100% for 3 minutes and pertained with a FiO₂ just under 30% throughout the procedure. We assessed all potential risk factors for bleomycin-induced pulmonary toxicity. Clinical signs for pulmonary damage were documented preoperatively (dyspnea, tachypnea, nonproductive cough, and postoperative oxygen saturation problems). No pathognomic clinical signs for pulmonary damage were detected up to 7 days postoperatively. Administration of 100% oxygen for 3 minutes during induction of anaesthesia and maintaining a FiO₂ < 30% during surgery was safe.

1. Introduction

The most feared side effect of bleomycin treatment is its pulmonary toxicity (bleomycin-induced pneumonitis: BIP), which occurs in 0 to 46% of the patients [1]. After oxygen exposure, ferrous bleomycin compounds can induce reactive oxygen-free radicals and cause cell damage. Damage occurs initially within the endothelium, resulting in increased permeability and oedema [2]. Destruction of the endothelium allows higher concentrations of bleomycin to reach the alveolar epithelium cells leading to necrosis of the pneumocytes and consequently an intraalveolar migration of macrophages resulting in the early inflammatory phase of BIP. Secreted tumor necrosis factor TNF- α and interleukine IL-6, reported to be strongly implicated in the pathogenesis of BIP, induce the second phase with intense lung fibrosis [3–5].

The mortality rate of BIP is approximately 3–10% [6], and 10–30% of the patients treated with bleomycin develop irreversible pulmonary fibrosis [7]. Oxygen exposure as a

risk factor in patients previously treated with bleomycin is matter of controversy. The time period between bleomycin treatment and perioperative exposure may also play a role for the development of BIP [8].

Using a high level of inspired oxygen (FiO₂ > 50%) has been shown to reduce the incidence of perioperative infections [9, 10]; however this approach has certain limitation and is disputable. There are numerous case reports and series on BIP showing a high lethality after hyperoxia [11–15]. The aim of this study was to retrospectively assess perioperative pulmonary complications after general anaesthesia with a controlled FiO₂ for retroperitoneal lymphadenectomy (RPLND) in patients who had undergone bleomycin treatment <6 months before surgery, therefore considered to be at risk for BIP.

2. Material and Methods

After obtaining approval of the Internal Review Board, clinical records of a consecutive series of 47 patients who

underwent RPLND after bleomycin treatment for testicular cancer between 1991 and 2007 were reviewed. Bleomycin was used in association with etoposide and cisplatin (BEP regimen) for 3-4 cycles. Because it is admitted that the risk of developing BIP is higher the closer the high oxygen exposure after bleomycin treatment is, only patients who underwent RPLND within 6 months (mo) after completion of chemotherapy were included. Patients who had undergone radiotherapy prior to surgery were excluded.

All patients underwent the same combined general anaesthesia with thoracic epidural analgesia (TEA), including induction with thiopental (2-3 mg/kg), fentanyl (2 µg/kg), rocuronium (0.1 mg/kg), or atracurium (0.5 mg/kg). Anaesthesia was maintained with nitrous oxide and isoflurane (0.6-0.8 MAC). Respiratory frequency and tidal volume were adjusted to maintain the end-tidal concentration of carbon dioxide between 32-35 mmHg including the use of a PEEP of 5 mmHg. For TEA, the catheter was placed at thoracic level T8-9 and activated during RPLND with bupivacaine 0.25% at a rate of 8-10 mL/h. For postoperative epidural analgesia a standard solution containing 0.1% bupivacaine combined with 2 µg/mL epinephrine and 2 µg/mL fentanyl was administered at a rate of 8 to 15 mL/h for at least 48 hours after surgery. In addition 1000 mg paracetamol i.v. was given every 6 hours.

Anaesthesia was performed with an inspired fraction of oxygen (FiO₂) of 100% for 3 minutes for induction of anaesthesia and then with a FiO₂ just under 30% during surgery, accepting a saturation of above 94%. After extubation, 2-3 L of oxygen was nasally administered for the next 2 days.

We assessed all potential risk factors for bleomycin-induced pulmonary toxicity (creatinin clearance <35 mL/min, cumulative bleomycin dose >300.000 IU, age >40 years, stage IV disease, blood transfusion, and fluid management) [16, 17]. Clinical signs for pulmonary damage were documented pre- and postoperatively (dyspnea, tachypnea, nonproductive cough, and postoperative oxygen saturation problems).

3. Results

Twenty-five patients were excluded: two with preoperative radiotherapy of the thorax (25 Gy and 11 Gy) and 23 with a delay between RPLND and chemotherapy of more than 6 mo (median 17 mo (range: 7-149). Twenty-two patients with a median age of 26 years (19-49) were finally included in the analysis: American Joint Committee on Cancer stage groups were as followed: IIa: 4 patients (18%), IIb: 8 (36%), IIc: 4 (18%), IIIa: 5 (23%), and IIIc: 1 (5%). The majority of patients had mixed tumours 14 (64%), nonseminomatous tumours 5 (22%), and seminomas 3 (14%). The median interval from the last bleomycin dose to surgery was 3 mo (1-6). Median bleomycin dose during chemotherapy was 270.000 IU (270.000-540.000). One patient received more than 300.000 IU (540.000). No patients had pulmonary disease documented preoperatively. A history of smoking was

present in 9 patients. The preoperative glomerular filtration rate was normal in all patients (>80 mL/min).

Of the 22 patients 5 were ASA classification 1, 15 ASA 2, and 2 ASA 3. The median duration of surgery was 240 minutes (120-800). The median volume of crystalloids and colloids administered intravenously was 2900 mL (1450-5500), and two patients (9%) needed a blood transfusion.

No pathognomic signs (dyspnea, tachypnea, and non-productive cough) for pulmonary damage could be detected up to 7 days postoperatively. In addition no desaturation was detected; the median oxygen saturation documented on the intermediate care unit was 97% (94-100).

4. Discussion

Administration of 100% oxygen for 3 minutes during induction of anaesthesia and maintaining an FiO₂ < 30% during surgery did not lead to any clinically observable pulmonary signs of toxicity in this young patient population at risk for BIP after a short delay between the end of bleomycin therapy and surgery. Our data outlines that strict intraoperative maintenance of an inspiratory 30% oxygen concentration is a safe procedure avoiding the development of BIP. This is in line with precedent publications [7, 18], recommending a low FiO₂ during surgery and administration of 100% oxygen during induction of anaesthesia. Indeed despite reports indicating that in animal models the risk of BIP is lowered when hyperoxymia after bleomycin exposition is delayed, many cases of respiratory failure after hyperoxia in patients with an interval to 6 months or more after bleomycin exposition have been reported with mostly catastrophic consequences for the patients and associated with high lethality [12, 14, 15, 19].

Aside from high oxygen saturation, BIP is also associated with other potential risk factors; smoking, age > 40 yrs, poor renal function, tumor stage IV and bleomycin dose of more than 300.000 IU are risk factors of lung toxicity [17]. Moreover, genetic predisposition to BIP has been postulated including various activity levels of the enzyme bleomycin hydroxylase in the lungs [20]. All our patients were younger than 40 yrs and had normal renal function. The only patient receiving more than 3000.000 IU bleomycin did not develop BIP. Another risk factor we excluded is radiotherapy to the chest: the incidence of BIP after radiotherapy before, during, or after bleomycin therapy is 10 to 19% [21, 22]. However the excluded patients because of thorax radiotherapy did not develop BIP after RPLND.

We are aware of the limitations of the study especially the lack of pulmonary function assessment. However, as no clinically relevant pulmonary complications were observed severe pulmonary damage seems unlikely. Exposure to bleomycin can result in interstitial pulmonary oedema and compromise pulmonary diffusion capacity, which would be clinically evident with shortness of breath, dyspnea or tachypnoea, and oxygen desaturation. Functional tests would possibly identify subclinical changes; however previous studies have shown that pulmonary function tests, including transfer factor (DLCO) may not detect subclinical pulmonary disease

[16]. A second limitation could be the lack of long-term assessment of pulmonary fibrosis. However the resulting inflammatory changes in the early stage should be recognizable within 3 days [23]. In addition, no markers like methylmalonic acid, citrulline in the urine, or nitrotyrosine in the plasma, assessing the level of free oxygen radicals, were routinely documented in our patients.

Supplemental perioperative oxygen administration (FiO₂ between 50–80%) during major abdominal surgery in general is advocated as it reduces the number of surgical site infections [9, 24]. Such an approach, however, is not advocated in patients who were previously treated with bleomycin.

5. Conclusion

Avoiding hyperoxia during surgery while respecting safety rules for preoxygenation with 100% of oxygen during induction in patients who underwent prior treatment with bleomycin seems to be a safe approach without negative effects on pulmonary function.

Disclosure

This paper was Presented in part at the SGAR (Swiss Anaesthesia and Reanimation) Congress in Interlaken in October 2010 and at the Euroanaesthesia 2011 in June 2011 in Amsterdam 2011.

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