Perioperative management of a patient with bleomycin lung injury and on dabigatran treatment for retro-peritoneal lymph node dissection: A case report

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ABSTRACT

Germ cell tumors (GCT) arise from the cells that develop into sperms or eggs. They are commonly seen in testes and ovaries. Here, we report the case of a patient with bleomycin-induced lung injury (BILI) and dabigatran therapy for prior pulmonary thromboembolism underwent retroperitoneal lymph node dissection. The patient had dyspnoea and hypoxia during chemotherapy with a thrombus in the pulmonary artery and was managed with parenteral anticoagulation followed by dabigatran. He subsequently developed BILI and recovered. Dabigatran was stopped five days prior to surgery and perioperative anticoagulation bridged with dalteparin. Intraoperatively, we used inspired oxygen <35%, lung protective ventilation, goal-directed fluid therapy and intravenous morphine infusion. Postoperatively, we performed rectus sheath block and commenced transnasal humidified rapid insufflation ventilatory exchange. The patient had an uneventful recovery.

Keywords: *Bleomycin lung injury, Dabigatran, Retroperitoneal lymph node dissection.*

Germ cell tumors (GCT) arise from the cells that develop into sperms or eggs. They are commonly seen in testes and ovaries. They represent the maximum life years lost per death among adult malignancies [1]. It has a response rate of 85% with the combined modality of chemotherapy with bleomycin, etoposide, and cisplatin (BEP) and retroperitoneal lymph node dissection (RPLND) surgery [2].

Here, we report a patient planned for RPLND with bleomycin-induced lung injury (BILI) and who was on dabigatran for prior pulmonary thromboembolism. Anaesthetic management is complicated by the delicate balancing of fluid replacement with the loss while protecting against interstitial pulmonary edema, balancing anticoagulation with the need for surgical hemostasis, ensuring adequate analgesia sans epidural and optimizing perioperative patient oxygenation with minimal supplemental oxygen therapy. In view of these unique challenges, we present this case report. This report adheres to the CARE guideline [3].

CASE REPORT

A 19-year-old male, non-smoker, weighing 63kg with GCT of testis was posted for RPLND. He received 4 cycles of BEP chemotherapy. Subsequent to the first cycle, he developed dyspnoea and hypoxia. Thrombi in the inferior pulmonary artery and inferior vena cava (IVC) were identified in the Computerised Tomography (CT) imaging and he was started on low molecular weight heparin (LMWH) which was switched over to dabigatran. Five weeks following the fourth chemotherapy, he developed dyspnoea and desaturation. BILI was diagnosed from CT chest showing bilateral patchy infiltrates and dramatic response to oral steroids which was continued and tapered over 6 weeks. Surgery was scheduled 4 months following last chemotherapy and 1 month after stopping steroids while the patient continued dabigatran 150mg twice a day (*b.d.*). The patient had no medical comorbidities.

On examination, the pulse rate was 90/minute with a normal character, blood pressure was 130/84 mmHg, respiratory rate was 16/minute and SpO2 in room air was 98%. Physical examination of the cardiovascular and respiratory system was unremarkable.

Patient's preoperative hemoglobin was 11.4 g%, blood urea was 28mg/dL and serum creatinine was 0.8 mg/dL. Creatinine clearance was 132 ml/minute. Liver function tests were normal. Echocardiogram was normal with an ejection fraction of 64%. Arterial blood gas analysis showed PaO_2 of 95 mmHg in room air. Pulmonary function tests showed Forced expiratory volume in one second (FEV1) of 75%, Forced vital capacity (FVC) of 63% and FEV1/FVC of 173% suggestive of restrictive disease.

Perfusion scan showed multiple perfusion defects in both lungs probably due to interstitial infiltration. Ventilation scan was not feasible due to the patient's inadequate efforts. The patient was assessed as American Society of Anaesthesiologists Physical Status (ASA-PS) III in view of BILI and was advised to stop dabigatran 5 days prior to surgery and started on dalteparin 5000 Units subcutaneous *b.d*. therapy. Activated partial thromboplastin

time (aPTT) on day of surgery was 51 seconds (control 10-42 seconds).

The patient was pre-oxygenated with air/oxygen at 40% inspired oxygen (FiO_2), anesthesia induced with fentanyl 2 ug/kg, propofol 2.5 mg/kg and vecuronium 0.1mg/kg was given for muscle relaxation. The trachea was intubated and the patient started on volume-controlled ventilation with tidal volume 375ml (6ml/kg), respiratory rate 14/min, positive end-expiratory pressure (PEEP) 8 cm-H_2O, FiO_2 35% and inspired airway pressure was maintained at 20-25mmHg by decreasing the pressure limit setting.

Anesthesia was maintained with air/oxygen/sevoflurane. His heart rate, oxygen saturation (SpO_2), electrocardiogram, intra-arterial blood pressure, FiO_2 and end-tidal oxygen concentrations, end-tidal carbon dioxide levels, minimum alveolar concentration, cardiac output, stroke volume, stroke volume variation (SVV), nasopharyngeal temperature, FloTrac/Vigileo™ hemodynamic monitoring and hourly urine output was monitored. Analgesia was maintained with morphine 5mg Intravenous (IV) bolus followed by infusion at 1mg/hour with paracetamol 1gm IV.

We used goal-directed fluid therapy (GDFT) targeting SVV <11. Ringer's lactate was used as fluid replacement and blood loss was replaced with Gelofusine. Duration of surgery was 6.5 hours and blood loss was 500 ml. The patient received 3000ml crystalloids and 500 ml Gelofusine. There were two brief episodes of hypotension concurrent with a rise in SVV which was managed with fluid boluses. Post-surgery, bilateral rectus sheath block was performed under ultrasound guidance with 0.25% bupivacaine 40ml.

Trachea was extubated after reversal and patient shifted to Intensive Care Unit (ICU) and connected to trans nasal humidified rapid insufflation ventilatory exchange (THRIVE) with AIRVO™ 2 Optiflow nasal cannula (Fisher Paykel, Auckland, New Zealand) at FiO_2 of 21%, temperature 37 C and flow rate of 35 L/min. SpO_2 was targeted at 90% which was maintained with the above settings. The patient was on morphine infusion at 0.5-1 mg/hour for 3 days postoperatively. He did not require supplemental oxygen, was started on dalteparin 5000 subcutaneously *b.d*. from 24 hours after surgery, was able to do incentive spirometry at 1200 ml and bedside lung ultrasound showed minimal basal B lines. He was mobilized on day 3 and was restarted on dabigatran on day 5. The patient had an uneventful recovery.

DISCUSSION

Restricted perioperative oxygen therapy is well known in the management of patients with BILI. The use of lung protective ventilation, goal-directed fluid therapy (GDFT) intra-operatively and use of THRIVE postoperatively in the management of BILI patients have not been reported before.

The risk factors for development of BILI are genetic predisposition, cumulative dose >450 IU, age >70 years, bolus administration as compared to infusions, concomitant use of cisplatin and Granulocyte Colony Stimulating Factor (G-CSF), creatinine clearance (Cr Cl) <35ml/min, smoking and radiation therapy within 4 weeks of bleomycin exposure [4]. Evidence of pre-existing BILI or bleomycin exposure within 2 months are the major risk factors for BILI with hyperoxia exposure [5]. The mechanism of BILI is by increased pulmonary capillary permeability, necrosis of type 1 pneumocytes and increased macrophage migration which further recruits inflammatory cells and fibroblasts leading to pulmonary fibrosis [3]. Our patient developed BILI at a cumulative bleomycin dose of 360 IU, onset was at 11 weeks after bleomycin and concomitant G-CSF was another risk factor.

A 10-15% decrease in single breath diffusion capacity of the lung for carbon monoxide (DLCO) is the most sensitive indicator of subclinical damage. The restrictive ventilatory defect is the next common abnormality seen which was evident in our patient [5]. Positron Emission Tomography (PET) scan is a useful tool when faced with a dilemma as to initiate or continue treatment with anti-inflammatory agents as the uptake of 18-fluorodeoxyglucose is absent after successful immunosuppression [6]. GCT is not uncommonly associated with IVC thrombus. Due to rapid shrinkage of tumor cells during chemotherapy, there is a greater possibility of pulmonary thromboembolism. A high index of suspicion is required in patients with right-sided testicular tumors (due to direct draining of right gonadal vein into IVC) with paracaval abdominal mass >5cm in maximum transverse diameter meriting prophylactic anticoagulant therapy prior to, during and after chemotherapy [7].

Dabigatran is a directly acting thrombin inhibitor with peak plasma concentrations achieved at 1-2 hours and half-life (T ½) of 12-17 hours. In mild renal impairment- creatinine clearance (CrCl) 30-60 L/min T ½ is 15-18 hours and in severe renal impairment - CrCl <30 ml T ½ is 28 hours. Bridging with heparin may increase the bleeding risk and warfarin is a safer choice for bridging therapy. Idarucizumab is an antidote for dabigatran and useful in reversing anticoagulation in patients needing emergency surgery. It is given as 5gm IV dose through 2 consecutive 2.5 g infusions. Contraindications for dabigatran are CrCl <30 ml/min, patients with mechanical heart valves and pregnancy [8].

Testing for anticoagulant effect of dabigatran is indicated in moderate renal impairment, in the perioperative setting and in the event of bleeding. Thrombin time is very sensitive with linear dose-response time and aPTT >80 seconds at trough drug level portends increased bleeding [8]. In patients with normal or mild renal dysfunction taken up for procedures with the potential for high risk of bleeding dabigatran is to be discontinued 48-72 hours prior to the procedure. For patients with Cr Cl 30-49 ml/min, it is to be discontinued 72-120 hours prior. Longer discontinuation is required in patients needing spinal or epidural catheter or port placement [10]. Preoperatively, bridging with heparin is only required in very high-risk thromboembolic patient and postoperative resumption is required between 48-72 hours after surgery.

RPLND is associated with large fluid shifts due to the extensive dissection of lymph nodes, large incision and prolonged duration of surgery making fluid management challenging in the setting of

pre-existing BILI. Post-operative pulmonary complications were associated with higher mean positive fluid balance (11.2 L vs. 6.1 L, p=0.0001) and higher transfusion requirement (5.3±3.9 L vs. 1.24±1.6 L, p<0.0001) [11]. GDFT is useful in this setting. The epithelial-mesenchymal transition which is a precursor for fibro-proliferative changes in BILI was less in low tidal volume as compared to high tidal volume ventilator strategy [12]. Hence, we used lung protective ventilation.

Postoperatively, the patient was started on THRIVE as it generates higher pressures in the expiratory phase, resembles application of PEEP and thereby increases lung volume, prevents atelectasis, improves lung compliance and decreases dead space ventilation [13]. These benefits were achieved at FiO_2 of 21% and helped prevent postoperative pulmonary morbidity. By utilizing technological advances such as goal-directed fluid management and THRIVE we ensured an uncomplicated recovery. We cannot generalize these recommendations based on a single case.

CONCLUSION

Restrictive perioperative oxygen therapy apart, the role of lung protective ventilation, goal-directed fluid therapy and THRIVE in the management of patients with BILI needs to be explored.

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