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Case Report

Ketamine/Dexmedetomidine Combination for Monitor Anesthesia Care in a Child With Chronic Graft-Versus-Host Bronchiolitis Obliterans: A Case Report-Based Literature Review

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ABSTRACT

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Graft-versus-host obstructive bronchiolitis, in pediatric patients, is a relatively common respiratory complication of chronic graft-versus-host disease, after allogeneic bone marrow transplant. It is irreversible, chronic and potentially life-threatening condition. Anesthetic management of these patients can be challenging. In this article we present a case report of monitor anesthesia care, in a 6-year-old pediatric patient with chronic graft-versus-host bronchiolitis obliterans and perform a short literature review on the subject.

Keywords: Pediatric Monitor Anesthesia Care, Graft-Versus-Host Disease, Bronchiolitis Obliterans, Ketamine, Dexmedetomidine.

INTRODUCTION

Bronchiolitis obliterans (BO) is a chronic, irreversible, obstructive lung disease leading to obstruction and/or obliteration of small airways[1,2]. It is characterized by pathologic luminal plugging with chronic inflammatory granulation tissue or luminal obliteration by fibrosis that can lead to airflow limitation, gas trapping, impaired gas exchange and eventually respiratory failure[3,4]. This small airway inflammation and injury can be post infectious BO (PIBO); post lung transplantation BO and after bone marrow transplantation (BMT) or hematopoietic stem cell transplantation BO (HSCT)[2].

Anesthesia management in pediatric patients with chronic graft-versus-host (cGVHD) BO can be very challenging for the anesthesiologist. In these patients, pulmonary complications of cGVHD should be considered, alongside with a possible difficult airway, problems with positioning and intravascular access, hypothermia, malnutrition, anemia, immunosuppression, hepatic dysfunction and cardiac involvement[5]. Dexmedetomidine, an α2-adrenergic receptor agonist, is used for procedural sedation in children. It has limited to no effect on respiration but potentially can cause hypotension and bradycardia. Ketamine produces dissociative anesthesia, analgesia, and amnesia with little or no respiratory or cardiovascular depression. Dexmedetomidine can effectively and safely attenuate the ketamine-induced hemodynamic pressor response and its psychomimetic effects, while ketamine may prevent the the adverse hemodynamic effects of dexmedetomidine[6].

We report a case of a 6-year-old pediatric patient with chronic graft-versus-host bronchiolitis obliterans, who underwent minor surgery (Hickman line insertion – open technique), under monitor anesthesia care, using ketamine and dexmedetomidine drug combination, with favorable outcome and review the literature on the subject.

CASE REPORT

A 6-year-old pediatric male patient (body weight: 29kg, height: 110 cm) was admitted to our pediatric surgery department for Hickman line insertion, after relapse of acute lymphoblastic leukemia (ALL). Past medical history involved the diagnosis of T-cell ALL, at 4 years of age. One year later, he underwent allogenic BMT. Two months after BMT, he was diagnosed with acute GVHD due to skin manifestations, liver function disorder and diarrheas. One year after the GVHD diagnosis, he presented the second relapse of ALL and he was diagnosed with chronic graft-versus-host bronchiolitis obliterans. His surgical history revealed an uneventful previous Hickman line

insertion, under general anesthesia, when he was firstly diagnosed with ALL. His medical drug regiments included ciprofloxacin, acyclovir, trimethoprim/sulfamethoxazole, fluconazole and ruxolitinib. The patient was scheduled to undergo a Hickman line insertion (open technique), for further treatment due to relapse of ALL.

During preanesthetic visit and physical examination the patient was uncooperative. Patient's general physical examination revealed a characteristic body trunk maculopapular rash and oral mucositis. Airway assessment showed normal neck movement and thyromental distance, but Mallampati class score was difficult to estimate due to oral mucositis. There was no shortness of breath or breathing difficulty, respiratory rate (RR) was 21 breaths per minute (bpm) and oxygen saturation (SpO_2) was 96% on room air. He had a heart rate (HR) of 110 beats per minute (bpm) and blood pressure (BP) was 118/75 mm Hg. Auscultation revealed normal breath and heart sounds. The clinical examination of the abdomen did not reveal any abnormality.

A pediatric pulmonologist assessed patient's respiratory system and reported severe obstructive pulmonary disease, as evident by his forced expiratory volume in 1 second (FEV_1) of 52% predicted, forced vital capacity (FVC) of 69% predicted and FEV_1/FEV ratio of 73% predicted (Table 1) with no bronchial responsiveness to bronchodilator therapy.

PARAMETERS	PATIENT'S VALUES	REFERENCE VALUES	LLN	ULN	% OF REFERENCE
FVC (L)	1.20	1.74	1.16	2.32	69
FEV_1 (L)	0.80	1.54	1.09	1.99	52
FEVl/FVC (%)	66.7	91.5	80.9	102.2	73
PEF (L/s)	2.31	2.69	-0.03	-5.41	86
FEF_{2575} (L/s)	0.54	1.91	0,87	2.94	28

LLN: lower limit of normal, ULN: upper limit of normal, FVC: forced vital capacity, FEV1: forced expiratory volume in 1s, PEF: peak expiratory flow, FEF_{2575}: forced expiratory flow between 25 and 75% of vital capacity.

Table 1. Patient's Pulmonary Function Tests

A high-resolution computed tomography of the lungs (HRCT) revealed extensive foci of air retention in lung parenchyma with significant obstruction and restriction, findings consistent with bronchiolitis obliterans. Preoperative chest radiograph was without pathologic

findings, which is considered typical in BO[3]. It must be noted that patient's previous spirometry results, 5 months earlier, were within normal range.

Pediatric cardiology assessment was also normal with unremarkable electrocardiogram (ECG) and echocardiogram findings. Patient's preoperative laboratory results are shown in Table 2. Preoperative evaluation exhibited a class III physical status of American Society of Anesthesiologists.

PARAMETERS	VALUES
White Blood Cell (WBC)/Ml	11760 (NEU%: 16.7, LYM%: 61.5, MONO%: 7.1, BASO%: 5.1, EOS%:9.6)
Hemoglobin (Hgb) g/dl	11.5
Hematocrit (Ht) %	33.4
Platelets (PLT) /μL	150000
Prothrombin time (PT) sec	11.1
International Normalized Ratio (INR)	1
Partial thromboplastin time (aPTT) sec	32.2
Glucose (Glu) mg/dl	77
Urea (U) mg/dl	20
Creatinine (Cr) mg/dL	0.29
Potassium (K) mmol/L	3.8
Sodium (Na) mmol/L	140.6
Aspartate Aminotransferase (SGOT) units/lt	105
Alanine Aminotransferase (SGPT) units/lt	187
Lactate Dehydrogenase (LDH) units/lt	1410

Table 2. Patient's preoperative laboratory results.

Upon arrival to the operating theater, standard monitoring {electrocardiogram, noninvasive blood pressure, peripheral oxygen saturation (SpO_2)} was applied. No premedication was given. The patient had SpO2: 96% (FiO2: 21%) and he was hemodynamically stable (BP: 128/82 mmHg, HR: 118 bpm). A simple face oxygen mask, in which capnography sampling line was directly connected, was placed at a flow rate of 6 L/minute. Through

an intravenous line (20-gauge IV cannula), which had been inserted in the pediatric surgical ward, monitored anaesthesia care was provided with 0.01 mg/kg atropine, an initial loading dose of 1 mg/kg ketamine and at the same time a continuous infusion of ketamine at a rate 0.15 mg/kg/h. Additionally, an initial loading dose of 1 mcg/kg bolus dosage of dexmedetomidine was administrated, within the first 10 minutes of anesthesia. Immediately after, a continuous infusion dexmedetomidine via pump was administrated at a rate 0.5-0.7 mcg/kg/hour, in order to target a modified observer assessment of alertness/sedation (MOAA/S) score 2[7].

Next, after positioning the patient for the insertion of Hickman central line (supportive neck shoulder rolls to facilitate left head-tilt/chin-lift positioning), local anesthesia (2% lidocaine hydrochloride) was administrated topically on the entrance site of right internal jugular vein. Maintenance of adequate sedation and hemodynamic stability was observed throughout the intraoperative period (duration of procedure 30 min).

After inserting the Hickman central line continuous infusions of ketamine and dexmedetomidine were stopped and patient regained consciousness within 10 minutes. He recovered with his vital signs returning to baseline. Patient maintained hemodynamic stability with an unobstructed airway and spontaneous ventilation and with no episodes of desaturation, hypoxemia, laryngospasm, apnea, or coughing throughout the perioperative period. Patient made an uneventful postoperative recovery (20 min) and he was transferred safely to a pediatric surgical ward with Modified Aldrete Score of 10.

DISCUSSION

Chronic GVHD is a syndrome resembling autoimmune collagen vascular disease with systematic manifestations, involving almost every organ and resulting in increased morbidity and mortality. Current laboratory evidence suggests that there is not any difference in the pathophysiologyof cGVHD between adults and pediatric patients[8]. Although improvements have been made to reduce the incidence of acute graft-versus-host disease (aGVHD), there has been little progress in preventing cGVHD, which occurs in 30% to 60% of pediatric patients[8]. Manifestations of cGVHD can include acute-type features such as erythematous rash, mucositis, diarrhea, transaminitis and also can be more fibrotic and chronic in nature such as sclerotic or lichen planus-type skin changes, fasciitis, esophageal strictures, bronchiolitis obliterans (BO), interstitial pneumonitis, and patchy pulmonary fibrosis.[9,5]. Maculopapular body rash, oral mucositis, liver dysfunction and bronchiolitis obliterans were the main preoperative findings of our patient.

The incidence of BO, following pediatric al-

logeneic bone marrow transplant, ranges from 2% to 6%[10]. Duncan et al. reported BO incidence, after pediatric allogeneic BMT, of 8.3%. The study retrospectively reviewed pediatric patients who underwent allogeneic BMT, over a 5-year period, and found 100% of those who subsequently developed BO had a previous history of GVHD[10,11]. Our patient was diagnosed with GVHD 12 months prior to the BO diagnosis.

The diagnosis of BO is usually made by a combination of medical history, clinical findings, lung function testing and HRCT, although biopsy and histopathology remain the diagnostic gold standard.[10,12]. By the time of diagnosis, the airway disease is frequently advanced and irreversible fibrotic changes and airway obliteration have been established, making the treatment difficult and often unsuccessful[12]. Non-specific symptoms such as tachypnoea, wheezing, breathlessness, cough and hypoxemia can be present, although in many cases, such as ours, there were no respiratory symptoms. Chest radiographs may be normal; therefore, HRCT is the imaging method of choice for evaluating patient's pulmonary status, as in the patient of this case report. Lung function tests are used for diagnosis of BO and provide information about the severity of BO and progression over time. Patient's previous spirometry results, 5 months earlier, were within normal range, while preoperatively they indicated severe obstructive pulmonary disease, with decreased of FEV_1, FVC and FEV_1/FEV. Jerkic SP et al reported that classical spirometry detects large airway obstruction and that it is insensitive in small airway disease and in gradual disease progression. Pulmonary function tests usually document an obstructive impairment; however, in early stages, in patients with BO, these tests may be normal[12]. Additionally, they noted that spirometry in very young children with BO is not feasible due to limited cooperation and that new techniques as lung clearance index (LCI) measured by multiple breath washout (MBW) is likely to be more beneficial in those patients[4,12].

Pediatric patients with cGVHD and BO present several considerations for the anesthesiologists, due to the systemic manifestations of cGVHD and their underlying pulmonary impairment. There are limited data in the current literature concerning anesthesia management in the these patients[3,5,13-15]. Information from patient's medical history, physical examination along with selected laboratory and diagnostic testing (PFTs, HRCT/LCI) can determine patient's pulmonary function. It should be remembered that the ultimate goals of preoperative medical assessment are to reduce the patient's perioperative morbidity or mortality, and to reinstate the patient to desirable functioning as quickly as possible.

Systemic features of cGVHD, their severity and the type of surgical procedure are the

main factors that influence the choice of anesthesia. Our anesthetic plan, for Hickman line insertion, was to provide monitor anesthesia care in order to preserve natural diaphragmatic function, as much as possible, due to the severe impairment of patient's lung function. General anesthesia, with the use of muscular relaxants in BO patients, can lead to air trapping, ventilation-perfusion mismatching, and difficult weaning/extubation[3]. As in other restrictive lung diseases, high peak pressures may occur with positive pressure ventilation (PPV), unless appropriate reductions in tidal volume are made. Rapid arterial hypoxemia can occur because of a decreased FRC. The use of low levels of PEEP will improve FRC and assist in the maintenance of oxygenation. Continuation of PEEP or continuous positive airway pressure (CPAP) in the postoperative period may be necessary to maintain functional residual capacity[14].

The incidence of respiratory adverse events makes up a considerable percentage (5.5%) of the complications of sedation in children[16]. The key anesthetic goal was to keep our patient with spontaneous breathing during surgery and avoid agents that cause respiratory depression (opioids, benzodiazepines). The combination of dexmedetomidine and ketamine was chosen, due to its many favorable qualities, that could be beneficial for MAC anesthesia in pediatric population with BO[6,7,16].

Despite the lack of approved pediatric labelling, dexmedetomidine is used with increasing frequency as an adjunctive anesthetic agent during sedation for pediatric patients. It is a short-acting central α2-adrenoceptor agonist, acts in the locus coeruleus in the central nervous system and has excellent sedative, anxiolytic, analgesic and antisialogogue properties with preservation of the respiratory drive. Additionally, it causes postoperative reduction of nausea and vomiting better than benzodiazepines and prevents and treats postoperative agitation and shivering in children. It is described as an excellent option for pediatric sedation[17]. Commonly reported side effects of dexmedetomidine include bradycardia and hypotension, due to its alpha-2 adrenoceptor agonist properties, in a dose-dependent way. In children, large doses of dexmedetomidine cause peripheral vasoconstriction, which may lead to systemic hypertension, whereas low doses cause central sympatholysis, which can lead to systemic hypotension and bradycardia[18].

Ketamine is a potent antagonist to the N-methyl D-aspartic acid receptors with a rapid onset of action and a predictable duration of 10 to 30 minutes. It is preferred for its amnesia, dissociative anesthesia, analgesia, maintenance of FRC, bronchodilation effect and cardiovascular stability. The fact that ketamine maintains normal airway reflexes and permits spontaneous respiration, makes it highly suit-

able for procedural sedation in children. The drug's side effects (increased salivation, nausea, nightmares, delirium, and excitation), along with its cultural image of being a drug of abuse, used in veterinary medicine, or a "date-rape drug" have sullied its reputation within the science of medicine[19]. Due to its cardiovascular boosting effect, ketamine is frequently used in conjunction with or in lieu of other anesthetics for sedation, in pediatrics. Ketamine and dexmedetomidine, when used in conjunction, lessen the side effects of each other, while the synergism of their sedative and analgesic effects can provide adequate sedation, maintaining spontaneous respiration and permit minor procedures, like Hickman line insertion, to be completed without compromising either respiration or cardiac output[17].

There are several studies in the current literature that have used a combination of dexmedetomidine and ketamine for procedural sedation in children[3,6,7,16-20]. Li et al performed a meta-analysis in order to summarize the effectiveness of combination of drugs - dexmedetomidine and ketamine - for pediatric procedural sedation or premedication. They demonstrated that dexmedetomidine and ketamine sedation in children was found safer and efficacious compared to either dexmedetomidine or ketamine alone. Also, the durations of the onset of sedation and recovery were better with the combination of dexmedetomidine and ketamine than dexmedetomidine alone, but the recovery time was shorter with the combination of propofol and ketamine compared to the combination of dexmedetomidine and ketamine. In their study, the incidence of adverse events was lower with the combination of dexmedetomidine and ketamine compared to the other study groups (dexmedetomidine alone, ketamine alone, combination propofol-ketamine, combination midazolam- ketamine)[17].

Hypotension and bradycardia were not observed in the patient of this case report, with the use of dexmedetomidine. According to literature, in children, loading dose between 0.5 and 1 mcg/kg dexmedetomidine, when administered over10 minutes, as the sole sedative, decreases systolic BP and HR, at 30% respectively from baseline. When a small loading dose of 0.5 mcg/kg dexmedetomidine is infused over 5 minutes during 1 minimum alveolar concentration sevoflurane or desflurane, systolic BP decreases only 10%, while HR decreases an initial 30% during sevoflurane and 15% with desflurane anesthesia[18]. Loading dosage and continuous infusion dosage of dexmedetomidine were given to our patient, according to those stated to other scientific papers concerning sedation in pediatric patients[3,6,7,16-20]. Perioperatively, our patient's cardiovascular status was normal. It seems that in a combination, dexmedetomidine can alleviate ketamine - induced tachycardia, hy-

pertension, hypersalivation, and emergence agitation, whereas ketamine can reverse dexmedetomidine - induced bradycardia and hypotension[17].

The patient of this case report had serum levels SGOT, SGPT and LDH elevated. The increased levels of these enzymes indicated liver dysfunction, that was attributed to patient's cGVHD. It must be noted that ketamine is metabolized by the liver within the P_{450} cytochrome system and accumulated in the body fat during a continuous infusion[19]. Also, dexmedetomidine is mainly metabolized in the liver, through glucuronidation and hydroxylation, mediated by cytochrome P450. Ketamine's and dexmedetomidine's pharmacokinetics, in children with compromised hepatic function, must be taken into account during anesthesia. Damian et al showed that after the use of 0.5 mg/kg dexmedetomidine followed by a 0.5 mcg/kg/h continuous dexmedetomidine infusion, in children 1 month-18 years of age, dexmedetomidine's clearance was not affected by body weight. Its clearance was inversely proportional to the international normalized ratio (INR). Specifically, they noted that when the INR increased to 3.2, dexmedetomidine clearance decreased by 50%. They concluded that is important to recognize that, in populations with compromised hepatic function, especially when involving shifts in INR, the dosage of dexmedetomidine must be modified[21]. Also, in pediatric patients with long-term administration of ketamine for treating chronic pain, several cases of ketamine-related liver injuries have been reported, as an increase in liver enzymes (approximately 3-fold higher). Our patient preoperatively was clinically stable with an increase in the levels of SGOT, SGPT and LDH but with normal values of PT and INR, probably due to cGVHD. The short duration of the surgical procedure, the dosages of the drugs used and since the patient had abnormal liver function even before the initiation of ketamine and dexmedetomidine, it is unlikely that this combination could have enhanced patient's liver dysfunction.

An argument can be made about the lack of sample of arterial blood gases during perioperative period in our patient. Although; a sample was ordered preoperatively; in order to evaluate the oxygenation status and acid–base balance; it was impossible to obtain because the patient was extremely uncooperative.

In conclusion, ketamine/dexmedetomidine combination seems to be promising for monitor anesthesia care, in a child with graft-versus-host bronchiolitis obliterans, providing fast onset, sedation, analgesia and hemodynamic stability. However, further research concerning dexmedetomidine is needed, since most of the published studies are observational or with limited control groups.

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