The potential impact of palivizumab on pediatric airway reconstruction

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Abstract

Purpose: To examine the role of palivizumab, a monoclonal antibody vaccine designed to prevent respiratory syncytial virus (RSV) infection, in the surgical setting, and to explore the feasibility, in terms of medical benefit and cost, of its use in pediatric airway reconstruction patients.

Materials and methods: Literature review of MEDLINE database using the following indexing terms (“respiratory syncytial virus,” “palivizumab,” “laryngotracheal reconstruction,” and “cricotracheal reconstruction”) and limited to following subcategories (English language, postoperative complication, and morbidity and mortality). All phase IV clinical trials reporting data regarding safety, efficacy, and application of palivizumab in the general pediatric population were selected, as well as all studies from any surgical specialty with data on postoperative outcome complicated by RSV infection.

Results: The literature demonstrates significant postoperative morbidity and mortality attributable to RSV infection within several surgical specialties including otolaryngology. Meta-analysis of the data from phase IV clinical trials suggests potential benefit from the perioperative use of palivizumab. The cost of vaccination is the principal limiting factor preventing its more widespread application.

Conclusion: Otolaryngologists need to be aware of the potential significant morbidity caused by perioperative RSV infection and should consider the prophylactic use of palivizumab in their pediatric airway reconstruction patients in high-risk seasons. A large multicenter study would be required to adequately perform a cost-benefit analysis of palivizumab use for this specific indication.

1. Introduction

The surgical treatment of pediatric laryngotracheal stenosis has evolved over the past century to consist of either excision of the stenotic upper airway segment (cricotracheal resection with thyrotracheal reanastomosis [CTR]) or expansion of the stenotic lumen with cartilage grafts (laryngotracheal reconstruction [LTR]). Each of these surgical procedures can be performed in either single- or multiple-stage fashion. With specific regard to single-stage airway reconstruction, much attention has been directed toward defining the operation specific success rate of these procedures and identifying the various factors that affect these rates. Established influential factors include the age and weight of the child, the severity and location of the stenosis, the overall medical condition of the child, and the presence or absence of significant tracheomalacia [1-9]. Perioperative respiratory syncytial virus (RSV) infection has also recently been shown to play a role in the outcome of single-stage CTR and LTR [8].

RSV infection is the most common cause of lower respiratory tract illness in infants and young children, accounting for 90,000 pediatric admissions per year and 4500 deaths [10]. Almost all infants are infected with RSV at least once by age 2 years. In a healthy child, RSV typically causes a mild upper respiratory tract infection. The consequences of RSV infection can be much more serious in children considered at “high risk,” such as premature infants born at gestational age of 32 weeks or earlier, and in children with chronic lung disease (CLD), congenital heart disease, and immune deficiencies.

Treatment of RSV infection is primarily supportive and symptom-directed. When the infection necessitates inpatient care, the child’s respiratory status is the most critical factor.
Supplemental humidified oxygen is administered to maintain adequate oxygenation. Chest physiotherapy is often provided. Adrenergic agonist bronchodilators may offer some benefit in the first 24 to 48 hours of the infection. The antiviral ribavirin, a synthetic purine nucleoside derivative of guanosine, is also approved for treatment. Early clinical trials using ribavirin showed decreased need for mechanical ventilation, shorter hospital stays, and improved pulmonary function; subsequent data, however, have not been as supportive questioning its overall cost/benefit ratio [11,12]. In most centers, the use of ribavirin is limited to immunocompromised patients and severely ill children. Ultimately, if all these measures fail to provide adequate support, ventilatory assistance may be required. This occurs in approximately 2% of all children requiring inpatient care. Steroids, antitussives, and antibiotics have no established role.

The lack of a definitively effective treatment of RSV infection led to a focus on protective vaccination. A live attenuated vaccine administrable at birth has been sought but has not yet been proven feasible. Instead, 2 forms of passive immunoprophylaxis have been developed: RSV immune globulin intravenous and palivizumab (Synagis). RSV immune globulin intravenous, an intravenous injection given over 4 hours, is cumbersome and poorly tolerated in the pediatric population; it is also contraindicated in children with cyanotic congenital heart disease. Palivizumab, in comparison, is administered intramuscularly as a monthly injection during the RSV season (November to April) and has no patient population restrictions [11]. Palivizumab is a humanized immunoglobulin G1 monoclonal antibody that binds to the F protein of RSV. The first large trial involving palivizumab, the Impact-RSV trial, was completed in 1998 [13]. This multicenter, randomized, double-blind, placebo-controlled trial was carried out in the United States, Canada, and United Kingdom. The Impact-RSV study established the safety of the drug and demonstrated several important points of efficacy of palivizumab administration. Hospitalization was decreased by 55% overall. Palivizumab recipients had fewer days in the hospital, fewer days with increased oxygen requirement, and fewer days with lower respiratory tract infection with an overall low incidence of intensive care unit (ICU) admissions and mechanical ventilation [14].

Our experience with the detrimental impact of RSV infection upon the course of a child undergoing laryngotracheal airway reconstruction prompted us to examine the potential role of palivizumab in the surgical setting.

2. Case report

CF is a 17-month-old boy with grade III subglottic stenosis who presented for LTR. He was a former 34-week gestation infant with no additional cardiac, pulmonary, or immunodeficiency comorbidities. A planned 2-stage procedure was performed including tracheotomy. On the postoperative day 2, the patient developed a fever to 103°F as well as increased oxygen and suctioning requirements. Chest radiograph was consistent with bronchiolitis. A viral culture was positive for RSV. Septic workup was negative. Supportive measures including oxygen, aggressive suctioning, nebulizer treatments, and chest physiotherapy were instituted. He ultimately required 6 days of ICU care and 8 days of additional inpatient care with gradual improvement in his respiratory status. He was discharged to home on postoperative day 14 with visiting nurse services and was readmitted on 2 occasions for dyspnea and increased secretions for a total of 4 days. Successful decannulation was eventually performed on postoperative week 9.

3. Methods

A MEDLINE search was conducted using the key words “palivizumab,” “respiratory syncytial virus,” “cricotracheal resection,” and “LTR.” Secondary searches were performed for postoperative complication, morbidity, and mortality. Results were limited to the English language. The total number of references was ultimately reduced to 18 when limited to clinical trials for palivizumab or impact on surgical patients. Five references specifically addressed the impact of postoperative RSV infection.

4. Results

Investigation of the role of palivizumab and RSV infection relative to postoperative outcome comes principally from the cardiac surgery and pulmonary transplant literature.

One cardiac surgery study assessed 25 patients undergoing cardiac surgery for congenital heart disease who had a documented RSV infection within the previous 6 months. The patients were divided into 2 groups: group 1 had surgery during the same hospital admission as the RSV infection, whereas group 2 had elective surgery 2 or more weeks after an RSV hospitalization [15]. Group 1 patients required 10.5 ± 12.0 days of ventilatory support and 19.8 ± 17.6 days of hospitalization, whereas in contrast, group 2 patients required only 1.2 ± 0.9 days of ventilatory support and 5.5 ± 2.8 days of hospitalization. Group 1 had 2 deaths secondary to RSV infection, both of which occurred in patients who underwent surgery within 2 weeks of their infection. The conclusion made was that cardiac surgery in symptomatic patients was fraught with postoperative complications, especially in those patients undergoing surgery early in the course of the RSV illness.

A second cardiac surgery study similarly examined the impact of RSV on the postoperative course in congenital heart disease patient, but in addition assessed the potential benefit of preoperative RSV screening [16]. Six patients were identified in whom RSV infection occurred within 5 days of surgery and complicated the postoperative course. The average length of stay for these patients was 27.6 hospital days of which 20.6 days were in the ICU. These hospital stays were 2.1 times greater than historical controls. Four of these
patients required prolonged mechanical ventilation, 1 died, 1 required LTR secondary to acquired subglottic stenosis, and 1 required tracheotomy. The conclusion was that RSV was a major contributor to postoperative mortality and morbidity. Cost analysis of these patients revealed a 2.6-fold increase in total hospital charges for the RSV patient group compared with historical controls. Preoperative serological screening for the RSV antigen before the upcoming cardiac surgery was subsequently implemented. By delaying surgery in 22 of 197 patients screened who tested positive, the incidence of postoperative RSV infection decreased from 6 to 2 patients the following year.

The role of perioperative RSV infection has also been investigated in solid organ transplant patients. One review identified 17 postoperative RSV infections, 13 of which were nosocomial, within 493 liver transplant patients; 2 of these infected patients died [17]. A second review of postoperative viral infections in 122 lung transplant recipients identified 10 patients who developed a community-acquired respiratory tract infection, 5 of which were caused by RSV. Despite treatment with ribavirin, 2 of these 5 patients required mechanical ventilation, 1 of whom ultimately died [18].

There is only 1 study published to date regarding perioperative RSV infection in airway reconstruction patients. An assessment of postoperative outcome in 82 cases of LTR and CTR identified 6 postoperative cases of viral bronchiolitis secondary to RSV [8]. In these 6 RSV cases, days of unexpected intubation increased from 0.84 to 2.75, and additional ICU hospitalization days increased from 1.50 to 3.25, compared with controls. Four of these 6 patients had significant complications; all had predisposing risk factors such as CLD, pulmonary hypertension, cystic fibrosis, immunosuppression, or prematurity. Notably, all RSV infections occurred in patients undergoing surgery between October and April, leading to the suggestion that these postoperative complications could be prevented by either not operating during the RSV season or by using perioperative respiratory isolation measures. The use of palivizumab or intravenous RSV immunoglobulin was also suggested, particularly in those regions where RSV epidemics are unpredictable or year-round and in those cases where the surgical procedure cannot be delayed.

5. Discussion

Currently, the American Academy of Pediatrics recommends palivizumab RSV prophylaxis in the following populations: infants and children younger than 2 years with CLD requiring medical therapy for their CLD in the 6 months before the RSV season, infants born at 32 weeks’ gestation or earlier, infants born at 32 to 35 weeks’ gestation with 2 or more of the following risk factors (exposure to tobacco smoke or pollutants, child care attendance, school-aged siblings, congenital airway abnormalities, or severe neuromuscular disease), and children younger than 2 years with congenital heart disease. Immunocompromised children are also likely to benefit from prophylaxis, although this is not a specifically defined recommendation [19].

Palivizumab is administered at a dose of 15 mg/kg, every 30 days, for a total of 5 doses during the months of November to March. The IMPACT study demonstrated the safety of the vaccine and showed the injections to be well tolerated. The principal factor preventing the widespread use of vaccine is cost. The manufacturer’s charge approximates US$1200 for a 100-mg vial. Depending on the weight of the child, 1 season of vaccine administration is a significant expense. For example, for a 10-kg child about to undergo airway reconstruction surgery, 150 mg (1.5 vial) would be required each month for up to 5 months, at a maximum cost of US$9000, depending on when the surgery was planned.

This “up-front” vaccination expense, however, needs to be considered relative to the alternative potential costs of a perioperative RSV infection. For example, our institution’s charge for a single day in the pediatric ICU approximates US$4000 and for a semiprivate bed on the floor approximates US$1600. Prolonged hospitalization stays, particularly in the ICU, significantly increase costs, particularly if these children require additional procedures such as a tracheotomy or revision of their airway reconstruction. This is true of even relatively minor complications of RSV infection as evidenced by the child in our Case report. Patient CF required an additional 1 to 2 days of ICU care and 4 to 5 days of initial inpatient hospitalization, as well as 2 hospital readmissions secondary to his RSV infection. Applying the room charges listed above, his cost of care was increased by US$16 900 to US$22 600. This figure does not account for additional outpatient nursing services and supplies.

Multiple economic analyses have been performed to determine whether the administration of palivizumab in high-risk pediatric populations is cost-effective. No such studies have been applied in children undergoing airway reconstruction [10].

6. Conclusion

The goal of this literature review is to raise awareness of the significance of perioperative RSV infection in children undergoing airway reconstruction procedures and of the potential benefit of palivizumab administration in preventing this morbidity. A multi-institutional study involving a large number of patients would be needed to do an appropriate cost-benefit analysis. Individual otolaryngologists, however, can examine the incidence of RSV infection in their own communities, as well as hospitalization costs at their own institution, to determine a relative sense of the potential benefit of RSV immunization in their airway reconstruction patient populations. Many children undergoing airway reconstruction, such as those undergoing other major surgeries such as cardiothoracic procedures and organ transplantation, are a high-risk population based on their
concomitant diseases and the nature of their operations. As demonstrated by our surgical colleagues, such children might indeed benefit from preoperative RSV immunization.

References