Choice of Diffusing Capacity Hemoglobin Correction Equation and Prediction of Mortality and Pulmonary Outcomes in Children Receiving Hematopoietic Stem Cell Transplantation

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Abstract

Objectives: The objective of this study is to compare the Dinakara and Cotes equations in their ability to predict post hematopoietic stem cell transplant (HSCT) pulmonary complications and mortality. Hypothesis We hypothesize the pre-transplant diffusing capacity adjusted for hemoglobin (DLCOHgb) by the Cotes equation in pediatric patients undergoing HSCT will predict morbidity and mortality more accurately than the Dinakara equation. Study-Design: Data was collected retrospectively from chart review of patients who underwent their first HSCT at Riley Hospital for Children using a database maintained by the Pediatric Stem Cell Transplant Program. Patient-Subject Selection: Patients who performed pre-transplant diffusing capacity for carbon monoxide (DLCO) that met ATS criteria, and a hemoglobin recorded within 7 days of their pulmonary function testing were included. Methodology: Paired t-tests and ANOVA models were used to define any differences between the two equations at baseline and when stratifying by hemoglobin level. Logistic regression models were used to determine associations between the Dinakara and Cotes equation with mortality at one- and three-years post-transplant. Results: 90 patients underwent HSCT during the study period, and 69 patients met inclusion criteria. Odds ratios for mortality using DLCO corrected for the Dinakara (1.08 SD 0.98-1.19) and Cotes (1.09 SD 0.97-1.22) were similar (p-value > 0.05). Neither Dinakara or Cotes corrective equation was superior at predicting pulmonary complications. (p-values 0.1388 and 0.5246 respectively) Conclusions: The Dinakara and Cotes equations differed in their calculation of DLCOHgb at lower Hb levels, their ability to predict mortality and pulmonary complications after HSCT was not different.

INTRODUCTION

Several studies have demonstrated that pre-transplant pulmonary function metrics in patients undergoing hematopoietic stem cell transplant (HSCT), including the diffusing capacity for carbon monoxide corrected for hemoglobin ($DLCO_{Hgb}$), are associated with early respiratory failure and lower overall survival[1-3]. A variety of algorithms have been developed to use pulmonary function tests (PFTs) as a way to predict post-transplant pulmonary complications [4, 5]. $DLCO_{Hgb}$ is a large part of these algorithms. There are two equations used to correct DLCO for hemoglobin (Hgb), the Dinakara[6] and Cotes[7] equations. At this it is unknown if one is superior to the other in regard to predicting morbidity and mortality in the pediatric stem cell transplant population.

There has yet to be a study directly comparing the ability of the Cotes and the Dinakara equations to predict morbidity and mortality following stem cell transplant in a pediatric population. Given that previous studies have corrected DLCO for hemoglobin inconsistently and have used different equations, determining if using the Dinakara or Cotes equations leads to statistically and clinically significant differences in this population could change the way physicians counsel patients and families prior to stem cell transplant. [4, 5, 8]

The objective of this study is to compare the Dinakara and Cotes equations in their ability to predict post HSCT pulmonary complications and mortality. We hypothesize that because the Cotes equation is more widely used, the pre-transplant diffusing capacity adjusted for Hgb by the Cotes equation in pediatric patients undergoing HSCT will predict morbidity and mortality more accurately than the Dinakara equation following HSCT.

METHODS

This was a retrospective study where data was collected from chart review of patients who underwent their first hematopoietic stem cell transplant at Riley Hospital for Children. A database maintained by the Pediatric Stem Cell Transplant Program was used and contained information on patients who underwent stem cell transplant from January 1, 2007 to April 30th, 2017. The database provided information such as demographics, date of diagnosis, and type of oncologic diagnosis. Additional inclusion criteria for the study were as follows: patients who performed pre-transplant DLCO that met American Thoracic Society (ATS) criteria, and a hemoglobin recorded within 7 days of their pulmonary function testing. This study was approved by the Indiana University Institutional Review Board.

Information on patients' demographics, primary disease, pre-transplant pulmonary function tests, and chest imaging prior to transplant was compiled in an Indiana School of Medicine RedCap database. Post-transplant data collected included additional transplants, relapse status, graft versus host disease (GVHD) status, all post-transplant PFT data, mortality, and pulmonary complications. Post-transplant data was collected, including mortality data at one and three years. Pulmonary complications were defined as documented and treated pulmonary infections as well as clinically significant abnormal chest imaging. Mortality was defined as death by any cause.

Paired t-tests and ANOVA models were used to define any differences between the two equations at baseline and when stratifying by Hgb level. Logistic regression models were used to determine associations between the Dinakara and Cotes equation with mortality at one- and three-years post-transplant. Results were reported as odds ratios with 95% confidence intervals and p-values. Two sample t-test statistical analysis were then used to compare PFT's and hemoglobin correction equations with and without pulmonary complications. Spirometry data were reported as z-scores while $DLCO_{Hgb}$ values were reported as percent predicted values and p-values produced from student's t- test were used for comparison. The Global Lungs Initiative reference equations for used for spirometry, and data from Kim et al. were used for DLCO reference equations. All analyses were performed using SAS v9.4 and all analytic assumptions were verified.

RESULTS

There were 90 patients who underwent HSCT during the study period, and 69 patients met inclusion criteria. Of the 21 patients who were not included in the analysis, 6 patients did not have a Hgb recorded within 7 days of pulmonary function testing and 15 patients did not have acceptable PFT data. (Figure 1). The clinical characteristics of this population study are summarized in Table 1. The average age of a child in this study was 14.2 years old. 62% of the study population had an active oncologic disease process, most commonly a form of leukemia.

Table 2 compares the corrected DLCO using Dinakara vs. Cotes for different baseline Hgb levels. DLCO corrected by Dinakara was consistently higher than that for Cotes, but this difference was only significant for Hgb<9. These differences did not affect the odds ratio (OR) for survival at 1 and 3 years after HSCT, which were similar for both and not significantly increased overall regardless of which reference equations was used (Table 3).

Pulmonary complications were common in the study cohort, with 61% of patients experiencing at least 1 complication (Table 4). As shown in Table 5, the mean FEV1 and FVC z-scores were significantly lower in patients with pulmonary complications compared to those with no complications (p=0.0022). However, there was no significant difference in $DLCO_{Hgb}$ between the two groups using either Cotes or Dinakara.

DISCUSSION

In this single center retrospective study of children who underwent HSCT, we found that using Dinakara to correct for Hgb when calculating DLCO resulted in less error at lower Hgb levels compared to Cotes. However, this difference did not affect the ability of either equation to predict survival, nor did pre-transplant DLCO predict post-transplant pulmonary complications. Our results suggest that the method of correction of DLCO for hemoglobin pre-transplant $DLCO_{Hgb}$may not be the most important factor in predicting post-transplant complications and mortality. Contrary to our hypothesis, the Cotes equation is not superior to Dinakara when predicting morbidity and mortality in the pediatrics HSCT population.

Our results differ from past studies by Coffey et al. and Ginsberg et al. [1, 8] Both studies look at the predictive value of DLCO in the context of two tools used in the adult population that help predict survivability. Coffey et al. demonstrated differences in predictive value of $DLCO_{Hgb}$ when using the Cotes equation versus the Dinakara equation in the context of the Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI), a validated decision making took in adult and pediatric populations. Ginsberg et al demonstrated that DLCO, as part of the Lung Function Score (LFS), was associated with post-transplant survival in a pediatrics population, but they did not investigate differences in how $DLCO_{Hgb}$ was calculated. In contrast, our study focused on the predictive value of $DLCO_{Hgb}$ alone in a pediatric population and we did not find that it was a good predictor for survival. This could be because we assessed $DLCO_{Hgb}$ as an individual predictor and not part of tool that takes other clinical factors into effect. Ginsberg et al. also focused the predictive values of DLCO and other pre-transplant spirometry values for survival; however they did not look specifically at post-transplant complications like infection or post-transplant imaging abnormalities.[8]

Similar to a study by Nitta et al. we found that the differences in corrected DLCO when using Dinakara and Cotes become more pronounced at lower hemoglobin levels, although this did not result in a difference in predicting pulmonary complications between the two methods.[9] The difference in the $DLCO_{Hgb}$ when calculated from Dinakara and Cotes highlight the importance of the effect of hemoglobin levels when adjusting DLCO and emphasizes the need to take other patient factors into account when calculating the adjusted DLCO. In this study we also reported other pre-transplant spirometry values and their relationship to post-transplant complications. Similar to findings by Srinivasan et al., we report that lower z-scores for FEV1, FVC, and possibly FEF25-75 are associated with higher risk for post-transplant pulmonary infections and complications.[2]

Our results suggest that using DLCO alone as a predictor of survival is insufficient. DLCO is only one aspect of overall pulmonary function and its clinical interpretation is affected by other factors like anemia and alveolar volume. The causes of death in the HSCT population are often related to respiratory failure in the setting of relapse of disease, GVHD, or infection.[10] The relationship between DLCO and these complications is not well-defined. Furthermore, the studies mentioned above demonstrate that most pediatric patients have normal pre-transplant DLCO values. [2, 6]

There are several limitations to our study. The retrospective and single center study design may have resulted in biased and missing data. The size of our study cohort was similar to other studies, but the relatively small number of patients made it difficult to conduct multivariate modeling to assess the independence of DLCO in the presence of covariates. Other reports have shown that type of transplant, GVHD status, and CMV status affect outcomes, however we were unable to look at these factors due to sample size and incomplete medical records.[11] It is possible that we would have observed significant associations between DLCO and pulmonary outcomes if we had a larger study population and were able to perform multivariable analysis.

In summary, although we found that the Dinakara and Cotes equations differed in their calculation of $DLCO_{Hgb}$ at lower Hb levels, their ability to predict mortality and pulmonary complications after HSCT was not different. In the future, prospective study design should focus on comparing risk stratification that incorporates the method used to correct DLCO for Hgb as this will help clarify the role of DLCO in the pediatric pre-stem cell transplant population.

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Table 5 DLCO.docx available at https://authorea.com/users/405733/articles/530445-choice-of-diffusing-capacity-hemoglobin-correction-equation-and-prediction-of-mortality-and-pulmonary-outcomes-in-children-receiving-hematopoietic-stem-cell-transplantation

Figure 1: Derivation of the study cohort