Can Receiver Operating Characteristics Analysis be Used to Predict Avascular Necrosis in Pediatric Sickle Cell Patients Using Magnetic Resonance Imaging?

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Background: Avascular necrosis (AVN) is a devastating complication of sickle cell disease (SCD) and other conditions which result in altered perfusion to at risk portions of the human skeleton. Early intervention in this condition is considered critical, particularly in young patients in whom a decision for arthroplasty would likely result in the patient requiring several revision arthroplasties in their lifetime. The goal of our study was to provide operating characteristics for a new magnetic resonance imaging (MRI) sequence to diagnose AVN early in SCD.

Methods: 44 hips in 25 patients were examined for clinical and MRI evidence of AVN. A new MRI sequence, called Diffusion Weighted Imaging (DWI) was applied in addition to standard MRI sequences. This sequence was used to generate a numeric apparent diffusion coefficient (ADC). This number was used to generate a receiver operating characteristic (which defines the optimum sensitivity and specificity for a given outcome of a diagnostic test) for this sequence.

Results: Our receiver operating characteristic revealed the optimum value to diagnose early AVN is 0.8550. This characteristic based on our data is associated with a sensitivity of 100% and a specificity of 94.4% . The positive predictive value was 75% and the negative predictive value was 100%.

Conclusions: DWI can be used to generate an ADC. With further study, it may be possible to validate this number to predict AVN in this patient population. With a negative predictive value of 100%, it is unlikely that a patient predicted not to get avascular necrosis would suffer this complication in close proximity to the performance of the MRI.

Level of Evidence: III Diagnostic, without gold standard comparison

Introduction

AVN of the hip is a devastating complication of sickle cell disease and other conditions which disrupt intraosseus blood flow. This is particularly important in children because a decision to perform an arthoplasty in a young patient would likely result in several revision surgeries in the patient's lifetime, with all the risks attendant to each of these surgeries.

The pathogenesis of AVN is thought to be in part due to increases in intraosseus pressure, and decreases in intraosseus blood flow.[1] Currently early diagnosis can be made based on patient symptoms along with various MRI protocols. Diagnosis via screening prior to symptoms in certain populations (such as oncology patients using high dose steroids) could allow for modification of their drug regimen such that AVN may be prevented. Diffusion Weighted Imaging (DWI) has been recently described as a potential way to demonstrate epiphyseal ischemia earlier and with more stable results than traditional MRI sequences [2,3]. This type of MRI sequence is appealing because it generates an apparent diffusion coefficient (ADC). This measurement has been shown in a pig model to increase and remain elevated with prolonged ischemia.[4,5] In addition, this ADC has been correlated to the stage of Legg Calve Perthes disease, and more recently has been shown to be elevated in patients with SCD with early AVN, compared to asymptomatic SCD patients and normal controls. [6,7]

ADC is a numeric quantity which, with further study, may allow for early identification and tracking of the pathogenesis of AVN. A similar thought process is used when inflammation caused by periprosthetic infection causes an elevation in erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Because the ADC measures altered water mobility resulting from vaso-occlusion and subsequent infarction in processes which cause AVN, the ADC should be detectable in disease, normal in health, and sensitive to change. Previous papers have described receiver operating characteristics of ESR and CRP to help generate a reasonable cutoff value that could be used to determine if periprosthetic infection was likely to exist at a given point in time. [8] Similarly, the goal of this study is to use receiver operating characteristic analysis to determine the optimum level of the ADC to determine when early AVN can be said to be present, thus detecting a threshold value which can be used for future study.

Patients and Methods

The study was approved by our hospital's Institutional Review Board. This study was conducted as a retrospective analysis of a

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database collected by the senior author for the purposes of comparing DWI in normal controls versus sickle cell patients. The study was a case control design where cases were represented by patients who had AVN both radiographically and clinically. Controls were the unaffected hips of patients with AVN and patients with SCD without AVN. Clinical AVN was defined as groin pain in the affected limb. Early AVN was defined as either normal plain radiographs with abnormal conventional T1 and T2 weighted MRI findings; or cystic and sclerotic changes in the femoral head on plain radiographs. [9] Signal intensity (SI) measurements were obtained by drawing a region of interest (ROI) around the femoral head epiphyses on diffusion-weighted images. Signal intensities were measured with the aid of Interactive Data Language Software v6.2 (IDL, ITT Visual Information Solutions, Boulder CO). These ROIs were drawn by a fellowship trained musculoskeletal radiologist, and confirmed to contain the area of interest by three readers. To quantify tissue specific diffusion properties, an ADC was calculated by the following equation from two diffusion-weighted images $-\ln (SI_1/SI_0)/(b_1-b_0)$, where SI_1 and SI_2 are the diffusion-weighted images obtained with the two b values ($b_1=0$ and $b_2=500$). [10]

We examined 25 patients (44 hips) with SCD previously documented by the hematology oncology division at our institution. The average patient age was 13.7 years (range 9-19.6).There were 11 females and 14 male patients. Of these patients, six hips developed AVN (12%).

Diffusion-weighted images in the axial plane were acquired through both hips using an axial fat-suppressed diffusion weighted spin-echo echo-planar sequence with 8b values on a 1.5 Tesla (Avanto; Siemens Medical Systems, Erlangen, Germany) or 3.0 Tesla (Trio; Siemens Medical Sysems, Erlangen, Germany) running VB13 software. Both hips were imaged simultaneously in the axial plane to minimize susceptibility artifact. Axial T1 and T2 weighted images were obtained and compared to plain radiographs in the AP-and frog lateral planes.

The mean and 95% confidence interval of the ADC for the AVN and no- AVN hips were determined. Difference between the groups was determined using the Mann-Whitney U test. A p value of <0.05 was considered statistically significant. Since age was found to be an important factor in ADC values in previous studies, multiple linear regression analysis was used to determine if age still provided important confounding to the relationship between ADC and AVN, and as such if the value of ADC needed to be adjusted for age for the purposes of ROC analysis. A value of 0.10 for multiple linear regression analysis was used to determine whether significant confounding existed. Receiver operating characteristics (ROC) curves illustrating the relationship between true positive (sensitivity) and false-positive cases (1- specificity) were constructed for the ADC in this sickle cell population (Figure 1; Table 1). The area under the curve (AUC) is a measure of the accuracy of the diagnostic test. An AUC of 1 corresponds to 100% sensitivity

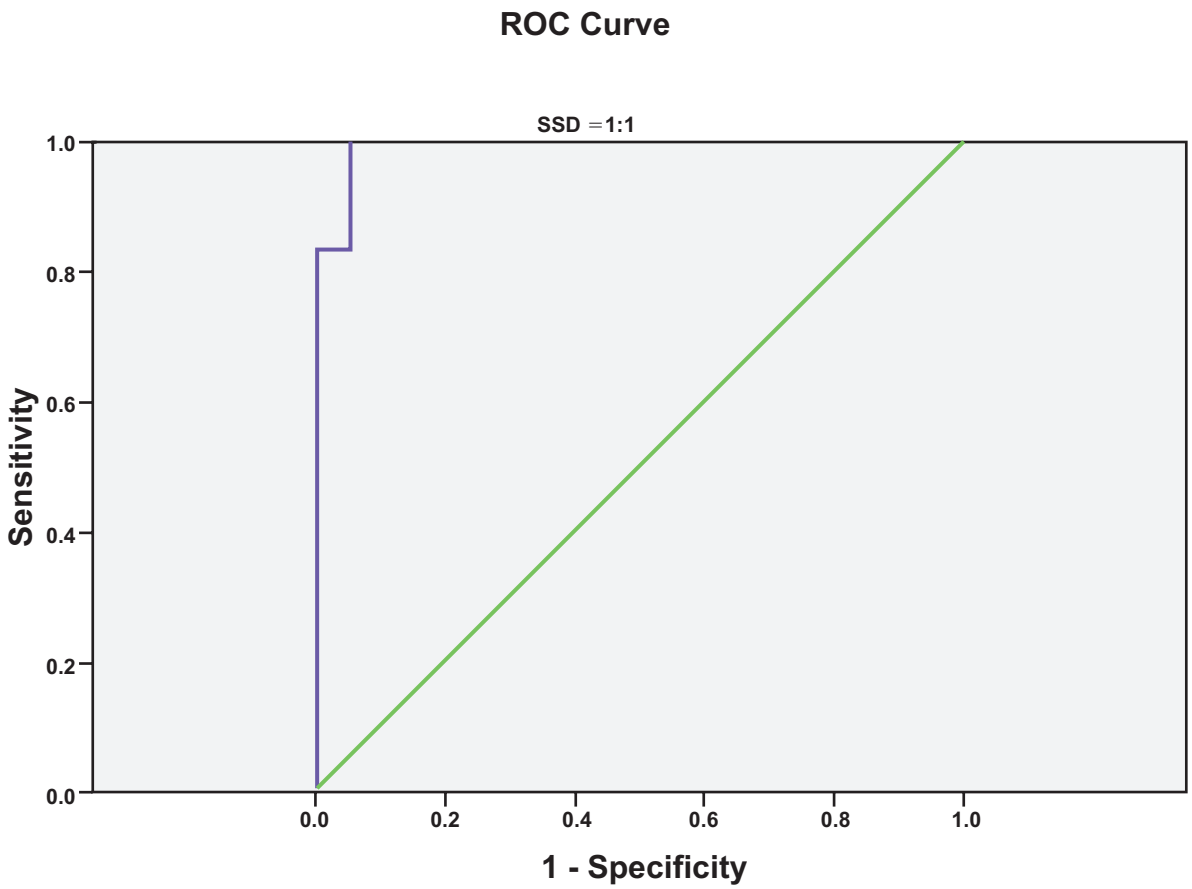

Figure 1. Reciever Operator Curve for ADC in the prediction of early AVN

Table 1- Results and Significance of the Area Under the Curve

Area Under the Curve

Test Result Variable(s):ADC 0 & 500

				Asymptotic 95% Confidence Interval	
SSD=1	**Area**	**Std. Errora**	**Asymptotic Sig.b**	**Lower Bound**	**Upper Bound**
1	.991	.012	.000	.968	1.014

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

and specificity. We used the non-parametric estimator to generate our AUC because the sample size was prohibitive in using the asymptotic parametric method. We derived the optimum value of the ADC from the receiver operating curve. Sensitivity, specificity, positive and negative predictive values of the optimum ADC were determined. All statistics were calculated with SPSS version 16.0 (SPSS Inc.; Chicago, Il).

Results

The mean ADC in SCD patients without AVN was 0.51 (0.42, 0.60), The mean ADC in patients with AVN was 1.54 (1.18, 1.9). The difference in ADC between groups was statistically significant (p value <0.001). The average age in AVN hips was 14.6 (11.2,17.9) years compared to 13.6 (12.5,14.7) years (p value 0.584) in non-AVN hips. In the SCD patients, age was not correlated with ADC value on univariate analysis ($r = -0.042$; p value 0.789) and was not found to be a significant confounder on linear regression analysis (p value 0.280). In addition, gender did not significantly affect ADC values (p value 0.123).

ROC analysis (Figure 1) revealed an area under the curve of 0.991 (0.968, 1.014) p value <0.001 (against a null hypothesis that the AUC = 0.50). Under this curve, the optimum value to detect early AVN is 0.8550. This value is associated in our sample with a sensitivity of 100% and a specificity of 94.4% the positive predictive value was 75% and the negative predictive value was 100%. There were two false positive children, one with an ADC of 1.26 was the right hip of a 9 year old male who was not symptomatic, the other patient was the right hip of an 11 year old male who was also not symptomatic.

Discussion

Diffusion Weighted MRI, and the ADC are relatively new concepts in the field of musculoskeletal imaging. These tools provide the opportunity to potentially diagnose conditions such as AVN in an early phase, when the disease process can be treated by less invasive techniques, or in some cases just by cessation of treatment with the offending agent. These tools are especially important because often patients who develop late stage AVN early in life have no option other than joint arthroplasty for pain relief. Arthroplasty when done early in life virtually guarantees several revision surgeries during the course of the patient's lifetime. If AVN can be addressed in an early stage, there is the potential for joint preserving procedures such as core decompression and bone grafting to be successful. In order for the ADC to be a worthwhile tool, optimum parameters must be derived for its usage. The purpose of this study was to use receiver operating characteristic analysis to determine the optimum value of the ADC to determine when early AVN can be said to be present. Additionally, this value may provide an important research tool for future studies aiming to define AVN in sickle cell patients using diffusion weighted MRI.

This study was not without its limitations. The study population was small, and so any negative results in the study must be interpreted with caution. Since some of these patients were referred specifically to rule out AVN, and some were prescribed MRI for unrelated reasons, we cannot say that the incidence in our population represents the population of sickle cell patients as a whole. This limits the external validity of our study. Additionally, as we strictly examined a population with sickle cell disease, we cannot generalize our results to other etiologies of AVN. Additionally, further study is necessary to generate normative values of the ADC, and establish a continuum of ADC values so we can better understand its utility.

Nonetheless our study demonstrates that the ADC has useful applications in the sickle cell population to provide a number to guide the diagnosis of AVN. Although we had no choice but to use conventional MR and physical exam findings to diagnose AVN, our study provides guidelines based on conventional measures that can be used as an objective measure that would be consistent and not dependant on radiologist read or physician's physical exam. This study also provides a number with favorable test characteristics in the setting of a sickle cell patient for ruling out AVN. It becomes important to identify AVN at an early stage in an effort to either alter potentially exacerbating medications or to undertake early treatment. Styles and Vichensky performed 13 coring procedures in 10 patients (mean 15 years olf) with SCD and AVN and evaluated outcomes at mean 3.7 years follow-up. All 5 stage I patients had substantial improvement in pain, and only one showed X-ray progression. Five of the 6 (83%) stage II patients had improvement in pain, and 2 patients progressed on X-ray. Both stage III patients progressed on X-ray, but one was clinically improved. [11] Mukisi-Mukaza et al conducted a prospective case-controlled study comparing core decompression and non-surgical management for avascular necrosis of the femoral head in sickle cell disease, finding that core decompression had a favorable clinical and radiological outcome superior to surgical abstention

with stages I and II disease remaining stable after drilling, necessitating no arthroplasty.[12] These results demonstrate that in early AVN, core decompression was beneficial for almost all patients, making early diagnosis an important factor in dictating treatment.

Future study should focus on using the ADC for other applications. SCD represents a group of patients who are not hematologically normal. Considerable expansion of hematopoietic marrow occurs and these patients have traditionally sluggish blood flow. As such, the results of this study, and specifically the ADC cutoff we noted, may not be generalizable to other applications. However, patients who are normal, and become abnormal such as patients with ALL being treated with steroids may benefit from this type of diagnostic study to alter the course of their treatment before it results in AVN. In the same vein, Ce et al demonstrated in a sample of patients with multiple sclerosis receiving pulse steroids that 15.5% had AVN without any AVN history or symptoms.[13] Diffuse weighted MRI could provide a similarly useful tool to diagnose early AVN in these populations. However, further study is necessary.

This study was conducted to generate an ROC for AVN in a sample of patients with sickle cell disease. As diffusion-weighted MRI provides a cutting-edge tool for early diagnosis of AVN in both research and clinical situations, an ROC is useful in providing a cut-off value to define AVN. As noted, this is a relatively new indication for diffusion-weighted MRI and further investigation is necessary to fully determine its implications and utility.

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