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ORIGINAL PAPER

Conservative gadolinium administration to patients with Duchenne muscular dystrophy: decreasing exposure, cost, and time, without change in medical management

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Abstract

Cardiac MR (CMR) is increasingly used to assess for cardiac involvement in patients with Duchenne muscular dystrophy (DMD). The frequent use of gadolinium based contrast agents (GBCAs) has been called into question with reports of intracranial gadolinium deposition in patients receiving multiple administrations. We adopted a conservative GBCA administration policy, limiting the frequency of GBCA exposure in patients with previously documented late gadolinium enhancement. The aim of our study was to evaluate the clinical effects of this policy change. Data were retrospectively reviewed on 405 consecutive patients with DMD who underwent CMR evaluation. Patients were grouped into conservative GBCA administration or historical control. CMR reports were evaluated and clinical reports were reviewed to determine actionable changes. Ohio Medicaid reimbursements were used to estimate costs. A total of 187 patients comprised the conservative GBCA group and 218 patients the historical cohort. The conservative GBCA group had lower contrast administration rates (84% vs. 99%, $p < 0.0001$), shorter scan times (35.2 vs. 39.0 min, $p < 0.0001$), and lower estimated medical costs ($339 vs. $351/study). There was no change regarding the initial presence of first-time late gadolinium enhancement, and no difference in actionable change. Contrast administration substantially decreased 7 months post-policy change (65%) compared to the initial 7 months (96%, $p < 0.0001$). In the current era with unclear concern for intracranial gadolinium deposition, thoughtful GBCA administration is warranted in patients anticipated to undergo multiple CMRs. Our updated approach has resulted in fewer patients receiving contrast, shorter scan times, and less medical costs, without appreciable changes to patient management.

Keywords Pediatrics · Cardiomyopathy · CMR contrast · Delayed myocardial enhancement

Abbreviations

CMR	Cardiac magnetic resonance
DMD	Duchenne muscular dystrophy
GBCA	Gadolinium based contrast agent
LGE	Late gadolinium enhancement
SSFP	Steady-state free precession

Introduction

Duchenne muscular dystrophy (DMD) is an X-linked disorder leading to progressive skeletal and cardiac myopathy [1]. DMD affects approximately 1 in every 5000 live male births, and given improvements in respiratory management, cardiac

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dysfunction is now a leading cause of morbidity and mortality in DMD patients [2–4]. Current recommendations are for annual cardiology assessments to evaluate for ventricular dysfunction, including noninvasive imaging [5–9]. Cardiac magnetic resonance imaging (CMR) has often replaced echocardiography for cardiac evaluation due to previous studies demonstrating suboptimal echocardiography imaging [5, 6, 8–10]. CMR has added benefits of tissue characterization, especially with the use of gadolinium based contrast agents (GBCAs), which allows for detection of myocardial pathology and earlier initiation of medical management [11, 12]. Historically our institutional approach to this patient population was to perform annual CMR evaluations with the administration of GBCAs to evaluate for late gadolinium enhancement (LGE) indicative of myocardial fibrosis. Once LGE was detected, the patient was started on therapies with known anti-fibrotic effects, or an additional agent was added if already on such a medication. Annual CMR was then repeated with GBCA to follow ventricular function and extent of LGE. This imaging approach has been called into question with reports of intracranial gadolinium deposition appearing late in patients receiving multiple contrast MR exams [13–16]. Based on these data and the observation that our neuromuscular service did not adjust medication dosage based on changes in LGE burden and extension, we adopted a more conservative GBCA administration policy in September 2017. In patients where LGE was already documented, and discussion with the patient or family could occur prior to their repeat scan, subsequent CMRs would be ordered and completed without contrast, and focus on volumetric and function assessment. The aim of this study was to evaluate the clinical effects of this process change.

Methods

This study was approved by the Institutional Review Board. We retrospectively reviewed 405 consecutive CMR evaluations for the indication of "Duchenne Muscular Dystrophy" performed at our institution from September 1, 2016 to October 31, 2018. Patients followed by the Comprehensive Neuromuscular Center were grouped into conservative GBCA administration (September 1, 2017 to October 31, 2018) and historical cohort (September 1, 2016 to August 30, 2017).

Patient characteristics (age, height, weight, body surface area, initial CMR scan, and previous reports of LGE) were obtained from the CMR reports. In addition, the administration of GBCA, the presence of LGE, and the volumetric and functional CMR data were obtained from the CMR report. The description of LGE included location based on the American Heart Association 17-segment model [17], and whether it was new, progressive, or stable compared to previous studies. Total scan time was determined from the DICOM header data.

Electronic medical records for each patient were reviewed focusing on the neuromuscular disorders clinic visit immediately following their CMR. The clinic is a multidisciplinary clinic including a pediatric cardiologist with expertise in heart failure. Actionable change was defined as either the initiation of a new cardiac medication or upward titration of a cardiac medication. These medications are recognized therapy for patients with neuromuscular disorders and cardiac involvement [9]. Examples include: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (lisinopril, losartan, sacubitril/valsartan, and valsartan), mineralocorticoid antagonists (eplerenone, and spironolactone), and β-adrenergic blocking agents (carvedilol, and metoprolol) [9]. When a medication was changed to an alternative in the same class for ease of dosing or per patient preference, this was not considered an actionable change.

CMR costs were estimated comparing 2018 Ohio Medicaid reimbursements for CPT 75,561 "MRI Cardiac with and without contrast" ($351.74) and for CPT 75,557 "MRI Cardiac without contrast" ($270.77).

All CMRs were performed using a 1.5 T Philips scanner (Ingenia; Philips Healthcare, Best, Netherlands). Volumetric and functional assessment was made using standard cine steady-state free precession (SSFP) short-axis stack from the mitral valve annulus to the apex (2-chamber and 4-chamber acquisitions were used for reference). Typical parameters for SSFP images were a field of view 300 × 112 mm, matrix size 168 × 158 mm, slice thickness of 6–7 mm with no gap, pixel resolution 1.8 × 1.8 mm, TR/TE 2.3/1.17 ms, 30 phases per R–R interval, parallel imaging factor 2. For those patients receiving a GBCA, macrocyclic, intravenous contrast (gadoterate meglumnine; Dotarem®; Guerbet LLC, Princeton, NJ, USA) was administered at a dose of 0.2 mmol/kg. The particular GBCA dosage is preferred at our institution due to improved contrast to noise ratio. LGE images were acquired using a standard inversion recovery gradient echo pulse sequence. Separate, single slice LGE acquisitions were obtained in the ventricular 2-chamber, 4-chamber, and 3-chamber planes. A short-axis LGE stack ensuring full ventricular coverage was performed with a slice thickness of 8 mm and a 2 mm gap. These acquisitions were obtained under suspended respiration if tolerated by the patient. The inversion recovery time was chosen to best null the myocardium. The presence of LGE is standardly reported if present in two imaging planes. Volumetric and functional data was clinically measured using QMASS MR (Medis® Medical Imaging Systems, Leiden, the Netherlands).

Summary statistics were expressed as means (standard deviation) for continuous variables, and counts (percentage) for categorical variables. Two-tailed T tests were performed comparing continuous variables between the conservative

GBCA group and the historical cohort. Chi-square tests were performed comparing categorical variables. For all statistical analyses, p values < 0.05 were deemed statistically significant.

Results

A total of 405 CMRs were available for analysis with the indication of DMD. The conservative GBCA group comprised 187 patients, while the historic cohort comprised 218 patients. The patient characteristics are demonstrated in Table 1. The age range of the entire cohort was 7 to 34 years. There was no differences between the two groups with regard to age, height, weight, body surface area, initial/first CMR scan, or previously documented LGE.

CMR variables between the two groups are demonstrated in Table 2. Overall GBCA administration decreased from 99 to 84% (p < 0.0001) with the implementation of the conservative GBCA paradigm. In the historical cohort, there were 2 patients who did not receive GBCA (1 based on family request, and another due to inability to obtain intravenous access). In the conservative GBCA group, 1 patient did not receive contrast due to inability to tolerate the CMR following volumetric assessment; this patient's CMR scan time was removed from evaluation. The remaining patients that did not receive contrast were secondary to previously documented LGE. Within the conservative GBCA group there was a notable decrease in contrast administration following the initial 7 months of the policy change. Among the patients 7 months post-policy change (April 1, 2017 to October 31, 2018), 65% (47 of 72 patients) received contrast. This is in comparison to the initial 7 month period (September 1, 2017 to March 31, 2018), where 96% (110 of 115 patients) received contrast (p < 0.0001). Compared to the historical cohort, the conservative GBCA group demonstrated shorter scan times (p < 0.0001). The average CMR scan time for those that did not receive GBCA was 21.17 ± 6.43 min.

Actionable change data are demonstrated in Table 3. The mean time from CMR study to neuromuscular disease clinic visit was 2.7 ± 5.3 days. There was no difference regarding the initiation of new cardiac medications between the conservative GBCA group and the historical cohort (p = 0.63). In addition there was no difference between the two groups regarding either a new or increasing dosage of a cardiac medication (p = 0.10).

Table 1 Patient characteristics

	Conservative GBCA administration N = 187	Historical cohort N = 218	p value
Age at CMR (years)	14.99 (±4.62)	14.63 (±4.28)	0.42
Height (cm)	140.6 (±14.22)	141.1 (±14.71)	0.73
Weight (kg)	48.90 (±15.94)	48.99 (±15.89)	0.96
Body surface area (m^2)	1.34 (±0.26)	1.37 (±0.28)	0.32
Initial CMR evaluation N (%)	13 (7%)	26 (12%)	0.09
Previous LGE N (%)	73 (39%)	84 (39%)	0.92

Data expressed as mean (±SD) unless otherwise stated

CMR cardiac magnetic resonance, *GBCA* gadolinium based contrast agent

Table 2 CMR variables

	Conservative GBCA administration N = 187	Historical cohort N = 218	p value
Gadolinium administration N (%)	157 (84%)	216 (99%)	**< 0.0001**
LGE presence N (%)	72 (39%)	117 (54%)	**0.002**
Initial presence of LGE N (%)	27 (14%)	33 (15%)	0.84
LV EF (%)	55.58 (±7.18)	56.09 (±7.22)	0.49
LVEDV (mL/m^2)	101.3 (±29.77)	101.4 (±28.01)	0.98
RV EF (%)	59.38 (±5.88)	60.48 (±5.61)	0.06
Total scan time (min)	35.3 (±9.02)	39.0 (±8.08)	**< 0.0001**

Bold values indicate the statistical significance for categorical variables was assessed using Chi-square tests (Gadolinium administration and LGE presence). Statistical significance for continuous variables was assessed using Two-tailed T tests (Total Scan Time)

Data expressed as mean (±SD) unless otherwise stated

CMR cardiac magnetic resonance, *EF* ejection fraction, *GBCA* gadolinium based contrast agent, *LGE* late gadolinium enhancement, *LV* left ventricle, *LVEDV* left ventricular end diastolic volume, *RV* right ventricle

Table 3 Actionable change

	Conservative GBCA administration N = 187	Historical cohort N = 218	p value
Initiation of new cardiac medication N (%)	45 (24%)	48 (22%)	0.626
New or increased dosage of cardiac medication N (%)	73 (39%)	68 (31%)	0.10

Estimated costs between the two cohorts were performed using Ohio Medicaid reimbursements for "MRI Cardiac with and without contrast" ($351.74) and for "MRI Cardiac without contrast" ($270.77) which represents a 23% lower cost without GBCA. Average medical costs were $339 per CMR study in the conservative GBCA group compared to $351 per CMR study in the historical cohort. The differences in cost per study became more noticeable over the final 7 months of analysis, where the estimated cost was $324 per CMR study (8% reduction compared to the historical cohort).

Discussion

This study is the first, to our knowledge, to evaluate the clinical effect of conservative contrast administration for CMR in the DMD population. Overall our results suggest that our policy change has resulted in a decrease in the frequency of GBCA exposure without a discernable effect in clinical management. In addition, our change of practice has resulted in decreased average scan times and decreased estimated medical costs.

The use of gadolinium as a contrast agent to aid in MR imaging was first published by Han Weinmann in 1984, with now a total of over 200 million doses of GBCAs administered worldwide [18–20]. Given that the free ionic form of gadolinium is toxic, it is chelated with a ligand molecule which varies in chemical structure and can be linear or macrocyclic, as well as ionic or nonionic [21]. Previously our institution and others reflexively gave contrast for CMR patients either for contrast enhanced angiography or tissue characterization, specifically LGE, as long as renal clearance was not a contraindication. However this approach has been called into question following reports as early as 2014 of intracranial gadolinium deposition appearing in patients receiving multiple contrast-enhanced MR exams [13–16, 22]. Since then multiple studies have demonstrated an increase in T1 hyperintensity in areas of the brain with linear GBCAs [13–16, 20, 22]. Most current research suggests that the more chemically stable, macrocyclic agents (used in our institution) do not demonstrate T1 hyperintensity of the brain, however that has been recently questioned [20, 23–25]. It should also be noted that as of yet, no clinical significance has been associated with the findings of gadolinium brain deposition. Despite this uncertainty, we and many institutions have reevaluated our GBCA administration policy, choosing to reserve administration to cases when it will provide clinical aid.

Patients with DMD represent a large proportion of CMR scan volume at our institution. Current recommendations are for annual assessments with cardiology to evaluate for ventricular dysfunction, which often relies on noninvasive imaging given that clinical symptoms can be unrecognized due to varying levels of ambulation [5, 6]. CMR has often replaced echocardiography for cardiac evaluation due to poor acoustic windows, with reports of suboptimal echocardiography imaging in 50% of patients 13 years of age and greater [10]. Our group has previously demonstrated the significance of LGE as an initial predictor of worsening cardiac function, demonstrating a significant decline in systolic LV function following the presence of LGE [11]. The previous study demonstrated that the presence and number of segments with LGE increases slowly at younger ages, accelerates, and then levels off in patients with DMD [11]. Other centers have found that initiation of an angiotensin-converting enzyme in these patients with fibrosis and normal cardiac function can attenuate the progression of LGE [26]. These and other studies have provided the clinical evidence to institute cardio-protective medications in this population following the initial presence of LGE [27]. However after the presence of LGE, LV function appears as the primary driver for medication changes. DMD cardiomyopathy is in contrast to other entities like hypertrophic cardiomyopathy, where worsening LGE burden has been associated with ventricular arrhythmias. In patients with hypertrophic cardiomyopathy the extent of LGE burden has been used as an important variable to determine implantable cardioverter-defibrillator placement [28]. In close collaboration between imagers and clinicians the above factors made patients with DMD highly appropriate for a conservative GBCA policy. Additional patient populations who undergo frequent repeated MR evaluations may also be candidates for a conservative GBCA policy after careful discussion of the important imaging variables with clinicians. House and colleagues have investigated whether abbreviated CMR studies alter care in repaired tetralogy of Fallot patients. The group found similar clinical decision making among imagers whether they were presented with the complete study or an abbreviated study which omitted several sequences including LGE imaging [29]. We hope that the previously mentioned study and our own will encourage imagers to scan efficiently and limit unnecessary GBCA exposure in populations receiving frequent CMR studies.

Regarding our CMR results, the primary outcome with our practice change was the decrease in contrast administration. This change was most notable after the initial 7 months the change was enacted. The percentage of GBCA administration 7 months post-policy change was more consistent with our expectation considering the percentage of our patients with DMD and previously reported LGE. The reasons for the GBCA decrease over the course of the evaluation are likely multiple. Practice changes require time to go into effect and over the time period more families were reached to discuss our practice change. In addition some CMR studies were ordered prior to the agreed upon policy change. Over time the CMR group improved the process of identifying DMD patients with previous LGE and were able to discuss with the clinical team whether repeat GBCA administration was necessary. Given that less total GBCA was administered to the conservative GBCA group, it was expected that the group had fewer studies where LGE was found. However the number of patients with initial first-time presence of LGE (a primary clinical decision driver) was not different between the two groups. The decrease in total CMR scan time, with nearly 18 min saved in non-contrast studies, was attributable to the omission of LGE sequences. These multiple LGE sequences, often breath-held, required additional time following the standard volumetric and functional assessment. Reduced scan time is important for CMR clinical efficiency, but more importantly limits patient discomfort. Patients with DMD have issues with respiratory function, immobility and contractures, often limiting the ability to tolerate prolonged CMR scan times [9]. Although not assessed, fewer patients requiring contrast may also shorten the overall time in the MRI suite. A non-contrast CMR avoids the need for intravenous line placement, which is particularly challenging in the DMD population and may require multiple attempts. Taken together, these changes might be expected to improve patient experience.

Most importantly with regard to this study was the finding that clinical decision making was not discernably different with the decreased GBCA exposure. This finding was anticipated given the collaboration between the clinicians and imagers, however was necessary to ensure that patient management was not significantly altered with our policy change. A possible limitation is that medication changes may not always be entirely secondary to CMR results, as symptoms, blood pressure elevation, tachycardia or arrhythmias, and other factors play a role in the initiation or titration of a cardiac medication. However this would be unlikely to introduce any particular bias between the two groups.

This study also evaluated the possible medical cost savings from a conservative GBCA strategy. Our results estimate a reduction in per study medical costs with our adopted policy, with estimated cost reduction over the final 7 months of 8% per CMR study, as the cost is reduced by 23% in each study where GBCA was not used. Reimbursements were chosen in place of hospital charges which overestimate actual medical costs. These results are still likely a conservative estimate as we used a single-payer to estimate costs, and Medicaid reimbursements are often lower than those of other third-party payers. Although not our primary objective with our systems change, given the continued escalation of US healthcare expenditures, providing cost-effective strategies to deliver high-quality care has never been more relevant, particularly with regard to diagnostic imaging studies [30].

This study is not without limitations. The study was retrospective and susceptible to those inherent limitations. Although the two groups were similar in regards to clinical characteristics and CMR variables, there were less patients noted in the conservative GBCA cohort compared to the historical group. This may reflect temporal variations in annual referrals, or patients with previous LGE and adequate acoustic windows undergoing echocardiography to assess for ventricular size and function. In review of the clinical documentation, the granularity to decide actionable change based solely on the CMR was occasionally limited. Therefore any initiation or titration of a cardiac medication was included as an actionable change. Our cost estimations used a single-payer model. Lastly, this is a single-center experience which may not be entirely representative of clinicians or imagers from other institutions. Taking all of these data into consideration, an important next step is to determine the optimal frequency for inclusion of GBCA in CMR for patients with DMD. While changes in fibrosis on an annual scale did not trigger changes in medical management, it may be the case that significant progression in the amount of fibrosis over several years could initiate consideration of other factors, such as risk of arrhythmias. Although we have previously shown late stabilization of LGE burden [11], we are currently discussing LGE imaging every 3–5 years to investigate whether fibrotic changes progress and whether these changes alter clinical management. Our group and others are interested in future strategies including pre contrast T1 mapping to guide decision making and assess disease progression in this population, however more large-scale parametric mapping studies are required at this time to inform clinical decision making in patients with DMD.

Conclusion

In the current era with unclear concern for intracranial gadolinium deposition, conservative GBCA administration is warranted in patients anticipated to undergo multiple CMR evaluations. Our updated clinical approach has resulted in fewer patients with DMD receiving contrast, shorter scan times, and less medical costs without appreciable changes to patient management. We believe similar strategies can be

applied to additional patient populations in close conjunction with clinicians.

Data availability The data that support the findings of this study are available on request from the corresponding author [SML]. The data are not publicly available due to records which may contain information that could compromise patient confidentiality.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests or funds to disclose.

Ethical approval This study was approved by the Institutional Review Board at Cincinnati Children's Hospital Medical Center.

Informed consent The requirement for informed consent was waived due to the retrospective nature of the study.

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