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Original Research

Safety of Gadolinium-Based Contrast Material in Sickle Cell Disease

Jonathan R. Dillman, MD,[1]* James H. Ellis, MD,[2] Richard H. Cohan, MD,[2] Elaine M. Caoili, MD,[2] Hero K. Hussain, MD,[2] Andrew D. Campbell, MD,[3] and Peter J. Strouse, MD[1]

Purpose: To assess the safety of intravenously administered gadolinium-based contrast material in sickle cell disease (SCD) patients.

Materials and Methods: All pediatric and adult SCD patients evaluated by magnetic resonance imaging (MRI) at our institution between January 1995 and July 2009 were identified. The medical records of SCD patients who underwent contrast-enhanced MRI as well as an equal-sized cohort of SCD patients who underwent unenhanced MRI were reviewed for adverse (vaso-occlusive and hemolytic) events within 1 week following imaging.

Results: Eight (five mild and three moderate) adverse events were documented within 1 week following contrast-enhanced MRI (38 patients and 61 contrast injections), while six (five mild and one moderate) similar events occurred within 1 week following unenhanced MRI (61 patients and 61 unenhanced MRI examinations). This difference in the number of adverse events was not statistically significant (odds ratio = 1.4; 95% confidence interval [CI] 0.4, 5.2). No severe adverse event occurred in either patient cohort.

Conclusion: Gadolinium-based contrast materials do not appear to be associated with increased risk of vaso-occlusive or hemolytic adverse events when administered to SCD patients. Larger, prospective studies using multiple gadolinium-based contrast materials would be useful to confirm the results of our investigation.

Key Words: magnetic resonance imaging (MRI); gadolinium-based contrast material (GBCM); sickle cell disease; adverse event
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THE INTRAVENOUS ADMINISTRATION of gadolinium-based contrast materials (GBCMs) in individuals with sickle cell disease (SCD) is controversial. It has been theorized that GBCMs may potentiate sickle erythrocyte alignment perpendicular to the magnetic field and increase the risk of vaso-occlusive crisis (1,2). According to the United States Food and Drug Administration (US FDA)-approved package insert for gadoversetamide (Optimark; Covidien, Mansfield, MA) (1): "Deoxygenated sickle erythrocytes have been shown in vitro studies [sic] to align perpendicular to a magnetic field; this may result in vasoocclusive complications in vivo. The enhancement of magnetic moment by gadoversetamide may potentiate sickle erythrocyte alignment.... The potential risk of hemolysis after injection of OptiMARK injection in patients with other hemolytic anemias has not been studied." The FDA-approved package insert for gadoteridol (ProHance; Bracco Diagnostics, Princeton, NJ) (2) contains similar statements, while analogous information has been removed from the package inserts of other GBCMs.

Review of the literature to date reveals no documented in vivo vaso-occlusive or hemolytic complication related to GBCM in an individual with SCD. A few small studies of SCD patients undergoing contrast-enhanced magnetic resonance imaging (CE-MRI) have reported no adverse effects related to GBCM administration (3–7).

The purpose of this study was to retrospectively evaluate the safety of intravenously administered GBCMs in children and adults with SCD.

MATERIALS AND METHODS

This study was Institutional Review Board (IRB)-approved and performed in a Health Insurance Portability and Accountability Act (HIPAA, USA)-compliant manner. Patient informed consent was not required based on institutional policy and the retrospective nature of our investigation.

All pediatric and adult SCD patients evaluated by MRI between January 1, 1995 and July 31, 2009 within the University of Michigan Health System were

[1]Department of Radiology, Section of Pediatric Radiology, C.S. Mott Children's Hospital, University of Michigan Health System, Ann Arbor, Michigan, USA.
[2]Department of Radiology, Division of Abdominal Imaging, University of Michigan Health System, Ann Arbor, Michigan, USA.
[3]Department of Pediatrics and Communicable Diseases, University of Michigan Health System, Ann Arbor, Michigan, USA.
*Address reprint requests to: J.R.D., University of Michigan Health System, C.S. Mott Children's Hospital/F3503, Department of Radiology, Section of Pediatric Radiology, 1500 E. Medical Center Dr., Ann Arbor, MI 48109-5252. E-mail: jonadill@med.umich.edu
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Table 1
Classification Sickle Cell Disease-Related Adverse Events by Severity

Mild	1. Vaso-occlusive crisis managed without hospital admission. 2. Exacerbation of preexisting inpatient vaso-occlusive crisis. 3. Hemolytic event not requiring blood transfusion.
Moderate	1. Vaso-occlusive crisis requiring hospital admission for management. 2. Hemolytic event requiring blood transfusion.
Severe	1. Life-threatening vaso-occlusive crisis. 2. Life-threatening hemolytic event.

identified by searching available institutional electronic medical records. Individuals with HbSS, HbSC, HbSD, and HbS-thalassemia hemoglobinopathies (both hemoglobin genes are abnormal) were included in this search, while individuals with sickle cell "trait" (one of two hemoglobin genes is normal) were intentionally excluded.

Electronic medical records of SCD patients who underwent CE-MRI were reviewed by a single author for adverse events within the 1-week period following GBCM administration. Electronic medical records from an equal-sized cohort of SCD patients who had undergone unenhanced MRI were also reviewed for adverse events within the 1-week period following imaging (also by a single author). This control patient cohort was established in the following manner. All SCD patients who were evaluated by unenhanced MRI during the study period were placed in consecutive numerical order by date of birth. Using a computerized randomization program (www.random.org), 61 numbers (corresponding to subjects) were randomly identified. The 1-week period following each of these subjects' most recent unenhanced MRI examination was chosen for review.

Medical records were specifically reviewed for vaso-occlusive (eg, acute chest syndrome, bone pain crisis, deep venous thrombosis, stroke, etc.) and hemolytic events. Potential sickle cell disease-related vaso-occlusive and hemolytic adverse events were defined as being mild, moderate, or severe based on a novel classification system (Table 1).

RESULTS

Thirty-eight SCD patients underwent 61 CE-MRI examinations during our study period. The mean age of these patients at the time of CE-MRI was 19.4 years (range, 2–55 years). Twenty-nine contrast injections were performed on male patients, while 32 contrast injections were performed on female patients. Twenty-seven SCD patients had one CE-MRI examination during the study period, five had two examinations, two had three examinations, two had four examinations, and two had five examinations.

Seventy-five SCD patients underwent 188 unenhanced MRI examinations during the study period. From these 188 unenhanced MRI examinations, 61 examinations (from 61 patients) were selected using the method described. The mean age of these patients at the time of their unenhanced MRI examination included in our study was 20.4 years (range, 11 months to 66 years). Twenty-nine of the unenhanced MRI examinations were performed on male patients, while 32 were performed on female patients.

Twenty-two SCD patients were included in both the CE-MRI and selected unenhanced MRI cohorts (meaning these patients had undergone both CE-MRI and unenhanced MRI at different times during the study period). There were no statistically significant differences between the ages ($P > 0.6$) and genders ($P = 1.0$) of patients in the two subject groups.

The majority of MRI examinations included in both subject groups were performed on individuals with HbSS hemoglobinopathy (classic sickle cell disease). Fifty-four CE-MRI examinations were performed in HbSS patients, while 55 unenhanced MRI examinations were performed in HbSS patients. A small number of examinations included in both the CE-MRI and unenhanced MRI subject groups had other hemoglobinopathies (two MRI examinations performed on HbSC patients in both cohorts, five MRI examinations performed on Hb-thalassemia patients in the CE-MRI cohort, and four MRI examinations performed on Hb-thalassemia patients in the unenhanced MRI cohort).

In the CE-MRI subject group, six patients received intravenous Magnevist (gadopentetate dimeglumine; Bayer HealthCare Pharmaceuticals, Wayne, NJ), while four received MultiHance (gadobenate dimeglumine; Bracco Diagnostics, Princeton, NJ). Unfortunately, the GBCM administered to 51 patients was not documented in the final imaging report. These 51 patients could have received one of four possible contrast agents used during the study period (including gadopentetate dimeglumine, gadobenate dimeglumine, gadoteridol, or gadodiamide).

No documented vaso-occlusive or hemolytic adverse event occurred within 24 hours of imaging in either patient cohort. Eight adverse events (in 61 injections/38 patients) occurred within the 1-week period following GBCM administration in the CE-MRI patient group. Five (63%) of these adverse events were mild, while three (37%) were moderate in severity (Table 2). Two of these adverse events (one mild and another moderate) occurred in the same patient ≈4 years apart.

Six adverse events (in 61 examinations/61 patients) occurred within the 1-week period following imaging in the unenhanced MRI patient cohort. Five (83%) of these adverse events were mild, while one (17%) was moderate in severity (Table 3). Four of these subjects also experienced adverse events following earlier or subsequent CE-MRI.

The difference in the number of adverse events between the two subject groups was not statistically significant (odds ratio = 1.4; 95% confidence interval [CI] 0.4, 5.2). Regarding moderate adverse events, the difference in number between the two subject groups also was not statistically significant ($P > 0.6$; Fisher's exact test). No hemolytic (of any severity) or severe vaso-occlusive adverse event was documented in either the CE-MRI or unenhanced MRI subject group.

Table 2
Sickle Cell Disease-Related Adverse Events in 38 Patients Undergoing 61 Contrast-Enhanced MRI Examinations

Severity	Age	Gender	Hem	Day	Adverse Event
Mild	8	M	HbSC	2	worsening of inpatient bone pain crisis
Mild	16	F	HbSS	2	worsening of inpatient bone pain crisis
Mild	25	F	HbSS	2	worsening of inpatient acute chest syndrome
Mild	16	M	HbSS	7	bone pain crisis, outpatient management*
Mild	27	M	HbSS	7	bone pain crisis, outpatient management
Moderate	2	M	HbSS	2	dactylitis, hospital admission & inpatient management
Moderate	23	M	HbS-Thal	2	bone pain crisis, hospital admission & inpatient management
Moderate	12	M	HbSS	6	LE DVT, hospital admission & inpatient management*

Hem = hemoglobinopathy; M = male; F = female; LE DVT = lower extremity deep venous thrombosis.
Day = number of days following CE-MRI adverse event occurred (day of imaging examination = day 1).
*Same patient.

DISCUSSION

MRI is frequently used to assess patients with SCD for disease-related complications. For example, MRI of the brain is commonly used to assess for sickle cell vasculopathy (secondary Moyamoya disease or Moyamoya syndrome) and stroke (8), while MRI of the musculoskeletal system may be used to attempt to differentiate acute osseous infarction from osteomyelitis (3). While unenhanced MRI may be adequate to confirm certain SCD-related complications, other complications may benefit from the intravenous administration of a GBCM in order to obtain a precise diagnosis.

A few small studies have administered GBCMs to SCD patients without reported vaso-occlusive or hemolytic adverse events. Umans et al (3) administered GBCM to nine SCD patients in an attempt to distinguish areas of osteomyelitis from medullary bone infarction. Westwood et al (4) administered GBCM to 30 SCD patients in order to assess delayed myocardial enhancement related to regional cardiac fibrosis (sickle cell cardiomyopathy). Several small studies have used GBCM to assess cerebral perfusion in sickle cell disease (5–7), as ≈17% of SCD patients experience silent cerebral infarctions (8).

Our investigation comparing SCD patients who underwent CE-MRI to SCD patients who underwent MRI without intravenous contrast material demonstrated no significant difference in the frequency of vaso-occlusive and hemolytic adverse events. At our institution, almost as many SCD patients experience adverse events following unenhanced MRI as do following CE-MRI. In fact, four of seven SCD patients who experienced adverse events following CE-MRI also experienced adverse events following unenhanced MRI. Based on our results, we believe it is likely that most (if not all) of the eight adverse events observed following CE-MRI would have occurred even if a GBCM had not been administered.

Our results are in agreement with a recent addition to the American College of Radiology's Manual on Contrast Media (v. 7) (9). In a recently added section, the authors of this document state "...it is our opinion that any special risk to sickle cell patients from IV administered GBCM at currently approved dosages must be extremely low, and there is no reason to withhold these agents from patients with sickle cell disease. However, as in nonsickle cell disease patients, GBCM should be administered only when clinically indicated" (9).

We believe the idea that GBCMs can "potentiate" sickle erythrocyte alignment perpendicular to a magnetic field in vivo based on local magnetic field changes at the cellular level and thereby resulting in an acute vaso-occlusive crisis may be based on a somewhat flawed understanding of the physics involved. GBCM T1 shortening is in part established by the rotational correlation times, or tumbling rates, of gadolinium chelates as they interact with water at the molecular level. Therefore, it is likely that the molecular-sized magnetic fields associated with these administered contrast agents at standard approved doses are actually changing several million times per second. Based on this fact, sickle erythrocyte alignment in a specific orientation due to GBCM exposure is quite unlikely. This information along with the absence of reports of adverse events related to these

Table 3
Sickle Cell Disease-Related Adverse Events in 61 Patients Undergoing 61 Unenhanced MRI Examinations

Severity	Age	Gender	Hem	Day	Adverse Event
Mild	16	F	HbSS	2	worsening of inpatient bone pain crisis*
Mild	19	M	HbSS	3	worsening of inpatient bone pain crisis
Mild	25	M	HbSS	3	worsening of inpatient acute chest syndrome
Mild	25	F	HbSS	5	new acute chest syndrome as inpatient*
Mild	16	M	HbSS	7	bone pain crisis, outpatient management*
Moderate	33	M	HbSS	4	bone pain crisis, hospital admission & inpatient management*

Hem = hemoglobinopathy; M = male; F = female.
Day = number of days following unenhanced MRI adverse event occurred (day of imaging examination = day 1).
*Patient also experienced adverse event following CE-MRI.

contrast agents in SCD patients may be responsible, at least in part, for recent modifications to the package inserts of several GBCMs regarding their use in individuals with hemoglobinopathies.

Our study has a few limitations. First, it was a retrospective review of selected patients and not prospective or randomized in design. Second, our study included a relatively small number of patients, as only 61 GBCM administrations occurred in SCD patients during our study period. Availability of a greater number of GBCM injections would decrease the potential for making a type II error (β error).

It is also difficult to definitively establish that an adverse reaction is directly related to GBCM injection (especially as SCD patients undergoing unenhanced MRI clearly experience similar adverse events). At least some (if not all) adverse events experienced by individuals undergoing both CE-MRI and unenhanced MRI most likely would have occurred in the absence of imaging, although some have theorized that placement of sickle erythrocytes in a magnetic environment in the absence of GBCM may, in and of itself, increase the risk of vaso-occlusive crisis based on in vitro research (10,11). Therefore, while our study does not allow us to make any conclusions about whether exposure of SCD patients to the magnetic field of MRI leads to adverse events, we can conclude, based on our study, that the use of GBCMs alone likely does not appear to provide added risk. Finally, our study is unable to account for other possible causes of adverse events following imaging, such as preceding or subsequent dehydration or hypoxia.

In conclusion, our study suggests that GBCM administration does not appear to be associated with increased frequency of adverse events in SCD patients undergoing CE-MRI in comparison with patients undergoing going unenhanced MRI. To date, there is no evidence to support the withholding of these contrast agents from SCD patients when deemed medically necessary. However, further investigation of this subject with larger patient cohorts and multiple GBCMs would be helpful to definitively establish the safety of these contrast agents in this patient population.

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