

Use of gadolinium as an intraarterial contrast agent for pediatric neuroendovascular procedures

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Object. The safety and efficacy of Gd as an intraarterial contrast agent for pediatric neuroendovascular procedures were investigated.

Methods. The authors retrospectively reviewed data regarding pediatric neuroendovascular procedures performed during a 1-year period. Seventeen procedures involving the use of gadodiamide in nine pediatric patients were identified.

All angiographic images were of diagnostic quality but usually required minimal postimage processing. In time-consuming cases, the use of gadodiamide allowed the procedure to continue when the dosage of iodinated contrast approached a toxicity level and would have otherwise prompted termination of the procedure. This likely reduced the total number of procedures necessary. No adverse events due to the intraarterial use of gadodiamide were identified.

Conclusions. Gadodiamide appears to be a safe and effective contrast agent for pediatric patients.

KEY WORDS • gadodiamide • gadolinium • endovascular therapy • pediatric neuro-

Insurgery
ODINATED contrast agents remain the standard for use in intraarterial diagnostic and interventional neuroendovascular procedures. Because of their low body weight, pediatric patients cannot tolerate large doses of iodinated contrast. Thus, many pediatric neuroendovascular procedures are terminated prematurely to prevent contrast toxicity. This then necessitates numerous staged procedures and attendant increased risk, discomfort, and cost. These procedures could be extended with the adjunctive use of a non-iodine-based contrast agent, allowing a greater extent of the patient's lesion to be embolized during each procedure and thereby decreasing the overall number of procedures required.

In several studies investigators have demonstrated the safe and efficacious use of Gd-based contrast agents for intraarterial diagnostic and interventional neuroendovascular procedures in adults.^{3,4,7,8,13,19,20,27} Based on the available information, we began using a Gd-based agent as an adjunct to iodinated contrast agents when treating pediatric patients likely to require multiple staged neuroendovascular procedures because of the contrast dosage limitation. If a procedure was likely to be lengthy, and contrast dosage would likely limit the procedure, then Gd-based agents were used intermittently during the procedure. This technique would maximize our ability to obtain necessary angiographic images while minimizing the pa-

tient's exposure to potentially toxic dosages of iodinated contrast. In a procedure in which both agents were used, iodine-based agents would be used when superior image resolution was required, such as roadmapping for microcatheter navigation.

We present our experience with a Gd-based agent as an adjunctive intraarterial contrast agent in the diagnosis and treatment of complex neurovascular diseases in pediatric patients.

Clinical Material and Methods

Approval was obtained from the University of Florida Institutional Review Board for a retrospective review of all pediatric neuroendovascular procedures performed before June 2002. During that time, 17 procedures involved the use of Gd-based contrast agents in nine pediatric patients. The agent was used as an adjunctive intraarterial contrast material in cases in which the anticipated iodinated contrast load would approach toxic levels (~ 3 ml/kg).

The patients ranged in age from 3 days to 7 years. The iodinated contrast agent used was iohexol (Omnipaque 300; Nycomed, Inc., Princeton, NJ). The Gd-based contrast agent used for all patients in this study was gadodiamide (Omniscan; Nycomed, Inc.). All images were obtained using a biplane digital subtraction angiography unit (Toshiba America, Inc., Tustin, CA) or a mobile C-arm angiography unit (9600 series Disonics; O.E.C., Miami, FL). The portable C-arm unit was used during four procedures in the operating room.

Of the 17 procedures performed, four were diagnostic angiography studies and 13 were major neuroendovascu-

Abbreviations used in this paper: AVF = arteriovenous fistula; AVM = arteriovenous malformation; ICH = intracerebral hemorrhage; MCA = middle cerebral artery.

TABLE 1

Summary of pre- and postprocedure data in nine pediatric patients requiring 17 neurovascular procedures*

Case No.	Proc No.	Age, Sex	Diagnosis	Op	Weight (kg)	Gd Vol (ml/kg)	Creatinine Level (mg/dl)		Clinical & Neurological Exam Postop	Op Extended by Gd
							Preop	Postop		
1	1	3 days, F	AVF, CHF	embol	3	4/1.3	0.9	0.8	unchanged	yes
	2	1 wk, F	AVF, CHF	embol	3	4/1.3	0.9	0.7	unchanged	yes
	3	2 wks, F	AVF, CHF	embol	3	5/1.7	0.4	0.4	unchanged	yes
2	4	18 mos, M	VGM	DSA	9	2/0.22	0.3	—	unchanged	no
3	5	4 yrs, M	AVM	DSA	15.8	2/0.12	0.5	—	unchanged	no
4	6	7 yrs, M	CCF	DSA	26.4	2/0.08	0.5	—	unchanged	no
5	7	7 yrs, M	CCF	embol	30	15/0.5	—	—	unchanged	yes
	8	5 wks, F	multiple AVFs, HHT, ICH	DSA	3.5	4.5/1.3	0.3	0.2	unchanged	yes
	9	6 wks, F	multiple AVFs, HHT, ICH	embol	3.5	6/1.7	0.3	0.3	mental status decline, resolved after evacuation of ICH	yes
6	10	20 mos, M	AVM	embol	15	0.6/0.6	—	—	unchanged	yes
7	11	4 yrs, M	AVM	embol	20	8/0.4	0.6	0.4	unchanged	yes
	12	4 yrs, M	AVM	embol	20	8/0.4	0.4	0.3	transient ataxia resolved	yes
8	13	4 days, M	VGM	embol	4.1	4/1	0.8	1.0	improved CHF	yes
	14	2 wks, M	VGM	TT embol	4.0	4/1	0.6	0.5	improved CHF	yes
9	15	3 wks, M	VGM	embol	4.1	8/2	0.6	0.4	unchanged	yes
	16	4 wks, M	VGM	embol	4.1	4/1	0.3	0.4	improved CHF	yes
	17	4 wks, M	VGM	TT embol	4.1	4/1	0.4	0.4	improved CHF	yes

* CCF = carotid cavernous fistula; CHF = congestive heart failure; DSA = digital subtraction angiography; embol = embolization; HHT = hereditary hemorrhagic telangiectasia (Osler-Rendu-Weber syndrome); TT = transtorcular; VGM = vein of Galen malformation; — = not available.

lar embolizations. After each procedure, the patients were observed for any signs of adverse reactions or vascular complications. Serum creatinine levels pre- and postprocedure were monitored in 12 cases. All listed preprocedure creatinine levels were obtained within 7 days of the procedure and all postprocedure levels within 24 hours of the procedure. It is not routine at our institution to obtain serum chemistry levels in patients in whom status is deemed stable and the patient is ready for discharge on postprocedure Day 1.

Three patients were treated for an intracranial AVM, one for multiple intracranial pial AVF, one for a complex dural AVF, one for a carotid-cavernous fistula, and three patients for vein of Galen malformations.

Results

Patient diagnoses, procedures, gadodiamide dosages, serum creatinine levels (when available), clinical results, and results of neurological examinations are summarized in Table 1. Also summarized in Table 1 is a subjective indication as to whether adjuvant gadodiamide allowed greater lesion embolization than would have been possible if iohexol alone was used (maximum dose 4 ml/kg [1200 mg I]). This iohexol dose limit is the pediatric standard of care practiced at our institution. Although no specific pediatric patient-dosage recommendation for cerebral angiography is included in the manufacturer's instructions, there is a recommended maximum dosage for pediatric cardiac angiography (1750 mg I). Our limit is slightly below this. The per kilogram dosages of gadodiamide ranged from 0.08 to 2 ml/kg (mean 0.85 ml/kg).

Iohexol-based digital subtraction angiography produced superior image quality to that involving gadodiamide. To achieve similar diagnostic quality images with gadodiamide, we performed minor postimage processing, increasing the contrast and decreasing the brightness lev-

els. The increased contrast level caused an increase in the quantum mottle of the image, resulting in slight background blurring. Despite the increased mottle, all images obtained in conjunction with gadodiamide were of good diagnostic quality (Figs. 1 and 2). Gadodiamide provided good diagnostic images of distal vessels when injected through a 1.5 French flow-directed microcatheter (Fig. 3).

One patient (Case 5) experienced two periprocedure complications. This patient suffered hereditary hemorrhagic telangiectasia, multiple previous spontaneous ICHs secondary to three distinct intracranial pial AVFs, and a poorly controlled seizure disorder. The first periprocedure complication was an additional seizure that occurred 1 hour after diagnostic angiography. At the time of the seizure, antiepileptic drug serum levels were subtherapeutic, prompting adjustment of the antiepileptic drugs, which resulted in better seizure control. The following week, this patient suffered another ICH after one of her three AVFs was obliterated with embolization. The patient required an emergency craniotomy and evacuation of ICH after the embolization. Neurological status recovered to baseline within a few days after the craniotomy. Neither event was believed to be related to the use of intraarterial gadodiamide.

The patient in Case 7, in whom a posterior fossa AVM was diagnosed, developed postembolization transient ataxia secondary to unintentional embolization of a distal branch of the posterior inferior cerebellar artery adjacent to the AVM.

Of the 12 cases in which serum creatinine levels were documented both before and after administration of intraarterial gadodiamide, a decrease in the creatinine was noted in seven, increase in the creatinine in two, and no change in three. In these 12 patients, the mean preprocedure creatinine level was 0.5 and the mean postprocedure level was 0.5.

The use of gadodiamide was very successful in allowing greater embolization during a single procedure than



FIG. 1. Case 2. Digital subtraction angiogram obtained in an 18-month-old girl with a history of macrocrania and in whom a Yaşargil Type III vein of Galen malformation was diagnosed. A transtorcular wire embolization of the vein of Galen malformation was performed 7 months previously, with a good result. After obtaining a diagnostic angiogram, any residual malformation was treated by transarterial glue embolization. In this gadodiamide-based left internal carotid artery angiogram (lateral view), no residual malformation was observed. Notice the good diagnostic quality of the angiogram. Because of postprocessing increase in digital contrast, there is a noticeable background image “mottling.”

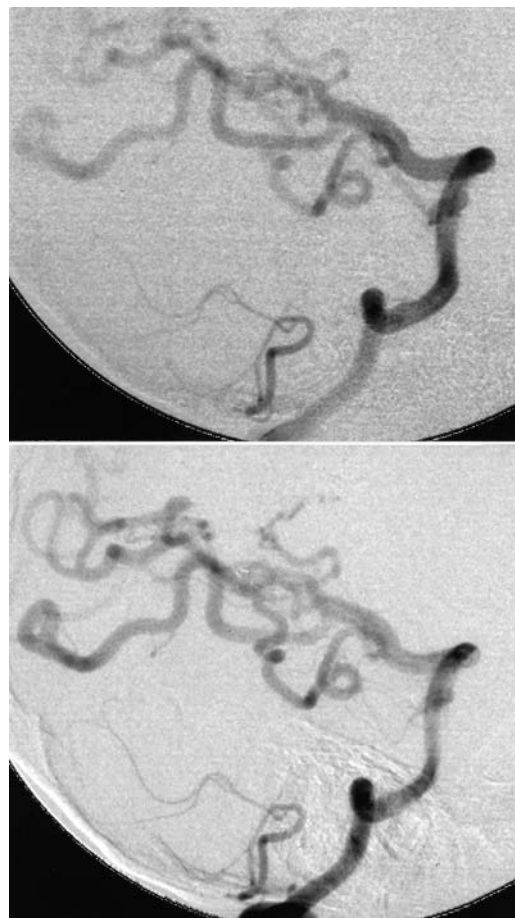


FIG. 2. Case 3. Digital subtraction internal carotid artery angiograms (lateral view) obtained in a 4-year-old boy with an occipital AVM. *Upper:* Gadodiamide-based angiogram clearly demonstrating the numerous feeding arteries to the AVM. *Lower:* Iohexol-based angiogram obtained later revealing slightly sharper detail of the AVM. Both contrast agents provided diagnostic quality images.

would have been possible if only iohexol were used, while avoiding potentially toxic dosages of iohexol. Fourteen procedures (82.4%) were extended with the use of gadodiamide. The other three cases (17.6%) involved acquisition of diagnostic angiograms in which gadodiamide was used initially in anticipation of a prolonged interventional procedure. When initial diagnostic angiogram findings indicated that embolization would not be necessary, iohexol was used for the remainder of the diagnostic procedure.

Illustrative Case

Case 6

A 20-month-old boy with an occipital lobe AVM initially presented with macrocrania. He had previously undergone three staged transarterial embolization procedures. A magnetic resonance angiogram obtained between procedures suggested persistent filling of the AVM from the right MCA. Repeated angiography was required, as

was possible reembolization if residual malformation was identified. Because diagnostic angiography and embolization in the same staged procedure would likely exceed potentially toxic dosages of iodinated contrast in this toddler, we began the angiographic session by administering gadodiamide. Two gadodiamide-based angiographic runs were performed (Fig. 4). Persistent filling was discovered and a single MCA branch was embolized using *N*-butyl cyanoacrylate (TruFill; Cordis Neuroendovascular, Miami Lakes, FL). Microcatheter selective angiograms were obtained using a combination of gadodiamide and iohexol. As previously described, iohexol was preferentially used when high-resolution imaging was critical and gadodiamide was used when maximal imaging resolution was less critical. This allowed for an overall decrease in the dosage of iohexol. An excellent angiographic result was obtained, and the patient remained neurologically intact. He was discharged home in excellent condition the next day.

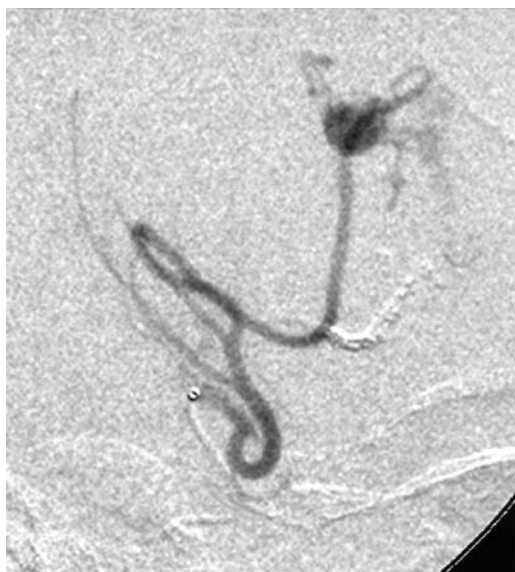


FIG. 3. Case 5. Gadodiamide-based selective digital subtraction angiogram (lateral view) obtained through a microcatheter in a 6-week-old girl with hemorrhagic telangiectasia with multiple intracranial pial AVFs and a history of multiple ICHs. Excellent angiographic detail was achieved. Notice the AVF and venous aneurysm. The malformation was embolized and obliterated with N-butyl-cyanoacrylate.

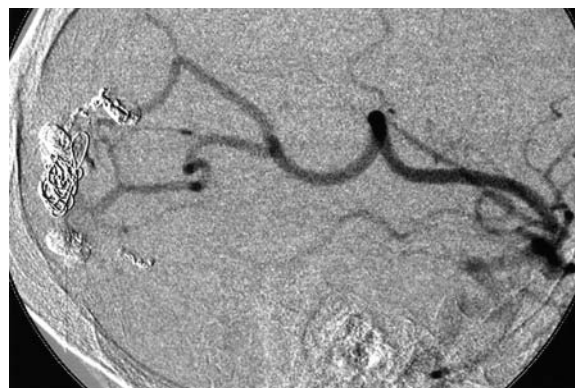


FIG. 4. Case 6. Gadodiamide-based digital subtraction angiogram (lateral view) obtained in a 20-month-old boy who presented with macrocrania and in whom a right occipital lobe AVM was diagnosed. Numerous MCA feeding vessels join the AVM. Note the coils and glue casts from previous embolizations.

Discussion

Iodinated media remain the standard intraarterial contrast agents for use in diagnostic cerebral angiography and major neuroendovascular procedures. Unfortunately, these agents are inappropriate for some patients. Dose-dependent toxicities can occur in patients with renal disorders, diabetes mellitus, and iodine allergies.^{3,4,7,13-15,19} Alternative intraarterial contrast agents are sometimes used in such patients. Recently, magnetic contrast agents containing Gd have been successfully used as intraarterial contrast agents in small numbers of adult patients with renal insufficiency or allergy to iodinated contrast.^{1,3-5,7,13,18,19,22,29} To the best of our knowledge, however, no reports have been published on the intraarterial use of Gd in pediatric patients.

Iodinated contrast agents must be used with caution in pediatric patients. Because of their low body weight, the allowable dosage of iodinated contrast is often inadequate for the completion of complex, lengthy neuroendovascular procedures. Occasionally, procedures in pediatric patients must be terminated and staged to reduce the iodinated contrast load during any one procedure. This staging of procedures increases the exposure to anesthetic and procedure risks, as well as increasing the costs of additional hospitalizations. Gadolinium-based contrast media can be used in pediatric patients who would be unlikely to tolerate the iodinated contrast load anticipated for lengthy endovascular procedures. At our institution, we have used the Gd-based contrast agent, gadodiamide, as an adjunctive or single contrast agent in selected pediatric patients.

Gadodiamide is a noniodinated intravenous contrast

agent widely used in magnetic resonance imaging. It is well tolerated by humans, and only a few serious side effects have ever been reported.^{6,10,16,17,23-25} According to the manufacturer's instructions, the adverse events occurring in more than 1% of patients are nausea, headache, and dizziness. Guidelines for the intraarterial use of gadodiamide do not exist; however, the current recommended maximum intravenous adult bolus dose of Gd is 0.3 mmol/kg, which is equal to 0.6 ml/kg of gadodiamide.^{3,4,7,17,23} In pediatric patients, the recommended intravenous bolus dose of Gd is 0.1 mmol/kg, which equates to 0.2 ml/kg of gadodiamide.^{2,10,16} Intraarterial cumulative Gd doses of up to 0.4 mmol/kg (0.8 ml/kg) have been reported without adverse events.^{3,19}

In *in vivo* studies investigators have found no nephrotoxicity in animals given Gd doses of 10-mmol/kg bolus or a 1.25-mmol/kg dose daily for 28 days.^{11,12} In patients with renal insufficiency, doses up to 2.9 mmol/kg have been administered during peripheral angiography, with a 15% incidence of permanent worsening of renal function.⁸

As we have discussed above and summarized in Table 1, several of our patients received a cumulative dose during their endovascular procedure that exceeded the intravenous bolus dosing recommendation. These cumulative doses were not single bolus injections, but rather, were boluses administered over the several hours of the procedure. No more than 1 ml (0.5 mmol) of gadodiamide was ever injected as a single bolus in a child weighing less than 25 kg. The higher gadodiamide dosage was used only in circumstances in which further iodinated contrast was believed to be toxic and the patient's severe medical condition precluded staging the remainder of the procedure.⁹ For example, the patient in Case 1 required more than 0.3 mmol/kg gadodiamide because of fulminant heart failure and refractory pulmonary hypertension secondary to her high-flow fistula. This neonate was in great danger of dying if the high-flow shunt could not be significantly reduced. As an additional example, the patient in Case 5 had suffered several *in utero* intracranial hemorrhages and

bilateral frontal lobe hemorrhages and was believed to be in serious danger of further hemorrhages.

In this small retrospective series, it was impossible to be certain that the intraarterial use of gadodiamide did not cause or exacerbate medical conditions in pediatric patients. A prospective study, including determination of pre- and postserum chemistry levels, is necessary to ascertain the exact degree of intraarterial gadodiamide that may be safely used in pediatric neuroendovascular procedures. A prospective study should also address the dearth of experience in the combined use of iodinated and Gd-based contrast agents and the appropriate combined dosages, although the results in this retrospective series suggests that these agents are safe and effective in combination.

The use of intraarterial Gd in adults has been of considerable interest in the last year, with nine articles published.^{1,18,20–22,26–29} Spirited debate has concerned imaging quality and allowable dose, and more clinical experience is necessary. We have described the first pediatric series involving intraarterial gadodiamide.^{20,21,26} We have shown its effectiveness in producing good diagnostic images, but its definitive safety in such cases remains to be proven. Gadodiamide appears useful in extending the procedure length, allowing a greater extent of embolization to be performed during one setting. Gadodiamide will likely represent an alternative or adjuvant to current iodinated contrast agents for use in time-consuming pediatric neuroendovascular procedures.

Based on the results of this study, we currently use the following guidelines. 1) If there is a possibility that a pediatric neuroendovascular procedure will be lengthy or require more than 4 ml/kg of intraarterial contrast, then gadodiamide is used during initial imaging. 2) Whenever maximum image quality and clarity are necessary for a particular image, iodinated contrast is used. 3) Gadodiamide can be used as an adjunct to iodinated contrast as needed throughout an interventional procedure until a maximum dose is reached.

Conclusions

Based on our findings, the Gd-based contrast material, gadodiamide can be used in pediatric patients as an alternative or adjunctive intraarterial contrast agent in the endovascular diagnosis and treatment of complex neurovascular diseases.

Disclaimer

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