Interventional Pain Medicine 1 (2022) 100105

Contents lists available at ScienceDirect

Interventional Pain Medicine

journal homepage: www.journals.elsevier.com/interventional-pain-medicine

Encephalopathy after unintentional intrathecal gadolinium: A letter to the editor

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A B S T R A C T

Objective: Raise awareness of gadolinium encephalopathy, a rare cause of neurological symptoms.
Setting: An L5-S1 interlaminar epidural steroid injection (IL-ESI) was performed with a gadolinium-based contrast agent (GBCA) due to the patient's history of allergic reaction to iodine-based contrast agents.
Discussion: Several hours after administration of GBCA, the patient had nausea and vomiting with altered mental status. Patient was treated with dexamethasone IV, and was discharged on day 2. Patient had no residual deficits at follow-up two weeks later. Current literature shows that caution should be used to prevent inadvertent intrathecal GBCA, and doses >2.0 mmols are associated with serious adverse effects, including death.
Conclusions: Intrathecal administration of GBCAs should be limited to less than 0.5 mmol. If adverse effects are experienced, IV steroids should be administered as soon as possible, and a CSF drain should be considered.

Dear Editor,

Contrast media is utilized for performing safe and effective fluoroscopically guided injections. Prior to delivery of the injectate to the intended target, real-time observation of contrast flow utilizing continuous fluoroscopy or digital subtraction imaging is used to confirm non-vascular epidural spread and confirm appropriate site of medication delivery.

Common agents utilized during procedures include non-ionic iodinated contrast medium, ie iohexol. In patients with prior documented hypersensitivity reaction to iodinated contrast medium, premedication protocols, no contrast agent administration, or contrast media alternatives such as Gadolinium are considered.

Gadolinium-based contrast agents (GBCAs) are FDA approved for Magnetic Resonance Imaging (MRI) studies requiring intravenous (IV) contrast media to enhance image quality. Eight of these agents are currently approved by the FDA. In addition to its use as an MRI contrast agent, GBCAs may be used during interventional spine procedures as an alternative for patients who report iodine-based contrast agent hypersensitivity reactions.

In 2021, Benzon et al. recently published a multi-society Practice Advisory (PA) on the use of contrast agents in interventional pain procedures with a large focus on GBCAs and recommendations on their use [1]. This manuscript's authors defer to the PA for their recommendations.

Previous case reports on encephalopathy after unintentional intrathecal gadolinium injection were published before the PA by Benzon et al. [1] Since we are reporting our 2012 complication after the 2021 PA, this letter's conclusions take into consideration these PA recommendations as they relate to our patient and these previous case reports.

We present a case of a patient with an unusual cause of encephalopathy post inadvertent intrathecal gadolinium administration, a rare cause of altered mental status (AMS) that should quickly be recognized. Awareness should help avoid the clinical syndrome or improve outcomes if expedient treatment is offered, including IV steroid. The use of GBCA for interventional spine procedures is off-label, as it is only approved for IV use [1].

Our 2012 case involves a 67-year-old female with a past medical history of depression, hypothyroidism, hyperlipidemia, hypertension, osteoarthritis, and restless leg syndrome who was being managed at our interventional spine center for complaints of right upper buttock pain

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https://doi.org/10.1016/j.inpm.2022.100105
Received 16 January 2022; Received in revised form 23 May 2022; Accepted 23 May 2022

radiating down the right lower limb. Her lumbar spine MRI demonstrated moderate foraminal stenosis due to anterolisthesis at L4 on L5, moderate disc desiccation at L5-S1, and bilateral facet arthropathy. Based on the patient's persistent and worsening radicular symptoms and imaging findings, the patient underwent an L5-S1 interlaminar epidural steroid injection (IL-ESI) with a right paramedian approach using GBCA (gadodiamide) due to the patient's self-reported history of reaction (bronchospasms) to iodinated contrast media (ICM). Of significant importance, the 2021 PA recommendations by Benzon et al. were not yet published.

The right L5-S1 epidural space was localized with loss of resistance technique using an 18 Gauge, 5-inch Touhy needle. Approximately 2 ml (1 mmol) of gadodiamide was injected for contrast media flow confirmation and intrathecal spread of the gadolinium contrast agent was suspected. The needle was withdrawn without anesthetic or steroid administration. The needle was re-inserted on the contralateral side with the goal of treating the L5-S1 pathology with an L5-S1interlaminar approach from the contralateral side since it was felt to be the best treatment option.

After final needle tip confirmation in the epidural space with additional gadolinium, optimal epidural spread was noted and a mixture of triamcinolone, preservative-free lidocaine 1%, and saline was injected. The total gadolinium volume injected was 4 ml [2 mmol total, 2 mL (1 mmol) each on the right and left sides]. The initial 2 ml (1 mmol) was suspected to be intrathecal. The patient was educated on the possible development of post-dural headache and recommended hydration and caffeine as a treatment/prophylaxis. After spending at least 30 min under observation in recovery, she was discharged in stable condition.

Within about 2 h after the procedure, the patient called to report unusual vomiting. The patient declined antiemetic medication (ondansetron) at that time. Approximately 4 h after the procedure, the patient's husband communicated with the on-call physician, notifying him of a second vomiting episode with altered mental status (AMS). The patient was advised to go immediately to the community emergency department (ED) for further evaluation and treatment.

She presented to the local ED, where the physician noted tachycardia (118 BPM), hypertension (184/81), hypoxia (O2 Sat 84%), and poor attention, requiring frequent redirecting without focal neurological deficits. Laboratory testing did not reveal any significant hematologic, electrolyte, or metabolic abnormalities. The patient was given normal saline, ondansetron, and lorazepam. Her head CT scan without contrast (Fig. 1) demonstrated diffuse cerebral edema with effacement of sulci (Fig. 1). The patient was subsequently transferred to a tertiary hospital system, with the diagnosis of encephalopathy, AMS, and hypoxia.

As shown in Fig. 2, the patient's non-contrast brain MRI T1-weighted and fluid attenuated inversion recovery (FLAIR) sequences showed bright (hyperintense) signals in the sulci and ventricles instead of the normal dark (hypointense) signals. These findings were consistent with the presence of Gadolinium in the CSF spaces. EEG demonstrated lack of occipital dominant rhythm with diffuse slowing without epileptiform activity or electrographic seizures. These findings were consistent with encephalopathy.

Due to the temporal association between the patient's symptoms and intrathecal injection of gadolinium, neuro-imaging findings confirming the presence of gadolinium within the CSF spaces, and the lack of any other laboratory abnormalities and alternative conditions, the neurology team diagnosed the patient with intrathecal gadolinium encephalopathy. The patient had already received a dose of dexamethasone (6 mg) by IV route in the ER. Upon transfer out of the ED, dexamethasone 4 mg IV every 6 h was administered for a total of 4 doses. Her mental status improved rapidly and a follow up examination the next day demonstrated normal orientation, attention, and memory. The patient was subsequently discharged.

She received a neurology follow-up at one and six months after discharge. She continued to do well without persistent sequelae. A repeat brain MRI 5 months post injection showed resolution of the hyperintense signals in the CSF spaces in T1 and FLAIR images (Fig. 3).

Upon follow up evaluation by phone two weeks after the procedure, the patient reported improvement in back and radicular pain overall and return to baseline with no remaining headaches, cognitive issues, or nausea since discharge.

Precise needle placement and targeted medication delivery is paramount during interventional spine procedures. Contrast enhanced, fluoroscopic guided spine procedures provide optimal safety and efficiency in delivering stated medication to the targeted structures. Suboptimal needle tip position and injection can result in dural punctures, intrathecal injection, spinal anesthesia, vascular injections, and/or incomplete target structure coverage. Dural punctures can lead to complications including CSF leaks, headaches, cranial nerve palsies, subdural hematomas, cerebral venous thrombosis, meningitis, and death [2,3].

Intravascular injections can cause serious adverse effects (AEs), including respiratory compromise, seizures, cord infarction, stroke, and/or even instantaneous death [2,4–7]. Factors associated with increased intravascular injection risk are the transforaminal epidural (compared to interlaminar) approach, cervical/thoracic/upper lumbar (compared to lower lumbar/sacral) level approach, and adhesiolysis procedures, to name a few [8–11]. Aspiration as a tool to detect a vascular injection is insufficient on its own to provide complete safety [4,7–9]. In 2015 the FDA endorsed a safe-use consensus paper with strong recommendations to inject contrast agents under live fluoroscopy and/or digital subtraction imaging to verify non-vascular placement [12,13].

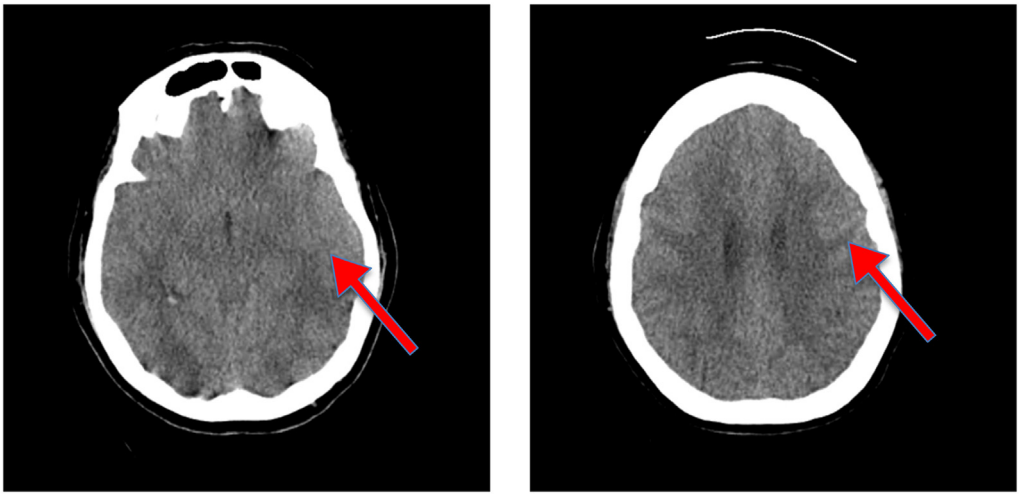

Fig. 1. CT of the brain on admission to the acute care hospital demonstrating diffuse cerebral edema and effacement of sulci (arrows).

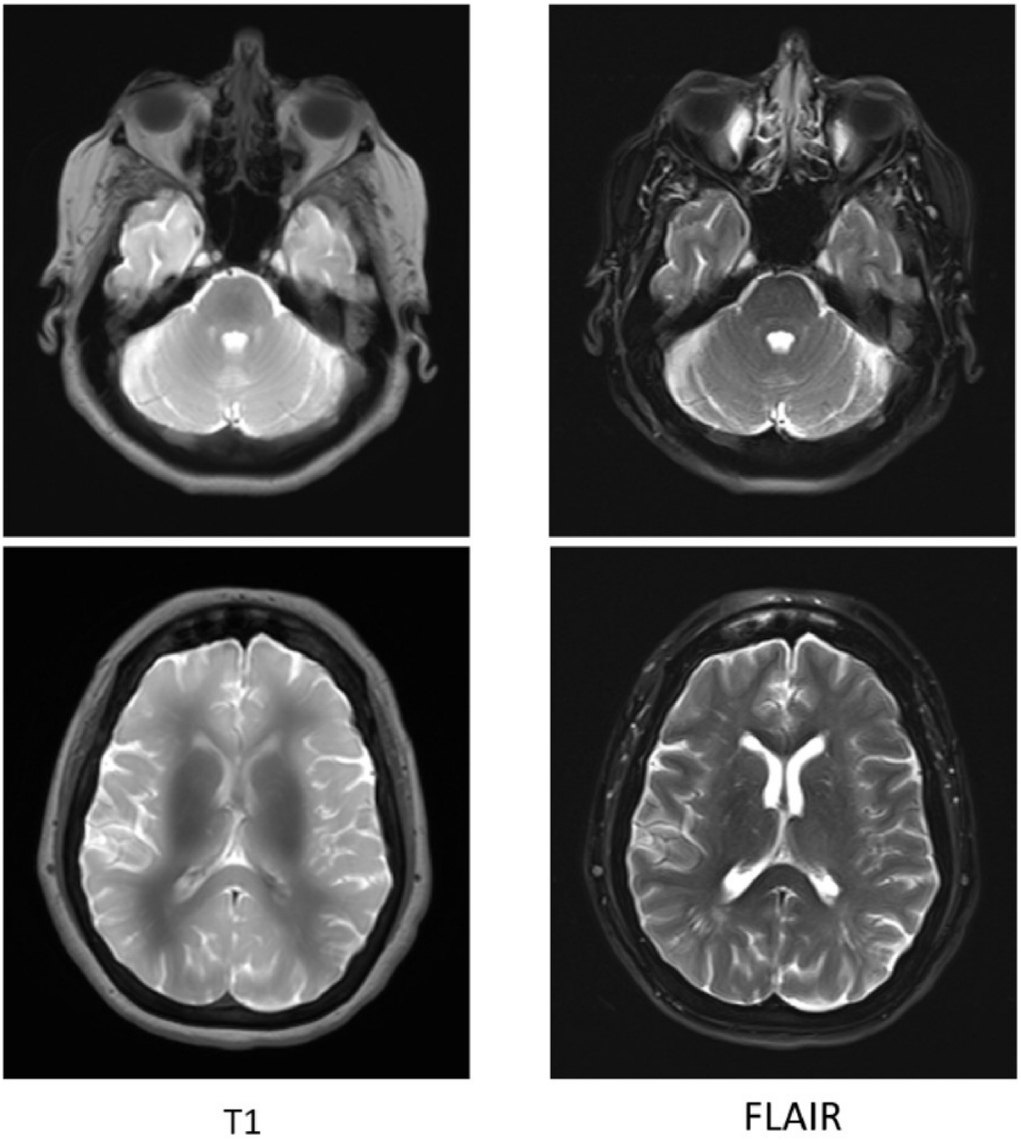

Fig. 2. MRI imaging of the brain on admission to the acute care hospital. No additional contrast was administered at time of imaging, the enhancement noted on these images was due to the gadolinium (inadvertent intrathecal) administration during the pain procedure. (CSF should be hypointense on T1 and FLAIR images, not hyperintense as seen here. Compare to absence of enhancement seen in Fig. 3.)

The standard loss of resistance technique is inherently unreliable on its own to verify access to the epidural space [14,15]. Evidence based literature shows loss-of-air-resistance without fluoroscopic guidance and contrast enhancement is inaccurate in 25–30% of injections, and loss-of-saline-resistance inaccurate 8% of the time [14,15].

Although gadolinium is generally considered to be a safe contrast agent, encephalopathy has been associated previously with both IV and intrathecal injection. Gadolinium encephalopathy is a relatively new concept first coined by Maramattom et al., in 2005 and is associated with poor renal function with subsequent accumulation of IV-administered gadolinium [1,17–21]. Even with normal renal function, IV-administered gadolinium is known to deposit into tissues, including the brain [1,19–22].

Intrathecal injection of gadolinium is considered off-label use for all forms of GBCAs. Intrathecal GBCA use has been adopted by neurologists and neurosurgeons due to better sensitivity for subtle CSF leaks after CT cisternography fails to find the source of the leak [23,24]. These imaging studies, however, are not without AEs. Patel et al. performed a systematic review including 1036 patients which showed a 13% rate of AEs (130 patients), most commonly postural headache (108 patients) [24]. Their review also examined 10 case reports of serious AEs from administration of intrathecal gadolinium, which included 1 death. Our literature review found 5 additional case reports of serious AEs from intrathecal gadolinium [25–30]. The manuscript by Nayak et al. had an additional case report (for a total of 2 case reports) which was not reported in the review by Patel et al. [25]. Of these 15 total case reports of serious AEs, 4 were due to ESIs with accidental intrathecal injection [27,28,31,32].

Current literature review demonstrates adverse effects with intrathecal gadolinium dose equal to or greater than 0.5 mmol or 0.73 μmol/g brain (assuming 1400g adult brain) [23,24,26–30,35]. Shah et al. presented a case of a pain pump catheter evaluation with 0.5 mmol of gadodiamide which resulted in generalized seizures and 45 days of hospitalization [30]. This is the lowest dose of intrathecal gadolinium that caused serious adverse effects found in the current literature. Halvorsen et al. performed a prospective safety study with 149 pts comparing a 0.25 mmol vs 0.5 mmol dose of intrathecal gadobutrol and concluded that both doses were safe, with non-serious AEs occurring in 76% of patients, most commonly nausea, headache, and dizziness, the majority of which resolved within 24 h [23]. Tali et al. performed a prospective safety study with 95 patients who received up to 0.5 mmol of

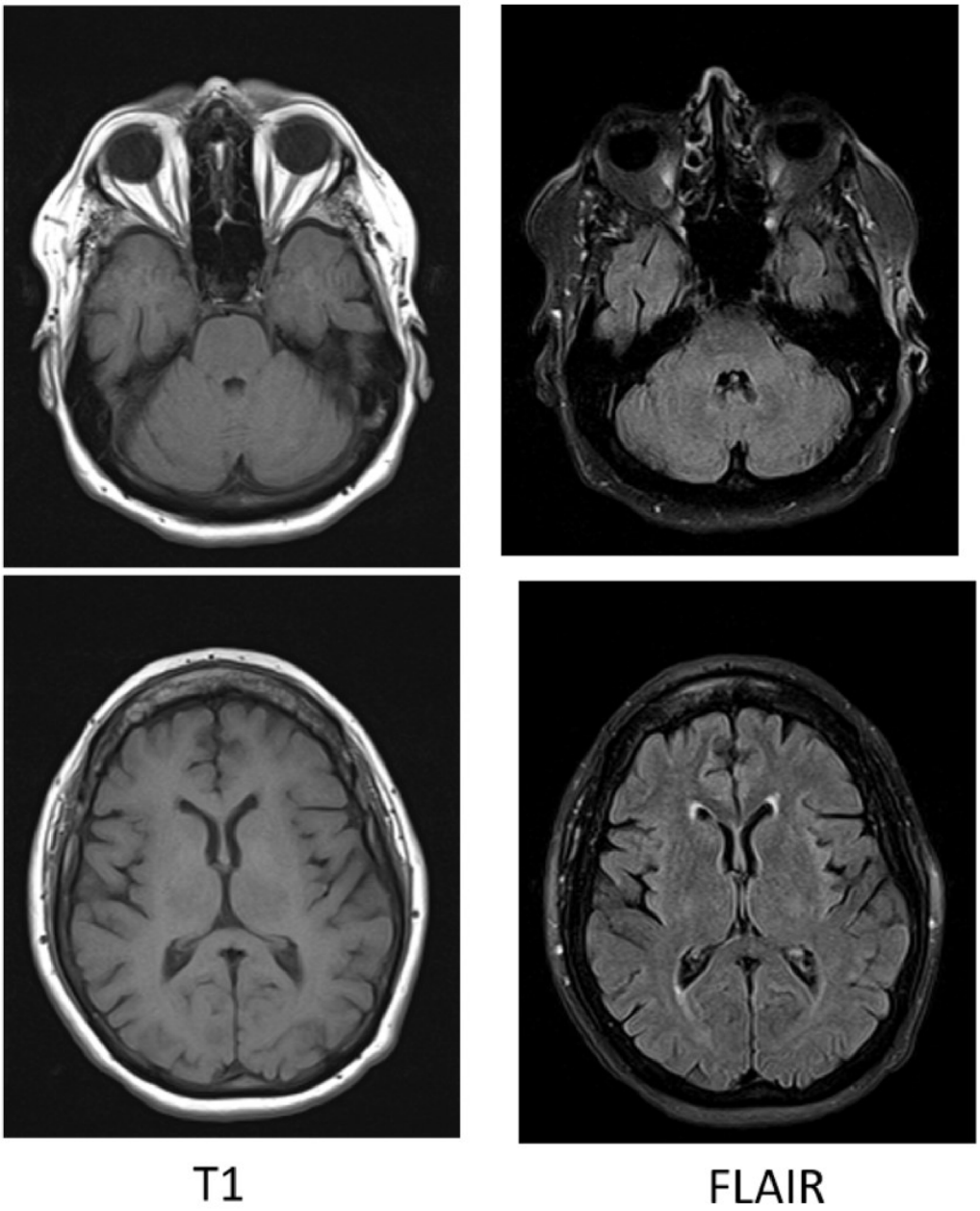

Fig. 3. MRI imaging of the brain 5 months post-injection showing resolution of gadolinium enhancement (Compare to the enhancement seen in Fig. 2.).

intrathecal gadopentetate dimeglumine and also showed that patients only experienced non-serious AEs of headaches (20%), nausea (6%), and vomiting (2%) that lasted less than 24 h [35]. In the review by Patel et al., all of the patients with non-serious AEs received 1 mmol or less of GBCA, mostly gadopentetate dimeglumine [24]. Additional studies by Dogan et al. and Algin et al. add an approximate additional 266 patients who safely received 0.25 mmol of intrathecal GBCA which is consistent with the aforementioned studies [36,37]. Benzon et al. reported with low certainty the occurrence of encephalopathy after intrathecal doses as low as 1.5 mL of gadobutrol (1.5 mmol), based off of Popescu et al.'s case report [1,28]. Shah et al.'s case report may represent a case with a lower dose of 0.5 mmol (gadodiamide) that caused encephalopathy (see Table 1).

If serious AEs occur, one must have high suspicion for gadolinium encephalopathy as the neurological symptoms may present similarly to an intracranial pathology and subsequent imaging may lead to a false-positive for intracranial hemorrhage [25,27]. Symptoms may include cognitive decline, headache, nausea, vomiting, dizziness, tremors, hallucinations, seizure, dysarthria, hearing deficit, vision deficit, taste alteration, hypertension, respiratory distress/failure, tachycardia, fever, chills, pruritus, back pain, paresthesias, and fatigue [23,24,34]. In the event that gadolinium encephalopathy is suspected, Li et al. suggests that draining CSF is a life-saving procedure, and that glucocorticoids may also help [38]. Of the 15 serious AE case reports, glucocorticoids were given to 7 patients, and CSF drains were used in 3 and considered in 1 (see Table 2) [25,31,38–40]. In this case report, a CSF drain was not placed, but the patient was given glucocorticoids within hours. Prompt administration of glucocorticoids are used to reduce possible cerebral edema that is seen on imaging [38,39,41]. Benzon et al. did not specify what measures to take but did recommend institution of immediate supportive measures [1].

A practical and safe alternative in a patient with hypersensitivity reactions to ICM, is not using any type of contrast media at all for the procedure. Since gadolinium is poorly visualized under fluoroscopic

Table 1
Gadolinium-based Radiocontrast agents and their molar concentrations [33,39].

Trade Name	Generic Name	Structure	Molar Concentration (mmol/L)
Ablavar, Vasovist	Gadofosveset trisodium	Linear ionic	0.25
Artirem, Dotarem, Clariscan	Gadoterate meglumine	Macrocyclic ionic	0.5
Eovist, Primovist	Gadoxetate disodium	Linear ionic	0.25
Gadavist, Gadovist	Gadobutrol	Macrocyclic nonionic	1.0
Magnevist	Gadopentetate dimeglumine	Linear ionic	0.5
MultiHance	Gadobenate dimeglumine	Linear ionic	0.5
Omniscan	Gadodiamide	Linear nonionic	0.5
Optimark	Gadoversetamide	Linear nonionic	0.5
ProHance	Gadoteridol	Macrocyclic nonionic	0.5

guidance (even when digital subtraction imaging is utilized), especially with lower molar concentration GBCAs, it is tempting to use even higher volumes [44]. Since intrathecal gadolinium is significantly more dangerous than an intrathecal injection of steroid, some interventionalists choose not to use any contrast agent at all. An obvious drawback is possible inaccurate needle placement which may occur 25%–30% of the time when relying solely on loss of resistance techniques with fluoroscopic imaging but without contrast confirmation [15]. In addition, intravascular injection may occur if relying on blood flashback in the needle hub or with aspiration, which is highly specific (97%–97.9%), but not very sensitive (44.7%–45.9%) [8,9].

The use of gadolinium may also be considered with injections with lower risk of intrathecal administration such as peripheral skeletal joints, facet joints, sacroiliac joints, or other procedures such as medial/lateral branch blocks, and even advanced procedures such as provocation discography [1,45].

This case report presents a patient who sustained a serious AE from the intrathecal administration of 2 mmol of Omniscan (Gadodiamide) during an interventional pain procedure and also reviews other patients with similar AEs in the currently available literature. Gadolinium-based contrast agents are commercially available in a wide variety of concentrations ranging from 0.25 to 1 mmol/mL. Due to the variation in GBCAs, the dose of gadolinium should be reported in volume, type and concentration of GBCA used [1]. The agent used should be properly named due to differences in the chelators for the gadolinium ion and possible relationship to immunogenicity [1]. If the patient suffers from a serious AE to intrathecal gadolinium, IV glucocorticoids are indicated on an urgent/emergent basis, with appropriate treatment guided by facility policy and available best practices, which fall outside the scope of this publication. In Table 3, we provide a premedication regimen list as a reference. For iodinated contrast media hypersensitivity reactions, multiple strategies exist, including premedication (steroids/antihistamine), allergy testing and/or both, and doing the procedure without contrast media. GBCA may have a reasonable role in peripheral procedures where there is no intrathecal delivery risk. However, GBCA should not be used for neuraxial spine procedures where there is a risk of unintended subarachnoid or intrathecal injection. Ultimately, the clinician must weigh the risks of contrast agent usage vs the risks of using none at all for each patient, contrast agent, and adjunct medications.

Future Research/Topics: We challenge scientists and interventionalists to search for safer agents that can be used to identify inadvertent intrathecal injection, eg. iron oxides of manganese [33]. The majority of intrathecal GBCA cases used gadopentetate dimeglumine or gadobutrol. We question if there is a GBCA that is safer than others for intrathecal use. In a case where the interventionist decides to proceed with the use of Gadolinium, we question if the use of a chelator may help improve symptoms or worsen them by increasing osmolarity. Lastly, it is not

Table 2
Cases reports of gadolinium neurotoxicity.

Study	Intrathecal Dose in mmol (mL), Type of GBCA	Treatments Administered		
		CSF drain	Glucocorticoids	Other
This case report. Moradian et al.	1 mmol (2 mL), Gadodiamide		dexamethasone 6 mg IV x1, 4 mg IV x4	ondansetron, lorazepam
Arlt et al., 2007 [39]	10 mmol (20 mL), Gadopentetate dimeglumine		dexamethasone 40 mg IV x1	antipsychotics for aggression and hallucinations
Besteher et al., 2019 [40]	2 mmol (2 mL), Gadobutrol		prednisolone 100 mg x1	dimentindene 4 mg, ranitidine 50 mg, intubation
Kapoor et al., 2010 [31]	4 mmol (8 mL), Gadodiamide		methylprednisolone IV	keppra, mag sulfate, intubation
Li et al., 2008 [38]	7.5 mmol (15 mL), Gadopentetate dimeglumine	Lumbar cisterna @ 0.3–0.5 mL/min	methylprednisolone 1g IV QD x7d	chlorpromazine 50 mg + phenergan 50 mg IV x2d, then naloxone 4 mg x7d
Malalur et al., 2020 [26]	6 mmol (12 mL), Gadopentetate dimeglumine		high-dose IV dexamethasone	supportive care
Nayak et al., 2013 [25]	5 mmol (10 mL), Gadopentetate dimeglumine	ventriculostomy set to 0 mmHg, lumbar drain placed 2d after gad admin		anti-epileptics for status epilepticus, ET tube converted to trach
Park et al., 2010 [42]	3 mmol (6 mL), Gadopentetate dimeglumine			IVF, anti-epileptics, supportive care
Platt et al., 2020 [27]	2 mmol (2 mL), Gadobutrol			levetiracetam
Popescu et al., 2018 [28]	1.5 mmol (1.5 mL), Gadobutrol			intubation
Provenzano et al., 2019 [34]	2.5 mmol (5 mL), Gadoteridol	neurosurgery considered CSF drain		
Reeves et al., 2017 [43]	2 mmol (2 mL), Gadobutrol			midazolam for spasms
Samardzic et al., 2015 [32]	2 mmol (4 mL), Gadodiamide		dexamethasone 4 mg IV q6hr ×4 doses	
Shah et al., 2015 [30]	0.5 mmol (1 mL), Gadodiamide			intubated
Singh et al., 2016 [41]	5 mmol (10 mL), Gadopentetate dimeglumine	EVD left open to drain, lumbar drain placed after edema improved on day 2	dexamethasone IV	intubation, hyperventillation, hypertonic saline, anti-epileptics

Table 3
Premedication regimens for contrast media reactions.

American College of Radiology [47]	
General Option 1	Prednisone-based: 50 mg prednisone PO at 13 h, 7hr, and 1hr before contrast medium administration, + 50 mg diphenhydramine IV, IM, or PO 1hr before contrast administration
General Option 2	Methylprednisolone-based: 32 mg methylprednisolone by mouth 12hr and 2hr before contrast administration. +/− diphenhydramine 50 mg
Emergency Option 1	methylprednisolone 40 mg IV or hydrocortisone 200 mg IV q4hr until contrast administration + diphenhydramine 50 mg IV 1hr before
Emergency Option 2	dexamethasone 7.5 mg IV q4hr until contrast administration + diphenhydramine 50 mg IV 1hr before
Emergency Option 3	methylprednisolone 40 mg IV or hydrocortisone 200 mg IV + diphenhydramine 50 mg IV 1hr before (No evidence of efficacy, use only when no alternatives)
Benzon et al [1]	
Emergency Option 1	methylprednisolone 40 mg IV or hydrocortisone 200 mg IV q4hr until contrast administration + diphenhydramine 50 mg IV 1hr before
Emergency Option 2	dexamethasone 7.5 mg IV q4hr until contrast administration + diphenhydramine 50 mg IV 1hr before
Kwon et al [46]	
Mild	chlorpheniramine 4 mg IV 1hr prior
Moderate	methylprednisolone 40 mg + chlorpheniramine 4 mg IV 1 h prior
Severe	prednisolone 50 mg PO 13 h, 7hr, and 1hr prior
Wu et al [48]	
Lasser et al.	methylprednisolone 32 mg PO 6hr and 2hr before contrast administration
ACR	as above
ESUR	prednisolone 30 mg PO or methylprednisolone 32 mg PO 12hr and 2hr before contrast administration
Schopp et al [49]	
Elective	ACR as above
Emergency Option 1	methylprednisolone 40 mg IV q4hr, or hydrocortisone 200 mg IV q 4 h until contrast administration + diphenhydramine 50 mg IV 1hr before
Emergency Option 2	dexamethasone 7.5 mg IV q4hr, or betamethasone 6 mg IV q4hr until contrast administration + diphenhydramine 50 mg IV 1hr before
Emergency Option 3	Omit steroids entirely (no desirable) + diphenhydramine 50 mg IV (antihistamines alone have not been proven to reduce occurrence of reactions)

known what the true cross reactivity is between the contrast agents, if any.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Benzon HT, Maus TP, Kang HR, et al. The use of contrast agents in interventional pain procedures: a multispecialty and multisociety practice advisory on nephrogenic systemic fibrosis, gadolinium deposition in the brain, encephalopathy after unintentional intrathecal gadolinium injection, and hypersensitivity reactions. Anesth Analg 2021 Mar;23. https://doi.org/10.1213/ANE.0000000000005443. PMID: 33755647.

[2] Epstein NE. Neurological complications of lumbar and cervical dural punctures with a focus on epidural injections. Surg Neurol Int 2017;8:60.

[3] Guglielminotti J, Landau R, Li G. Major neurologic complications associated with postdural puncture headache in obstetrics: a retrospective cohort study. Anesth Analg 2019;129:1328–36.

[4] MacMahon PJ, Huang AJ, Palmer WE. Spine injectables: what is the safest cocktail? AJR Am J Roentgenol 2016 Sep;207(3):526–33. https://doi.org/10.2214/AJR.16.16379. Epub 2016 Jun 24. PMID: 27341350.

[5] Kuek DKC, Chung SL, Zishan US, et al. Conus infarction after non-guided transcoccygeal ganglion impar block using particulate steroid for chronic coccydynia. Spinal Cord Ser Cases 2019 Nov 5;5(1):92. https://doi.org/10.1038/s41394-019-0237-1.PMID:33144556.

[6] Wybier M. Transforaminal epidural corticosteroid injections and spinal cord infarction. Jt. Bone Spine. 2008 Oct;75(5):523–5. https://doi.org/10.1016/j.jbspin.2008.07.001. Epub 2008 Sep 17. PMID: 18801685.

[7] Malhotra G, Abbasi A, Rhee M. Complications of transforaminal cervical epidural steroid injections. Spine (Phila Pa 1976 2009 Apr 1;34(7):731–9. https://doi.org/10.1097/BRS.0b013e318194e247. PMID: 19333107.

[8] Furman MB, O'Brien EM, Zgleszewski TM. Incidence of intravascular penetration in transforaminal lumbosacral epidural steroid injections. Spine (Phila Pa 1976 2000 Oct 15;25(20):2628–32.

[9] Furman MB, Giovanniello MT, O'Brien EM. Incidence of intravascular penetration in transforaminal cervical epidural steroid injections. Spine 2003;28:21–5.

[10] Manchikanti L, Malla Y, Wargo BW, Cash KA, Pampati V, Fellows B. A prospective evaluation of complications of 10,000 fluoroscopically directed epidural injections. Pain Physician 2012 Mar-Apr;15(2):131–40. PMID: 22430650.

[11] Christelis N, Simpson B, Russo M, et al. Persistent spinal pain syndrome: a proposal for failed back surgery syndrome and ICD-11. Pain Med; 2021. https://doi.org/10.1093/pm/pnab015.

[12] Food and Drug Administration. FDA Drug Safety Communication: FDA requires label changes to warn of rare but serious neurologic problems after epidural corticosteroid injections for pain. Published April 23, 2014. Last accessed, https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-requires-label-changes-warn-rare-serious-neurologic-problems-after; October 11, 2021.

[13] Rathmell JP, Benzon HT, Dreyfuss P, et al. Safeguards to prevent neurologic complications after epidural steroid injections: consensus opinions from a multidisciplinary working group and national organizations. Anesthesiology (Hagerst) 2015;122:974–84. https://doi.org/10.1097/ALN.0000000000000614.

[14] Bartynski WS, Grahovac SZ, Rothfus WE. Incorrect needle position during lumbar epidural steroid administration: inaccuracy of loss of air pressure resistance and requirement of fluoroscopy and epidurography during needle insertion. AJNR Am J Neuroradiol 2005 Mar;26(3):502–5. PMID: 15760856.

[15] Johnson BA, Schellhas KP, Pollei SR, et al. Epidurography and therapeutic epidural injections: technical considerations and experience with 5334 cases. AJNR Am J Neuroradiol 1999;20:697–705.

[17] Maramattom BV, Manno EM, Wijdicks EFM, Lindell EP. Gadolinium encephalopathy in a patient with renal failure. Neurology 2005;12(7):1276–8. Apr,64.

[18] Hui FK, Mullins M. Persistence of gadolinium contrast enhancement in CSF: a possible harbinger of gadolinium neurotoxicity?. 30 Am J Neuroradiol 2008;7(1). Aug,e1–e1.

[19] Ramalho J, Ramalho M, Jay M, Burke LM, Semelka RC. Gadolinium toxicity and treatment. Magn Reson Imaging 2016 Dec;34(10):1394–8. https://doi.org/10.1016/j.mri.2016.09.005. Epub 2016 Sep 28. PMID: 27693607.

[20] Ramalho M, Ramalho J, Burke LM, Semelka RC. Gadolinium retention and toxicity-an update. Adv Chron Kidney Dis 2017 May;24(3):138–46. https://doi.org/10.1053/j.ackd.2017.03.004. PMID: 28501075.

[21] Layne KA, Wood DM, Dargan PI. Gadolinium-based contrast agents - what is the evidence for 'gadolinium deposition disease' and the use of chelation therapy? Clin Toxicol 2020 Mar;58(3):151–60. https://doi.org/10.1080/15563650.2019.1681442.Epub.2019.Oct.30. PMID: 31663374.

[22] Food and Drug Administration. Update on FDA approach to safety issue of gadolinium retention after administration of gadolinium-based contrast agents. Published September 20, https://www.fda.gov/media/116492/download. [Accessed 28 September 2021]. Last accessed.

[23] Halvorsen M, Edeklev CS, Fraser-Green J, et al. Off-label intrathecal use of gadobutrol: safety study and comparison of administration protocols. Neuroradiol 2021 Jan;63(1):51–61. https://doi.org/10.1007/s00234-020-02519-4.Epub.2020.Aug.15. PMID: 32803338; PMCID: PMC7803712.

[24] Patel M, Atyani A, Salameh JP, McInnes M, Chakraborty S. Safety of intrathecal administration of gadolinium-based contrast agents: a systematic review and meta-analysis. Radiology 2020 Oct;297(1):75–83. https://doi.org/10.1148/radiol.2020191373. Epub 2020 Jul 28. PMID: 32720867.

[25] Nayak NB, Huang JC, Hathout GM, Shaba W, El-Saden SM. Complex imaging features of accidental cerebral intraventricular gadolinium administration. J Neurosurg 2013;118(5):1130–4.

[26] Malalur P, Rajacic PC. Neurotoxic manifestations of high-dose intrathecal gadolinium administration for CT myelogram. Radiol Case Rep 2020 Aug 22; 15(10):1992–5. https://doi.org/10.1016/j.radcr.2020.07.084. PMID: 32874398; PMCID: PMC7452073.

[27] Platt A, Ammar FE, Collins J, Ramos E, Goldenberg FD. Pseudo-subarachnoid hemorrhage and gadolinium encephalopathy following lumbar epidural steroid injection. Radiol Case Rep 2020 Aug 19;15(10):1935–8. https://doi.org/10.1016/j.radcr.2020.07.075. PMID: 32884607; PMCID: PMC7452023.

[28] Popescu A, Patel J, McCormick ZL, et al. Fact finders for patient safety: are gadolinium-based contrast media safe alternatives to iodinated contrast agents for the safe performance of spinal injection procedures? Pain Med 2018;19(10): 2089–90.

[29] Hagedorn JM, Bendel MA, Moeschler SM, Lamer TJ, Pope JE, Deer TR. Intrathecal gadolinium use for the chronic pain physician. Neuromodulation 2019 Oct;22(7): 769–74. https://doi.org/10.1111/ner.13043.Epub.2019.Aug.25. PMID: 31448498.

[30] Shah G, Ing J. Gadolinium encephalopathy after catheter dye study. December: North American Neuromodulation Society Conference in Las Vegas, NV. Poster Presentation; 2015.

[31] Kapoor R, Liu J, Devasenapathy A, Gordin V. Gadolinium encephalopathy after intrathecal gadolinium injection. Pain Physician 24 June 2010.

[32] Samardzic D, Thamburaj K. Magnetic resonance characteristics and susceptibility weighted imaging of the brain in gadolinium encephalopathy. J Neuroimaging 2015;25(1):136–9.
[33] Hao D, Ai T, Goerner F, Hu X, Runge VM, Tweedle M. MRI contrast agents: basic chemistry and safety. J Magn Reson Imag 2012 Nov;36(5):1060–71. https://doi.org/10.1002/jmri.23725.PMID:23090917.
[34] Provenzano DA, Pellis Z, DeRiggi L. Fatal gadolinium-induced encephalopathy following accidental intrathecal administration: a case report and a comprehensive evidence-based review. Reg Anesth Pain Med 2019;44(7):721–9 [Published correction appears in Reg Anesth Pain Med 2019;44(9):908.
[35] Tali ET, Ercan N, Krumina G, Rudwan M, Mironov A, Zeng QY, Jinkins JR. Intrathecal gadolinium (gadopentetate dimeglumine) enhanced magnetic resonance myelography and cisternography: results of a multicenter study. Invest Radiol 2002 Mar;37(3):152–9. https://doi.org/10.1097/00004424-200203000-00008. PMID: 11882795.
[36] Dogan SN, Kizilkilic O, Kocak B, Isler C, Islak C, Kocer N. Intrathecal gadolinium enhanced MR cisternography in patients with otorhinorrhea: 10-year experience of a tertiary referral center. Neuroradiol 2018;60:471–7.
[37] Algin O, Turkbey B. Intrathecal gadolinium-enhanced MR cisternography: a comprehensive review. AJNR Am J Neuroradiol 2013;34:14–22.
[38] Li L, Gao FQ, Zhang B, Luo BN, Yang ZY, Zhao J. Overdosage of intrathecal gadolinium and neurological response. Clin Radiol 2008;63:1063–8.
[39] Arlt S, Cepek L, Rustenbeck HH, Prange H, Reimers CD. Gadolinium encephalopathy due to accidental intrathecal administration of gadopentetate dimeglumine. J Neurol 2007;254(6):810–2.
[40] Besteher B, Chung HY, Mayer TE, Witte OW, Kirchhof K, Schwab M. Acute encephalopathy and cardiac arrest induced by intrathecal gadolinium administration. Clin Neuroradiol 2019. https://doi.org/10.1007/s00062-019-00845-6. Published online, . [Accessed 2 November 2019].
[41] Singh S, Rejai S, Antongiorgi Z, Gonzalez N, Stelzner M. Misconnections in the critically ill: injection of high-dose gadolinium into an external ventricular drain. A Case Rep 2016;6(5):121–3.
[42] Park KW, Im SB, Kim BT, Hwang SC, Park JS, Shin WH. Neurotoxic manifestations of an overdose intrathecal injection of gadopentetate dimeglumine. J Kor Med Sci 2010;25(3):505–8.
[43] Reeves C, Galang E, Padalia R, Tran N, Padalia D. Intrathecal injection of gadobutrol: a tale of caution. J Pain Palliat Care Pharmacother 2017;31(2):139–43.
[44] Maus TP, Schueler BA, Magnuson DJ, Magnuson D. Relative conspicuity of gadolinium-based contrast agents in interventional pain procedures. Pain Med April 2017;18(4):p651–654.
[45] Falco FJ, Moran JG. Lumbar discography using gadolinium in patients with iodine contrast allergy followed by postdiscography computed tomography scan. Spine (Phila Pa 1976 2003 Jan 1;28(1):E1–4.
[46] Kwon OY, Lee JH, Park SY, et al. Novel strategy for the prevention of recurrent hypersensitivity reactions to Radiocontrast media based on skin testing. J Allergy Clin Immunol Pract 2019 Nov-Dec;7(8):2707–13. https://doi.org/10.1016/j.jaip.2019.04.036. Epub 2019 May 10. PMID: 31078762.
[47] American College of Radiology. ACR manual on contrast media." Contrast Manual. www.acr.org/Clinical-Resources/Contrast-Manual; 2021. Accessed March 30.
[48] Wu YW, Leow KS, Zhu Y, Tan CH. Prevention and management of adverse reactions induced by iodinated contrast media. Ann Acad Med Singapore 2016 Apr;45(4):157–64. PMID: 27292007.
[49] Schopp JG, Iyer RS, Wang CL, et al. Allergic reactions to iodinated contrast media: premedication considerations for patients at risk. Emerg Radiol 2013 Aug;20(4):299–306. https://doi.org/10.1007/s10140-012-1081-9. Epub 2013 Feb 21. PMID: 23430296.