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Safety of Intrathecal Administration of Gadolinium-based Contrast Agents: A Systematic Review and Meta-Analysis

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Conflicts of interest are listed at the end of this article.

See also the editorial by Kanal in this issue.

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Background: The use of MR cisternography with intrathecal administration of gadolinium-based contrast agents (GBCAs) is limited by a lack of understanding of the relationship between intrathecal GBCA exposure and dose-related adverse events.

Purpose: To perform a systematic review to establish an understanding of the dose-response relationship of intrathecal GBCAs and to characterize related adverse events, particularly at higher doses.

Materials and Methods: Medline, Embase, CINAHL, and Central databases were searched for studies reporting intrathecal GBCA use. Data extraction included studies focused on rates and types of adverse events after intrathecal GBCA exposure. A two-tailed independent sample *t* test statistic was used to evaluate the relationship between GBCA dose and the presence of serious versus nonserious adverse events. Meta-analysis was used to determine the overall incidence of adverse events. Study quality and publication bias were assessed using the modified Newcastle-Ottawa scale and a funnel plot (effect size measured using Hedges' *g* followed by the Egger test), respectively.

Results: Fifty-three studies with a total of 1036 patients were included for analysis. The overall rate of adverse events after intrathecal administration of GBCA was 13% (95% confidence interval [CI]: 9.3%, 18%). Meta-analysis revealed moderate heterogeneity (I^2 = 62%). Serious adverse event rates could not be determined with meta-analysis. They were reported in 10 studies and were primarily neurologic in nature, with two cases of coma—one resulting in death. Serious adverse events were associated with significantly higher GBCA doses when compared with nonserious adverse events (mean difference, 4.5 mmol; 95% CI: 2.3 mmol, 6.6 mmol; P = .008). For serious adverse events, there was no clear dose-dependent increase in severity above 2.0 mmol.

Conclusion: Overall, intrathecal administration of GBCAs at doses greater than 1.0 mmol are associated with serious neurotoxic complications with relative clinical safety at lower doses.

Online supplemental material is available for this article.

Intravenously administered gadolinium-based contrast agents (GBCAs) are commonly used during MRI procedures to aid in the visualization of central nervous system lesions. Although conventional MRI with intravenous GBCA provides excellent delineation of cerebrospinal fluid (CSF) spaces, complex CSF-related pathologic findings, such as cranial or spinal CSF leaks, and communicating or noncommunicating cystic masses are often poorly visualized (1–3).

Recently, MR cisternography with intrathecal GBCA has proven useful in helping detect subtle CSF leaks and flow disturbances (4,5). Furthermore, GBCA-enhanced MR cisternography seems to have a higher sensitivity than contrast material–enhanced CT cisternography in the detection of CSF leaks (5,6), particularly in patients with rhinorrhea (7). Although the adverse effects and overall safety of intravenous GBCA administration in humans have been well explored (8,9), very few studies have evaluated the safety profile of intrathecal administration of GBCAs. As of today, intrathecal administration would be considered off-label use for all U.S. Food and Drug Administration–approved GBCAs.

Previous literature has demonstrated that intrathecal GBCAs can be used relatively safely at low doses. In their 2013 review, Algin and Turkbey (10) reported on a cohort of more than 100 patients across multiple studies who underwent GBCA-enhanced MR cisternography without major adverse events after receiving 0.25 mmol of gadopentetate dimeglumine. Other safety trials also reported no changes in physical examination, electroencephalography, and CSF findings of patients who received similarly low doses of GBCAs (10–12).

Conversely, evidence shows that intrathecal GBCA administration poses an increased risk of neurotoxic adverse events (13). Animal studies have demonstrated that a high dose of intrathecal GBCAs, such as gadopentetate dimeglumine and gadodiamide, can result in signs of neurotoxicity such as gait disturbance, myoclonus, ataxia, tremors, and seizures (14–16). These adverse events occur at doses equivalent to 5–15 μmol per gram of brain tissue and are associated with histopathologic findings, including loss of oligodendroglia, astrocytic hypertrophy, and eosinophilia (10,14–16). Several case reports in humans have displayed evidence of neurotoxicity after intrathecal injection (17–26). Most of these cases involved accidental overdoses, which resulted in signs and symptoms such as

Abbreviations

CI = confidence interval, CSF = cerebrospinal fluid, GBCA = gadolinium-based contrast agent

Summary

Intrathecal administration of gadolinium-based contrast agents is associated with serious neurotoxic adverse effects at doses greater than 1.0 mmol.

Key Results

- According to meta-analysis of 33 studies, the overall rate of reported adverse events after intrathecal gadolinium-based contrast agent (GBCA) exposure was 13%; although the rate of serious adverse events was not amenable to meta-analysis, serious events were noted in 10 patients.
- Serious adverse events were associated with higher GBCA doses compared with nonserious adverse events (mean difference, 4.5 mmol; $P = .008$), with serious events noted with doses between 2.0 mmol and 10 mmol and nonserious events noted with doses between 0.01 mmol and 1.0 mmol.

confusion, global aphasia, vomiting, stupor, rigidity, seizures, and hypertension (21).

Although it is generally accepted that intrathecal GBCAs are relatively safe for clinical use at low doses, we lack a clear understanding of the dose-response relationship, thus making clear recommendations for clinical use of GBCAs equivocal. Therefore, the purpose of our study was to perform a systematic review of intrathecal GBCA administration in humans to establish an understanding of the dose-response relationship and to characterize the adverse events due to intrathecal GBCAs, particularly at higher doses.

Materials and Methods

This systematic review was conducted as per contemporary methodologic guidance (27) and was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (28).

Study Selection

Medline, Embase, Cochrane Central Register of Controlled Trials, and CINAHL databases (inception to November 31, 2019) were searched using medical subject headings and keywords for variations on GBCAs and intrathecal injection. The detailed search strategy can be found in Appendix E1 (online). Title and abstract review was performed for the references identified in our search, and articles were retrieved for full-text review according to our inclusion and exclusion criteria. The inclusion criteria for the systematic review were as follows: *(a)* GBCA method of administration was through the intrathecal route, *(b)* the study focused on human subjects, *(c)* the study commented on presence or absence of adverse events after intrathecal GBCA exposure, *(d)* the study reported the type of GBCA administered, and *(e)* dosage and injection procedure were specified. Articles that were reviews, commentaries, or response letters were excluded. Studies that were not available in English were also excluded. Reference lists of the retrieved articles were screened, and additional manual citation searching was performed; any duplicates were removed. After the full-text review, any remaining studies that did not comment on the presence or absence of adverse events after intrathecal GBCA exposure were excluded. The literature search and study selection were conducted and reconciled between two independent authors (M.P. and A.A., each with 4 years of experience).

Data Extraction

For each included study, the outcome of interest was the development of adverse events after intrathecal GBCA administration. Additional data on the study design, patient population, number of patients, type of adverse event, specific GBCA used, dilution process, dose administered, rate of injection, and follow-up time were also extracted. Patients were classified as experiencing either serious or nonserious adverse events according to U.S. Food and Drug Administration guidelines. According to the U.S. Food and Drug Administration definition (29), an adverse event is considered serious when it results in death, substantial risk of dying, initial or prolonged hospitalization, disability, intervention to prevent permanent impairment or damage, or events that may require treatment to prevent progression to one of the previously mentioned outcomes. Seizures requiring hospitalization or treatment were also classified as serious adverse events under the guidelines.

Nonserious adverse events included mild symptoms such as postural headaches, mild nonpostural headaches, nausea, vomiting, and fever lasting less than 24 hours. Nonserious adverse events also included patients without any reported adverse events due to the risk of underreporting of mild symptoms in the included studies.

Patients were categorized into six groups depending on the GBCA they received: gadopentetate dimeglumine, gadobutrol, gadodiamide, gadobenate dimeglumine, gadoteridol, or gadoterate meglumine. Data on the dose administered were standardized across the different GBCAs by converting the volume of GBCA injected to a molar amount using each GBCA's concentration according to the following equation: molar dose = (GBCA volume) × (GBCA concentration). For instance, 1 mL of gadopentetate dimeglumine with a concentration of 0.5 mmol/mL is converted to 0.5 mmol. Data extraction was independently performed by two reviewers (M.P. and A.A.), and any discrepancies between the two reviewers were resolved with a third reviewer (S.C.).

Data Analysis

Each patient was only counted once, even if she or he had multiple adverse effects. A random-effects model was used to determine the overall incidence of adverse events for patients from prospective and retrospective studies (excluding case reports). Meta-analysis was planned to determine the incidence of both overall and serious adverse events; however, serious adverse events were only reported in case studies that were excluded from analysis. Heterogeneity was assessed using I^2 statistics. Publication bias was assessed using a funnel plot followed by the Egger test. Two-tailed independent sample t test statistics were used to evaluate differences in serious and nonserious event groups according to GBCA doses. The mean

dose value was determined and used whenever the identified studies reported a dose range. Correlation between rate of administration and adverse event rates was also assessed with the Pearson correlation coefficient. Study quality was assessed using a modified Newcastle-Ottawa scale (30) ranging from 0 to 6 points (Appendix E1 [online]). We considered a type I error value of $P < .05$ to indicate a statistically significant difference. All statistical analyses were performed using R software (version 3.5.1; R Project for Statistical Computing, Vienna, Austria) (31).

Results

Study Flow and Characteristics

The literature search yielded 475 studies, of which 53 studies met the criteria for qualitative synthesis. Among the 53 articles, 33 were included in the meta-analysis (Fig 1). Among the included studies, 20 were case studies (included in the systematic review but not in the meta-analysis), 31 were prospective studies, and two were retrospective studies. No randomized controlled trials were identified. The literature search and study selection by two reviewers (M.P. and A.A.) yielded a high interrater reliability (κ = 0.91) (Appendix E1 [online]).

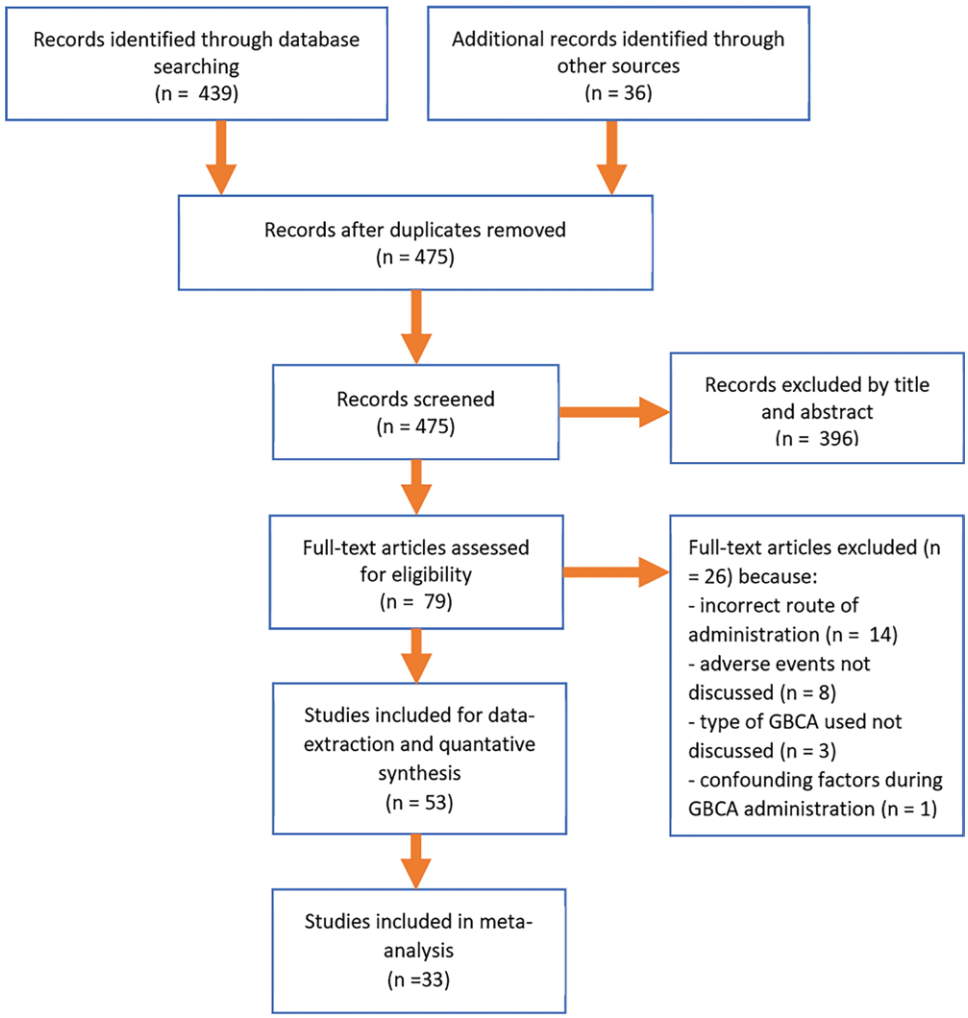

Figure 1: Flowchart of identification and selection of studies. GBCA = gadolinium-based contrast agent.

The included studies identified a total of 1036 patients with intrathecal GBCA administrations, with 130 reported to have adverse reactions (Tables 1, 2). Three studies examined adverse events associated with intrathecal GBCAs in children (1,3,57), while the remaining 50 studies focused on adult patients. Gadopentetate dimeglumine was the predominant GBCA examined, used in 36 of the 53 studies (68%) and administered to 895 patients. Gadobutrol and gadodiamide were used in eight of the 53 studies (15%) and five of the 53 studies (9.4%) and were administered to 106 and 31 patients, respectively. Other GBCAs were used in four of the 53 studies (7.5%) and administered to four patients. None of the patients included in the analysis reported renal failure. Injection procedures and follow-up length are discussed in Tables E1 and E2 (online).

Adverse Events Analysis

According to meta-analysis of 33 studies, the overall rate of reported adverse events after intrathecal GBCA exposure was 13% (95% confidence interval [CI]: 9.3%, 18%) (Fig 2a) combined across all GBCAs. The analysis revealed moderate heterogeneity (I^2 = 62%). Study quality measured with the Newcastle-Ottawa scale ranged from 4–6 points (Table 2; Table E2 [online]). Most studies lost points as they did not confirm that the outcome of interest was not present at the start of the study in addition to variable quality in reporting the follow-up response rate. Furthermore, the funnel plot revealed substantial asymmetry in the data ($P < .001$, Egger test) (Fig 2b). Postural headache was the most common adverse reaction reported, present in 108 of the 130 patients who experienced adverse events. Among the 108 patients with reported cases of postural headaches, 107 received gadopentetate dimeglumine and one received gadodiamide. The postural headaches were transient in nature, resolving within 24 hours. Other nonserious adverse events observed in 13 patients included nausea, vomiting, delayed headaches, and fever. One study reported a patient with symptoms of meningitis shortly after intrathecal GBCA administration; however, the case was not included as an adverse event because the authors determined that the bacterial meningitis was secondary to a documented ethmoidal CSF leak, rather than the intrathecal GBCA administration

Table 1: Studies Describing Serious Adverse Events after Intrathecal Administration of GBCAs

Study and Year	Patient Description	Description of Adverse Events	Dose (mmol)	Type of GBCA	Injection Procedure
Arlt et al, 2007 (17)	64-year-old man with accidental injection of intrathecal GBCA instead of an iodine-containing contrast agent during CT myelography	Immediate: confusion, nausea, vomiting 1–3 hours: progressive dysarthria, somnolence, blurred vision, delirium, limb ataxia, gaze-evoked nystagmus After day 1: alert but disoriented and restless, visual and auditory hallucinations, acalculia, concentration deficits, mild concentration deficits, mild gait ataxia	10	Gadopentetate dimeglumine	2 mmol of GBCA followed by 20 mL of iodine
Besteher et al, 2019 (44)	69-year-old woman with severe bitemporal headaches; contrast material–enhanced MR myelography with intrathecal GBCA was used to detect site of cerebrospinal fluid leakage	15 minutes: progressive sacral pain, uncontrolled defecation, agitation, vomiting, nausea, vertigo, myoclonic jerks followed by disorientation and physical aggression >4 hours: cardiac arrythmia Long term: no arrythmia, improved mood but disturbed concentration, amnesia for 1 day after GBCA injection	2	Gadobutrol	2 mL of GBCA with 20 mL of saline
Kapoor et al, 2010 (18)	61-year-old woman received intrathecal GBCA during an epidural steroid injection and epidural blood patch 3 hours later	Acute: mental status changes, grand mal seizure, unresponsive to verbal or noxious stimuli, respiratory distress requiring endotracheal intubation, hyperglycemia Long term: normal neurologic examination but amnesia of entire event, questionable intermittent seizure-like activity	2 plus 2	Gadodiamide	GBCA injected with autologous blood
Li et al, 2008 (19)	34-year-old woman with left brachial plexus injury accidentally received a high dose of intrathecal GBCA	Immediate: headache, nausea, vomiting 1 hour: comatose, systemic seizures Long term: normal neurologic examination, no symptoms	7.5	Gadopentetate dimeglumine	GBCA alone
Nayak et al, 2013 (20)	59-year-old man who had undergone surgical resection of meningioma and inadvertently received intrathecal GBCA during assessment of residual tumor mass	Immediate: agitation, labile blood pressure Day 1: aphasia, dysarthria, depressed mentation, right facial droop, increased urine output Long term: required ventilatory support (tracheostomy at 1 month after exposure), nonconvulsive status epilepticus	5	Gadopentetate dimeglumine	GBCA alone
Park et al, 2010 (21)	42-year-old man with accidental injection of intrathecal GBCA instead of an iodine-based contrast agent	6 hours: confusion, global aphasia, vomiting, stupor, severe rigidity, intermittent seizures, hypertension, fever Long term: recurrent visual disturbances, bilateral optic atrophy with some improvement at the 1-year mark	3	Gadopentetate dimeglumine	GBCA alone
Provenzano et al, 2019 (23)	67-year-old woman with a history of lumbar spinal stenosis received inadvertent intrathecal GBCA for fluoroscopic guidance during her minimally invasive lumbar decompression procedure	Immediate: severe headache, mental status changes, agitation, apnea, increased extremities muscle tone Acute: thrashing around, eye and tongue twitching, crying out, decreased respirations, myoclonic activity, wide-complex pulseless tachycardia, fever, recurrent seizures Long term: multisystem organ failure, coma, death	2.5	Gadoteridol	GBCA alone
Reeves et al, 2017 (24)	60-year-old woman received intrathecal GBCA to assess integrity of intrathecal catheter	5 minutes: severe spastic pain with visible spasms of lower extremities Long term: no long-term sequalae	2	Gadobutrol	GBCA alone
Samardzic et al, 2015 (25)	67-year-old woman with allergy to iodinated contrast agents received GBCA for needle localization	3 hours: dyspnea, nausea, chills, disoriented to place and time Day 2: discharged in good neurologic condition	2	Gadodiamide	4 mL of GBCA followed-by a mixture of 2 mL of triamcinolone and 4 mL of saline
Singh et al, 2016 (26)	59-year-old man who had undergone cranial surgery accidentally received intrathecal GBCA via an external ventricular drain	Immediate: nausea, acutely hypertensive at 1 hour Day 1: rapidly progressive aphasia, right facial droop, delirium Long term: awake but not interactive with environment	5	Gadopentetate dimeglumine	GBCA alone

Note.—GBCA = gadolinium-based contrast agent.

Table 2: Studies Describing Nonserious Adverse Events after Intrathecal Administration of GBCAs

Study and Year	Study Design	Patient Age (y)	No. of Patients*	No. with Adverse Effects	Adverse Events†	Dose (mmol)†‡	Type of GBCA	Injection Procedure	Newcastle-Ottawa Scale Score
Akbar et al, 2012 (33)	Retrospective	22–80	41 (27/14)	1	Headache	0.25	Gadopentetate dimeglumine	Iodine followed by GBCA diluted in saline	5
Albayram et al, 2008 (35)	Prospective	25–77	19 (12/7)	5	Headache	0.25	Gadopentetate dimeglumine	GBCA plus saline	5
Algin et al, 2009 (39)	Prospective	0.5–67	21 (8/13)	7	Headache	0.25–0.5	Gadopentetate dimeglumine	GBCA alone	5
Algin et al, 2010 (37)	Prospective	11–70	17 (4/13)	6	Headache [5], fever [1]	0.5	Gadopentetate dimeglumine	GBCA alone	5
Algin et al, 2010 (41)	Prospective§	1–67	34 (16/18)	7	Headache	0.25–0.5	Gadopentetate dimeglumine	GBCA alone	5
Algin et al, 2011 (40)	Prospective§	40–78	51 (28/23)	10	Headache	0.5	Gadopentetate dimeglumine	GBCA alone	5
Algin et al, 2011 (38)	Prospective§	2–35	21 (7/14)	0	Headache	0.25–0.5	Gadopentetate dimeglumine	GBCA alone	5
Arbeláez et al, 2007 (43)	Prospective	7–61	22 (8/14)	8	Headache	0.5	Gadopentetate dimeglumine	GBCA alone	4
Aydin et al, 2004 (32)	Prospective	19–56	20 (8/12)	4	Headache	0.25	Gadopentetate dimeglumine	GBCA plus CSF	4
Aydin et al, 2008 (7)	Prospective	19–61	51 (19/32)	12	Headache	0.25	Gadopentetate dimeglumine	GBCA alone	5
Dogan et al, 2018 (12)	Retrospective	4–83	166 (93/73)	3	Severe headache 3–4 weeks later	0.25	Gadopentetate dimeglumine	GBCA plus saline	5
Ecin et al, 2013 (49)	Prospective	18–70	60 (27/33)	6	Headache	0.25–0.5	Gadopentetate dimeglumine	GBCA alone	4
Goel et al, 2007 (52)	Prospective	13–56	10 (5/5)	1	Headache	1	Gadodiamide	Iodine followed by GBCA	5
Jinkins et al, 2002 (4)	Prospective	9–68	15 (7/8)	3	Headache	0.25	Gadopentetate dimeglumine	GBCA alone	5
Muñoz et al, 2007 (1)	Prospective	15 d–16 y	10 (2/8)	2	Headache	0.4–1.0	Gadopentetate dimeglumine	GBCA plus CSF	5
Ragheb et al, 2014 (58)	Prospective	33–62	25 (16/8)‖	6	Headache	0.25	Gadopentetate dimeglumine	GBCA plus CSF	4
Selcuk et al, 2010 (2)	Prospective	15–72	85 (40/45)	5	Headache	0.25	Gadopentetate dimeglumine	GBCA plus saline	5
Tali et al, 2002 (63)	Prospective	1 mo-78 y	95 (45/50)	27	Headache [19], nausea [6], vomiting [2]	0.25 [63], 0.35 [13], 0.4 [12], 0.5 [7]	Gadopentetate dimeglumine	GBCA plus CSF	5
Tali et al, 2004 (64)	Prospective	5–67	20 (8/12)	6	Headache	0.25	Gadopentetate dimeglumine	GBCA plus CSF	4
Tan et al, 2015 (3)	Prospective§	0.25–9.67	23 (3/20)	1	Headache	0.25	Gadopentetate dimeglumine	GBCA plus CSF	5

Note.—CSF = cerebrospinal fluid, GBCA = gadolinium-based contrast agent.

* Data in parentheses are numbers of female and male patients.

† Data in brackets are numbers of patients.

‡ Fixed doses, not normalized by weight.

§ Prospective study with disease-specific controls.

‖ Information unavailable for one patient.

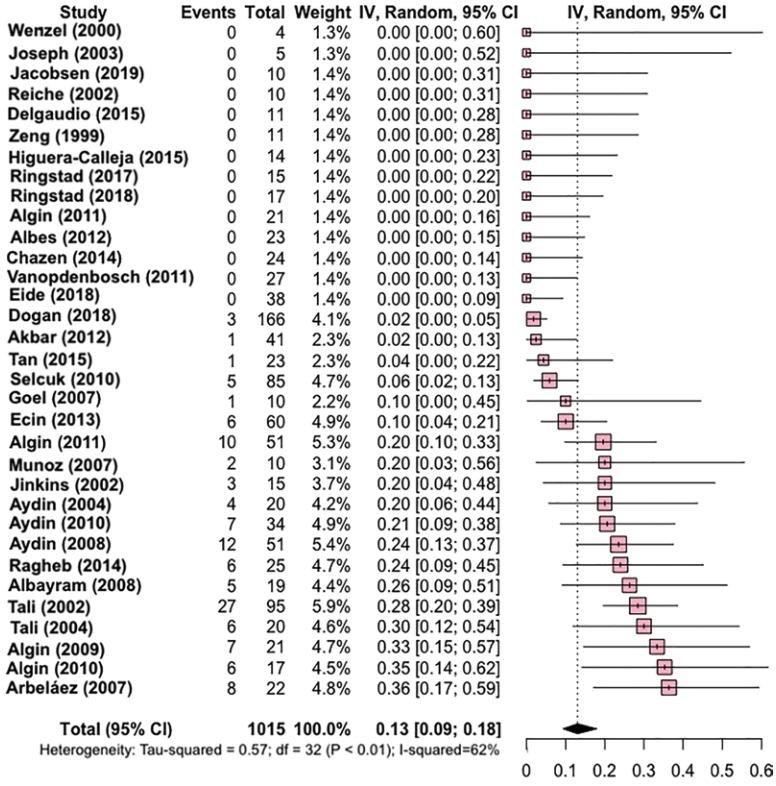

Figure 2: **(a)** Forest plot shows incidence of adverse events for prospective and retrospective studies included in the meta-analysis. **(b)** Funnel plot shows prospective and retrospective studies included in the meta-analysis. The substantial asymmetry is indicative of potential publication bias within the pool of identified studies. CI = confidence interval, df = degrees of freedom, IV = inverse variance.

(65). An abbreviated breakdown of studies reporting nonserious adverse events can be found in Table 2. For a comprehensive breakdown of all studies with nonserious adverse events, please refer to Table E2 (online).

Meta-analysis of serious adverse events was not possible because these were only reported in case studies. Serious adverse events were reported in 10 cases and were primarily neurologic in nature. Notable reported neurologic symptoms included seizures, dysarthria, ataxia, confusion, visual disturbances, vertigo, myoclonic jerks, aphasia, changes in extremity muscle tone, and mental status changes. Other systemic symptoms, such as cardiac arrythmias, respiratory distress, hyperglycemia, and hypertension, were also reported (18,20,21,44). Two studies (19,23) described progression to coma, one of which eventually resulted in death (23). The onset of serious adverse events was acute in nature, with nine of 10 studies describing onset of symptoms within 6 hours after intrathecal GBCA exposure and one study reporting onset while the patient was recovering in the clinic without indicating the specific time of onset (18). Among the 10 patients with serious adverse events, three had no long-term sequalae, four reported deficits in one to two neurocognitive domains at their last follow-up, one reported ongoing seizures at the last follow-up, and two experienced severe consequences, such as coma, one of which resulted in death. Breakdowns of studies reporting serious adverse events can be found in Table 1 (see Table E1 [online] for further details).

Independent sample *t* test analysis revealed a significant difference in GBCA doses across the two adverse events groups, with significantly higher GBCA doses associated with the serious adverse event group (mean difference, 4.5 mmol; 95% CI: 2.3 mmol, 6.7 mmol; $P = .008$) (Fig 3). Nonserious adverse events were noted at doses between 0.01 mmol and 1.0 mmol, with a mean and median dose of 0.34 mmol and 0.25 mmol, respectively (Table E2 [online]). On the other hand, serious adverse events were noted at doses between 2 mmol and 10 mmol, with a mean and median dose of 4.3 mmol and 4.5 mmol, respectively (Table 1).

The rate of intrathecal GBCA administration was reported in only 12 of the 53 studies (23%) and ranged from 1 mL/min to a single push. Pearson correlation analysis revealed no correlation between the rate of injection and the rate of adverse events ($R = 0.22$; $P = .54$) (Fig E1 [online]).

Discussion

Intrathecal gadolinium-based contrast agents (GBCAs) have been useful for detecting complex cerebrospinal fluid abnormalities. Although GBCAs are well tolerated at low doses, neurotoxic manifestations have been reported in cases of accidental overdose (17–26). Clinical manifestation of adverse events at higher doses are currently poorly characterized; hence, we sought to address this gap in knowledge. Among 1036 patients identified from 53 studies, the overall rate of adverse events was identified as 13% (95% confidence interval: 9.3%, 18%), with serious adverse events reported in 10 patients. The adverse event rate could not be calculated for serious events, as these were limited to case reports. For com-

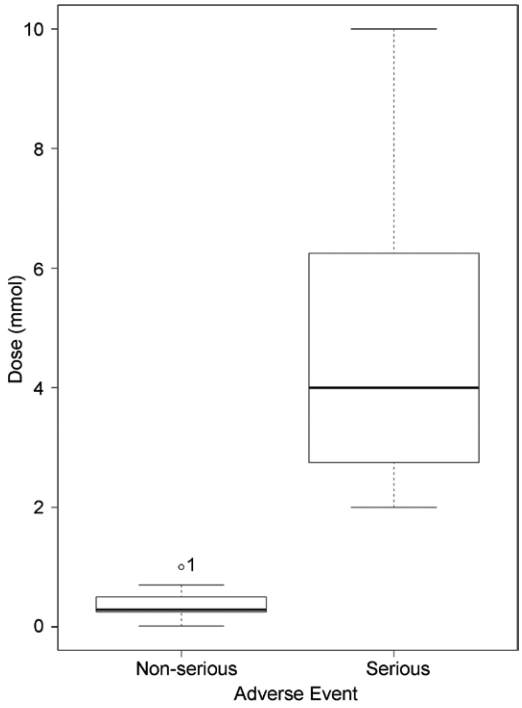

Figure 3: Box-and-whisker plot shows the range of intrathecal gadolinium-based contrast agent doses (in millimoles) associated with nonserious and serious adverse events. Serious adverse events were noted at higher doses compared with nonserious adverse events. Boundaries of boxes indicate upper and lower quartiles, and lines in boxes indicate medians. Outliers are plotted as individual points.

parison, overall adverse event incidence after iodinated myelography has been reported between 7.4% and 40% (68–71). A significant difference was identified for GBCA doses between serious and nonserious adverse events ($P = .008$), with nonserious adverse events reported at doses between 0.01 mmol and 1.0 mmol and serious adverse events reported at doses between 2.0 mmol and 10 mmol. The gap between the dose ranges indicates evidence of an increasingly small margin of safety between the range of 1.0–2.0 mmol doses where the incidence of severe neurotoxic events increases significantly.

The most commonly reported adverse effect associated with intrathecal injection of GBCA was a transient postural headache lasting less than 24 hours. Postural headaches are common after lumbar puncture procedures, with a reported incidence of up to 49% in the literature (72,73). However, our analysis revealed a lower incidence, with postural headaches reported in only 108 of 1036 patients. The discrepancy between the incidence of postural headaches in our analysis and the literature is likely due to an underreporting of minor symptoms associated with lumbar puncture given that adverse events after intrathecal administration of GBCAs was not the primary focus for most studies. This is further shown by the unexplained variability in the rates of postural headaches among GBCAs, with gadopentetate dimeglumine associated with a significantly higher rate of postural headaches (107 of 895 patients, 12%) compared with other GBCAs such as gadodiamide (one of 31 patients, 3%) and gadobutrol (zero of 106 patients, 0%). To our knowledge, no mechanism has been proposed to explain this interagent difference in postural headaches. To account for underreporting of minor symptoms, all patients who did not experience a serious adverse event were grouped into the nonserious adverse events group, thereby precluding any statistical comparisons for minor adverse events.

Serious adverse events were associated with every dose greater than 1.0 mmol and were primarily neurologic in nature with notable neurologic symptoms, including seizures, dysarthria, ataxia, confusion, visual disturbances, vertigo, myoclonic jerks, aphasia, changes in extremity muscle tone, and mental status changes. Severe systemic symptoms, such as cardiac arrythmias, respiratory distress, hyperglycemia, and hypertension, have also been associated with a dose greater than 1.0 mmol (18,20,21,44). In severe cases, progression to coma (19,23) and death (23) is also possible. All serious adverse events occurred acutely, with nine of 10 studies reporting adverse events within the first 6 hours after intrathecal GBCA exposure and one study reporting a serious adverse event while the patient was recovering in the clinic (18). It is important to note that although serious adverse events were associated with doses greater than 1 mmol, the severity of serious adverse events was not predictable using dose. For instance, administration of 2.5 mmol GBCA resulted in death in one patient (23), while a patient given 10 mmol GBCA experienced minimal neurocognitive deficits at 2-month follow-up (17). Although not strictly an adverse event, users may consider the issue of increased central nervous system gadolinium tissue deposition associated with intrathecal administration of linear GBCAs compared with macrocyclic agents (74,75). However, it should be noted that most of the cases included in our study used the linear agent gadopentetate dimeglumine.

Several limitations to our analysis should be considered. Despite a broad search, our literature review was unable to identify any randomized controlled trials. Because of its off-label use, we were limited to observational studies with no control groups for intrathecal GBCA administration, thereby adding the possibility of confounding variables mediating the dose-dependent relationship between GBCAs and adverse events. For example, many included studies did not directly assess adverse events related to intrathecal GBCA as a primary objective. Instead, many of them consisted of case reports that may have discussed severe adverse events due to accidental overdoses, rather than directly assess and report on milder adverse events that may have been more prevalent. As a result, we were unable to accurately assess mild intrathecal GBCA-related adverse events, such as postural headaches, which actually represented most of the symptoms that patients experienced. Our conclusion on the adverse events is also limited by the lack of a control group exposed only to the lumbar puncture procedure without GBCAs to more accurately isolate the rate of postural headaches due to the lumbar puncture procedure itself from the rate attributable to GBCAs. As a result of these factors, our analysis was unable to determine dose-range cutoffs and was limited to a descriptive characterization of severe neurotoxic adverse events occurring at high doses. Furthermore, as identified in the Newcastle-Ottawa scale analysis, many studies failed to demonstrate that the outcome of interest was not present prior to GBCA administration, and some studies failed to provide adequate follow-up, thereby contributing to risk of

bias. In addition, the studies were heterogeneous in intrathecal injection procedures, the rate of injection, and follow-up between the different studies, adding further variability. Furthermore, publication bias within the identified studies may play a role in artificially increasing the incidence rate as indicated by the asymmetric funnel plot. Finally, our literature search identified considerably more studies investigating the linear agent gadopentetate dimeglumine than any other GBCA, skewing the adverse event rate closer to the rate of gadopentetate dimeglumine.

In conclusion, our analysis of the available literature identified 10 patients with serious neurotoxic adverse events after intrathecal administration of a gadolinium-based contrast agent (GBCA). Although our study supported the relative clinical safety of intrathecal GBCAs at low doses of up to 1.0 mmol, an increasingly small margin of safety was identified between 1.0 mmol and 2.0 mmol because doses as low as 2.0 mmol resulted in serious adverse events with similar severity to those occurring at higher doses (eg, 10 mmol). To more accurately assess the dose-dependent relationship between intrathecal GBCAs and adverse events, randomized controlled trials or prospective studies with intrathecal GBCA-specific control groups are required to minimize the influence of potential confounding variables, including differing patient populations, indications, doses, and rates of administration of varying GBCAs. Because of the ethical constraints associated with administration of an off-label substance, it would be difficult to conduct randomized controlled trials to assess intrathecal GBCA safety. We believe that the information from our study will be valuable for informed decision making regarding intrathecal GBCA procedures during physician and patient discussions, and we hope this will serve as a basis for further studies investigating intrathecal GBCA safety.

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