AMERICAN UNIVERSITY OF BEIRUT

DO GADOLINIUM BASED CONTRAST AGENTS CAUSE PAIN? A SYSTEMATIC REVIEW

by
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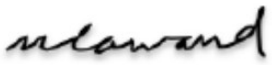

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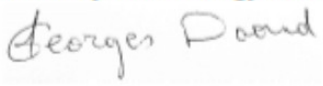

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ABSTRACT
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Title: Do Gadolinium Based Contrast Agents Cause Pain? A Systematic Review

Introduction: Gadolinium based contrast agents (GBCAs) are FDA approved compounds used to enhance the quality of magnetic resonance imaging (MRI). These chemicals shorten the T1 and T2 relaxation times of the adjacent hydrogen nuclei, and consequently improve the characterization of different pathologies. More than 30 million doses of GBCAs are administered annually worldwide; however, despite the advantages of these paramagnetic pharmaceuticals, many studies have described high signal intensity in the Globus Pallidus and Dentate Nucleus on unenhanced T1-weighted images, indicating residual gadolinium deposition in the brain parenchyma. Our previous studies have provided the first evidence of Gd deposition in the peripheral nervous system. This evidence of Gadolinium retention in nerves raised significant concerns regarding the toxicity of GBCAs and its long-term impact on the sensory system. This systematic review combines data from multiple papers to study the effect of repeated gadolinium based contrast agents (exposure to GBCAs or gadolinium deposition) on pain development (including central torso pain, arm or leg pain, bone pain, joint pain, pain, chronic pain, myalgia, musculoskeletal system pain, and burning sensation) in patients with normal renal function.

Methods: Our search strategy, using Medline, Embase, Cochrane library, Web of science, Google scholar, and Grey Literature, yielded a total of 14 studies, which include 1 randomized controlled trial (RCT), 7 cohort studies, 1 case series and 5 case reports. Only patients with normal renal function were included in this study; those with central or peripheral nervous system lesions were excluded. Data were extracted directly from the selected articles and organized in standardized tables by one investigator and verified by a second. Risk of bias was assessed using Newcastle-Ottawa Quality Assessment Scale criteria for non-randomized studies and Cochrane risk of bias assessment for RCTs. Meta-analysis was not conducted because only one RCT and because of the high risk of bias in all 14 studies.

Conclusion: This is the first systematic review of the literature concerning the impact of GBCAs on acute and chronic pain development in patients with normal renal function. Reports of pain induced by GBCAs have been documented in many studies; however, the magnitude of association between GBCAs and pain requires further study.

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CHAPTER 1

INTRODUCTION

1.1. Gadolinium Based Contrast Agents (GBCAs): Definition and Uses

Gadolinium based contrast agents (GBCAs) are intravenous agents consisting of a toxic lanthanide heavy metal Gadolinium(III) (Gd^{3+}) , a polydentate ligand (a carrier molecule), and one or more water ligands (Caravan et al., 1999). They are nine-coordinate complexes in which eight coordination sites at the metal center are occupied by the polydentate ligand and the ninth binding site is occupied by a solvent water molecule (Caravan et al., 1999). GBCAs are used for contrast enhancement with magnetic resonance imaging (MRI) and with magnetic resonance angiography (MRA) (Agency, 2010). They improve structural visualization, enhance lesions' visibility, and provide information on tissue perfusion (Ponrartana et al., 2021).

1.2. GBCAs: Types and Properties

The commercially available GBCAs can be classified into four different groups based on the type of ligand (linear or macrocyclic) and charge (ionic or nonionic) (Dekkers, Roos, & van der Molen, 2018). The four different types are: linear ionic, linear non-ionic, macrocyclic ionic, and macrocyclic non-ionic (Frenzel, Lengsfeld, Schirmer, Hütter, & Weinmann, 2008). Linear GBCAs are formed of flexible, not fully closed cages that wrap around the Gd^{3+} ion (gadolinium ion is bound to an open-chain ligand), while macrocyclic GBCAs are formed of a rigid, fully closed cage of a cubic chemical structure including a preorganized cavity for Gd^{3+} ion (gadolinium ion is bound to a closed-chain ligand) (Idée et al., 2006) (Frenzel et al., 2008) (Dekkers et al., 2018). The four different groups have different thermodynamic and kinetic stability due

to differences in the chemical structure of the ligands, by which the ionic macrocyclic chelates are the most stable and the non-ionic linear chelates are the least stable (Dekkers et al., 2018).

1.3. Gadolinium Deposition in Tissues

Gadolinium deposition is evidenced by high signal intensity on unenhanced T1-weighted images and brain histological analysis. The association between previous GBCAs administrations and T1 hyperintensity in deep brain has become a hot topic since 2014. Many human studies on adults reported high signal intensity (SI) in the dentate nucleus (DN) and globus pallidus (GP) on unenhanced T1-weighted images as a consequence of repeated exposure to linear GBCAs (Kanda, Ishii, Kawaguchi, Kitajima, & Takenaka, 2014) (Errante et al., 2014) (Weberling et al., 2015) (Zhang, Cao, Shih, Hecht, & Prince, 2017) (Kuno et al., 2017), indicating gadolinium retention in the brain. Increased SI was seen not only in the DN and GP but also in the posterior thalamus, substantia nigra, red nucleus, cerebellar peduncle, and colliculi (Zhang et al., 2017) (Kuno et al., 2017). Moreover, in pediatric patients, the same findings were described (Miller, Hu, Pokorney, Cornejo, & Towbin, 2015) (Roberts & Holden, 2016) (Hu, Pokorney, Towbin, & Miller, 2016) (Roberts, Chatterjee, et al., 2016) (Flood, Stence, Maloney, & Mirsky, 2017). Although numerous studies have linked linear GBCAs to gadolinium deposition in the human brain, others have found that macrocyclic chelate GBCAs can also cause T1 hyperintensity in the brain both in adults (Stojanov, Aracki-Trenkic, Vojinovic, Benedeto-Stojanov, & Ljubisavljevic, 2016) (Bjørnerud et al., 2017) and pediatrics (Rossi Espagnet et al., 2017). Brain histological analysis verifies gadolinium accumulation in the brain of subjects exposed repeatedly to GBCAs (R. J.

McDonald et al., 2015) (Kanda et al., 2015) (Murata et al., 2016) (R. J. McDonald, McDonald, Kallmes, et al., 2017).

GBCAs can be retained not only in the brain but also in the bone, skin, liver, peripheral nervous system, spinal cord, etc., which is confirmed by both human and animal studies. Introduced in chelated form, Gd is confirmed to be incorporated into bone and retained for more than 8 years (Darrah et al., 2009). Moreover, it is shown that Gadolinium can accumulate in the bone and retain for 5 years after only one dose of GBCA in healthy subjects (Lord, Chettle, Gräfe, Noseworthy, & McNeill, 2018). Interestingly, histological analysis demonstrated that gadolinium deposition occurs in the bone at 23 times higher levels than in the brain (Murata et al., 2016). Extremely high cumulative doses of GBCAs caused significant gadolinium deposition in the skin of one patient with normal renal function (Roberts, Lindhorst, et al., 2016). Pediatric patients with iron overload but normal renal and hepatic function developed liver gadolinium deposition after receiving GBCA (Maximova et al., 2016). Following the administration of high dosages of GBCAs, the rat models demonstrated that elemental gadolinium was accumulated in hepatic, splenic, and renal tissues in significantly high levels, even though no tissue injury was detected in these organs (R. J. McDonald, McDonald, Dai, et al., 2017). Furthermore, exposure of rats to multiple doses of linear and macrocyclic GBCAs lead to gadolinium deposition in their spinal cords and peripheral nerves (Alkhunizi, Fakhoury, Abou-Kheir, & Lawand, 2020).

1.4. Side Effects: Gadolinium Toxicity

1.4.1. Causes and Mechanisms of Toxicity

To understand the clinical significance of brain and other tissue gadolinium deposition, it is better to understand the mechanisms associated with the development of gadolinium toxicity. The ability of GBCAs to liberate free Gd^{3+} ions, which depends on their kinetic and thermodynamic stability, determines their toxicity (Idée et al., 2006) (Port et al., 2008). First, the role of transmetallation is one of the leading theories for gadolinium toxicity. Transmetallation is a mechanism whereby endogenous metals such as zinc (Zn) and iron (Fe) attract the ligand, causing Gd^{3+} dissociation from the complex, which then deposits in the tissue as gadolinium phosphate (Swaminathan, 2016). Second, the size of free Gd^{3+} is similar to that of $Ca^{2+}$and this can bring about competitive inhibition of biological mechanisms that require $Ca^{2+}$and cause toxicity. For instance, the binding of Gd^{3+} to Ca^{2+} binding enzymes disturbs the function of voltage-gated calcium channels, leading to adverse biological effects (Sherry, Caravan, & Lenkinski, 2009). Third, the release of Gd^{3+} stimulates the release of chemokines, which subsequently attract CD34+ fibrocytes causing fibrosis (Del Galdo, Wermuth, Addya, Fortina, & Jimenez, 2010; Idee, Fretellier, Robic, & Corot, 2014). Fourth, the expression and release of the cytokines involved in the development of tissue fibrosis are stimulated by gadodiamide and gadopentetate (Newton & Jimenez, 2009). Fifth, GBCAs induce fibroblasts to elevate the expression of type I and II collagen and monocytes to increase the expression of a number of profibrotic chemokines and cytokines: IL-4, IL-6, IL-13, and VEGF (Wermuth & Jimenez, 2014). Sixth, gadodiamide induces the expression of fibronectin in fibroblasts and lead to both fibroblasts' apoptosis and necrosis. Moreover, GBCAs induces CD34 and procollagen

type I fibrocyte markers (Semelka, Ramalho, Vakharia, et al., 2016). Seventh, administration of GBCAs induces iron mobilization and peripheral blood mononuclear cells differentiation into ferroportin-expressing fibrocytic cells, indicating iron participation in GBCA-toxicity mechanisms (Bose et al., 2015). Eighth, treating alveolar macrophages with gadolinium trichloride causes apoptotic cell death (Mizgerd, Molina, Stearns, Brain, & Warner, 1996). Moreover, gadolinium may elevate the levels of reactive oxygen species (ROS), which subsequently induces apoptosis in hepatocytes, demonstrating a role of ROS in gadolinium-induced toxicity (Liu, Yuan, Yang, & Wang, 2003). Ninth, oxidative injury and endoplasmic reticulum (ER) stress-related signal transduction in neurons are induced by gadolinium chloride treatment, leading to reduction in neuron cell viability and disruption of intracellular calcium homeostasis (Xia et al., 2011). Finally, gadolinium stimulates angiotensin II AT1 receptors, which subsequently blocks ATP and ADP hydrolysis (Angeli et al., 2011).

1.4.2. Acute Adverse Reactions

Acute adverse reactions to GBCAs are separated by the American College of Radiology (ACR) Manual on Contrast Media into two types: physiological (non-allergic-like) and allergic-like (anaphylactoid) ("American College of Radiology (2020) Manual on contrast media," 2020). Physiological acute reactions probably affect structures such as heart, blood vessels, and the brainstem. They result in fleeting symptoms including nausea, vomiting, arrhythmia, vasovagal reaction, flushing sensation, chest pain, coolth, heat sensation, altered (metallic) taste, dizziness and headaches, among others. Allergic-like acute reactions are anaphylactoid as they are mediated by mast cell degranulation and the release of histamine and can cause

urticaria, pruritus, cutaneous edema, “itchy” or “scratchy” throat, laryngeal edema, anaphylactic shock, bronchospasm, etc. (Dillman, Trout, & Davenport, 2018).

Acute physiological and allergic-like reactions are separated into three categories according to their severity: mild, moderate, and severe reactions ("American College of Radiology (2020) Manual on contrast media," 2020). Mild reactions are self-limiting in general. For instance, limited nausea and vomiting, headache and dizziness are mild physiological acute reactions and limited urticaria, pruritus, and limited cutaneous edema are allergic-like acute reactions. Moderate reactions need treatment to avoid progression. For example, protracted nausea and vomiting, and vasovagal reaction that requires treatment are moderate physiological acute reactions and diffuse urticaria and pruritus, throat tightness or hoarseness with dyspnea are moderate allergic-like reactions. Severe reaction can be fatal, so immediate and appropriate treatment is a necessity. To illustrate, treatment-resistant vasovagal reaction, convulsions and seizures are severe physiological acute reactions and anaphylactic shock, laryngeal edema with hypoxia, and facial edema with dyspnea are severe allergic-like acute reactions (Dillman et al., 2018; Ponrartana et al., 2021).

Acute adverse reactions are rare and usually occur within 60 min of GBCA administration. The incidence has been reported to be between 7 and 240 per 10,000 doses ("American College of Radiology (2020) Manual on contrast media," 2020). The overall rates of allergic-like reactions were found to be 9.2 per 10,000 administrations in a large meta-analysis including nine GBCA studies with 716,978 cumulative doses. Allergic-like reactions were distributed as follows: 81 percent mild, 13 percent moderate, and 6 percent severe reactions (Behzadi, Zhao, Farooq, & Prince, 2018). According to a large institutional retrospective study of GBCA acute reactions, higher

rates of physiological reactions are caused by gadoterate meglumine, gadobenate dimeglumine and gadobutrol compared to gadodiamide. Moreover, higher rates of allergic-like reactions are caused by gadobenate dimeglumine and gadobutrol compared to gadodiamide or gadoterate (J. S. McDonald et al., 2019). However, acute adverse reactions' rates in pediatrics are not much known. Pediatric allergic-like reaction frequency was 0.04 percent (6 allergic-like reactions per 13,344 pediatric) in a single-institution retrospective study (Dillman, Ellis, Cohan, Strouse, & Jan, 2007). A second single-institution retrospective study found that the frequencies of allergic-like reactions among different GBCAs are not significantly different (Forbes-Amrhein et al., 2018). Physiological reactions in pediatrics are greater than allergic-like reactions, but the exact frequencies of physiological reactions are unknown (Dillman et al., 2018).

1.4.3. Chronic Adverse Reactions

1.4.3.1. Nephrogenic Systemic Fibrosis (NSF)

Nephrogenic systemic fibrosis (NSF) is a rare, progressive, life-threatening, scleroderma-like disease that occurs in patients with advanced renal insufficiency following administration of GBCAs (Thomsen, Morcos, & Dawson, 2006). It is hypothesized that the pathophysiology of NSF is due to Gd^{3+} dissociation from its ligand. The dissociated Gd^{3+} undergoes competitive inhibition of Ca^{2+} binding enzymes and precipitates as gadolinium phosphate (Cowper, Bucala, & Leboit, 2006; Swaminathan et al., 2007), stirring up an exaggerated fibrotic response (Wagner et al., 2012). Exaggerated fibrosis, as a result of fibroblasts accumulation in tissues and production of large amounts of collagen, causes the appearance of papules and nodules in the skin and causes fibrosis of joints, muscles, liver, lungs, kidneys and heart, among

others (Agency, 2010; Attari, Cao, Elmholdt, Zhao, & Prince, 2019; Thomsen et al., 2006).

In January 2006, NSF association with the GBCAs was first reported when five patients of end-stage renal failure developed NSF signs two to four weeks after Gadolinium-enhanced MRA. Then 25 patients with severe renal insufficiency developed NSF after their exposure to gadodiamide (Agency, 2010). A systematic review of reported NSF cases found that, after 2008, seven patients out of 639 patients with biopsy-confirmed NSF were linked to GBCA exposure (Attari et al., 2019).

The degree of renal impairment has been linked to the risk of developing NSF. Patients who have stages 4–5 chronic kidney disease, have acute kidney injury, or are dialysis-dependent account for most of NSF cases reported(Abu-Alfa, 2011). In addition, the risk of developing NSF correlates with the specific type of administered GBCA. Most NSF cases have been reported after exposure to linear nonionic agents. This is because of the low thermodynamic stability of these agents compared to other GBCAs, fostering Gd^{3+} dissociation from its ligand. FDA reporting data shows that gadodiamide, a linear nonionic agent, accounts for 70 percent of NSF unconfounded cases, gadopentetate, a linear ionic agent, accounts for 25 percent of cases, and gadoversetamide, a linear nonionic agent, accounts for 4.8 percent of cases (Krefting, 2011). On the other hand, two NSF cases have been associated with gadoteridol (a macrocyclic nonionic agent), two cases have been associated with gadobutrol (a macrocyclic nonionic agent), and one case has been associated with possible gadoterate meglumine (a macrocyclic ionic agent) (Agency, 2010).

1.4.3.2. Gadolinium-Associated Plaques (GAPs)

Researchers have proposed the term "gadolinium-associated plaques" (GAPs) to characterize sclerotic bodies with calcification in the skin, associated with the exposure of patients with chronic renal disease to gadolinium. Sclerotic bodies are plaques or hardened tissue that is formed as a result of an immune system response to a foreign body (Fox-Rawlings & Zuckerman, 2020). They are eosinophilic, collagen-based, round to oval structures with ensnared elastic fibers (Bhawan, Perez-Chua, & Goldberg, 2013). Generally, these plaques have been reported in NSF patients due to repeated exposure to GBCAs (Bhawan, Swick, Koff, & Stone, 2009; Kartono, Basile, Roshdieh, Schwimer, & Shitabata, 2011). Conversely, four patients without NSF developed these plaques and have been described in a number of case reports. In case one, a patient with no renal disease developed erythematous plaques with itching and burning after exposure to high doses of gadodiamide (omniscan). In case two, a patient with renal disease, but without any other symptoms characteristic of NSF, developed tan-brown plaques that were asymptomatic, after gadodiamide administration as well (Gathings, Reddy, Santa Cruz, & Brodell, 2015). In case three, sclerotic bodies were reported in a squamous cell carcinoma (SCC) re-excision specimen from the forearm of a patient with chronic renal dysfunction (Bhawan et al., 2013). In case four, sclerotic bodies with entrapped elastic fibers and CD34 positivity were demonstrated in a patient with renal disease, which is consistent with cutaneous reaction to gadolinium (Olayiwola, Ronkainen, Miller, High, & Farah, 2019).

1.4.3.3. Gadolinium Deposition Disease (GDD)

Patients with normal renal function have been reported to develop some or many of the NSF symptoms. Researchers have proposed the term "gadolinium deposition disease" for a disease process observed in patients with normal or nearby-normal renal function who develop long-term symptomatology several hours to two months following GBCA administration, with no alternative pre-existing or newly developed diseases and causes that present to explain the symptomatology (Fox-Rawlings & Zuckerman, 2020; Semelka, Ramalho, AlObaidy, & Ramalho, 2016). Many of GDD symptoms are similar to NSF symptoms but not identical, and they are less severe. Bone pain, joint pain and persistent headache are typical clinical features of GDD. Moreover, pain in tendons and ligaments and their thickened appearance are considered a GDD symptom. Intense pain in arms and legs, torso pain and generalized pain are also common symptoms of GDD, and it is described as a burning sensation or sensation of uncomfortable tingling or prickling (sharp pins and needles) or as feeling like cutting. In addition, stiffness in hands and feet that resembles the feeling of wearing extremely tight gloves or stockings might be experienced by patients. Brain fog- a clouded mentation- is also complained frequently by patients, and it is not considered one of the NSF symptoms. Finally, thickening of the subcutaneous soft-tissue, a deep tissue layer, and its spongy or rubbery appearance is often experienced by patients. This spongy tissue is similar to that observed in NSF but without being rigid and red (Fox-Rawlings & Zuckerman, 2020; Semelka, Ramalho, AlObaidy, et al., 2016).

1.4.3.4. Pain

Pain, most in the extremities, is reported in patients with normal renal function after exposure to GBCAs. Many studies reported cases of patients who developed pain symptom including arthralgia, myalgia, burning sensation, and fibromyalgia after exposure to GBCAs (Takebayashi, Sugiyama, Nagase, & Matsubara, 1993; Wexler & Spencer, 1993) (Prieto-García et al., 2017) (Boehm et al., 2018) (Lattanzio & Imbesi, 2020). In 2016, one study reported four patients with normal renal function who developed central torso pain and arm or legs pain following administration of GBCAs (Semelka, Commander, Jay, Burke, & Ramalho, 2016). This study grasped researchers' attention onto the possibility of developing symptomatology due to gadolinium toxicity and deposition in patients with normal renal function. Thus, it is followed by two online surveys completed by patients who self-reported normal renal function and who complained of bone/joint pain, central torso pain and arm or legs pain, believing it is linked to gadolinium toxicity (Burke et al., 2016) (Semelka, Ramalho, Vakharia, et al., 2016). In addition, a recent animal study found that multiple injections of gadodiamide, a linear GBCA, causes pain hypersensitivity to thermal and mechanical stimuli (Alkhunizi et al., 2020).

1.5. Aim of the Study

This systematic review aims to combine data from multiple papers to study the effect of repeated gadolinium based contrast agents exposure and gadolinium deposition on pain development-including some of symptoms that have been proposed in the debated definition of gadolinium deposition disease (GDD)- in patients with normal renal function. The outcomes of this systematic review are: central torso pain, arm or

leg pain, bone pain, joint pain, generalized pain, chronic pain, fibromyalgia, myalgia, musculoskeletal system pain, and burning sensation.

CHAPTER 2

DATA AND METHODS

We developed the protocol of this systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance ("PRISMA TRANSPARENT REPORTING of SYSTEMATIC REVIEWS and META-ANALYSES," 2021). The protocol has been published in the PROSPERO registry, and its registration number is: CRD42020215864. The PRISMA checklist outlines recommendations for reporting systematic reviews, ensuring transparency. It includes 7 sections: title, abstract, introduction, methods, results, discussion, and other information, and each section is divided into checklist items ("PRISMA TRANSPARENT REPORTING of SYSTEMATIC REVIEWS and META-ANALYSES," 2021) (see Appendix 1 for a checklist of items to include while reporting a systematic review and meta-analysis, taken unchanged from the PRISMA 2020 checklist).

2.1. Eligibility Criteria

2.1.1. Type of studies

2.1.1.1. Inclusion criteria:

- Human studies
- No restriction on publication date eligible for inclusion
- No restriction on countries eligible for inclusion
- No restriction on languages eligible for inclusion
- Randomized controlled trials (RCTs), non-randomized studies, case reports and case series

2.1.1.2. Exclusion criteria:

- Animal studies

2.1.2. Type of participants

2.1.2.1. Inclusion criteria:

- Patients with normal renal function
- No restriction on age eligible for inclusion
- No restriction on sex eligible for inclusion
- No restriction on socio-demographic characteristics eligible for inclusion

2.1.2.2. Exclusion criteria:

- Patients with central or peripheral nervous system (CNS or PNS) lesions

2.1.3. Type of intervention

2.1.3.1. Inclusion criteria:

- Intravenous injection
- No restriction on GBCA type eligible for inclusion
- No restriction on the number of GBCA injections eligible for inclusion (at least one injection)

2.1.3.2. Exclusion criteria:

- Intrathecal injection
- Intramuscular injection

2.1.4. Outcomes

- Pain related or possibly related to GBCA exposure
- Types of pain include: central torso pain, arm or leg pain, bone pain, joint pain (arthralgia), myalgia, musculoskeletal system pain, general pain, chronic pain, fibromyalgia, and burning sensation.
- No restriction on onset of symptoms eligible for inclusion

2.2. Data Sources and Searches

We searched MEDLINE, EMBASE, The Cochrane Library (Cochrane Central Register of Controlled Trials (CENTRAL)), Web of Science, Google Scholar databases, and Grey literature including World Health Organization (WHO) and OpenGrey from October 1, 2020 to 22 January 2021. The search strategy included a combination of database-specific subject headings and keywords related to pain and gadolinium (appendix 2). The search terms were adapted for use with other bibliographic databases. There were no search limitations regarding year of publication.

2.3. Study Selection

We included studies that documented exposure to GBCAs; assessed pain development after GBCA exposure; and had one of the following study designs: randomized controlled trials, non-randomized studies on intervention effects (NRSI), cohort studies, and case reports.

Titles and/or abstracts of studies were retrieved using the search strategy and those from additional sources were screened independently by two review authors to identify studies that potentially met the inclusion criteria. The full texts of these

potentially eligible studies were retrieved and independently assessed for eligibility by two review team members. Any disagreement between them over the eligibility of particular studies was resolved through discussion with a third reviewer.

2.4. Data Extraction

A standardized, pre-piloted form was used to extract data from the included studies for assessment of study quality and evidence synthesis. Extracted information included: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control conditions; study methodology; outcomes and times of measurement; information for assessment of the risk of bias. Two review authors extracted data independently, discrepancies were identified and resolved through discussion (with a third author where necessary).

2.5. Data Synthesis

We provided a narrative synthesis of the findings from the included studies, structured around the type of intervention, target population characteristics, type of outcome and intervention content.

2.6. Risk of Bias (Quality) Assessment

Two reviewers performed risk of bias assessments independently. We used the Cochrane risk of bias tool for randomized controlled trials, which includes seven domains: random sequence generation, allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting

(reporting bias) and other bias. We used Newcastle Ottawa scale for non-randomized studies, which includes three categories: selection, comparability, and outcome. Selection includes 4 domains: representativeness of exposed cohort, selection of the non-exposed cohort from same source as exposed cohort, ascertainment of exposure, and outcome of interest was not present at start of study, and a maximum of four stars can be allotted in this category (a maximum of one star per domain); comparability incudes one domain: comparability of cohorts, and a maximum of 2 stars can be allotted in this category; outcome includes three domains: assessment of outcome, follow-up long enough for outcome to occur, and adequacy of follow-up, and a maximum of three stars can be allotted in this category. Disagreements between the review authors over the risk of bias in particular studies were resolved by discussion, with involvement of a third review author where necessary. We did not assess the risk of bias for case reports due to unavailability of validated tools.

2.7. Certainty of Evidence Assessment

We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology to assess the certainty of evidence of pain outcome. To rate the certainty of evidence, GRADE accounts for study design, risk of bias, inconsistency, indirectness, imprecision and other considerations. RCTs provide high certainty of evidence when there are no important limitations. Limitations downgrade the certainty of evidence of RCTs into moderate or low. However, observational studies provide low certainty of evidence when there are no special strengths or important limitations. Special strengths upgrade observational studies' certainty of evidence into moderate or high quality and limitations downgrade it into very low.

CHAPTER 3

RESULTS

The search strategy identified a total of 6,635 citations (Figure 1). After duplicate removal, 5,020 citations remained for title and abstract screening. We excluded 4943 citations, and we identified 77 citations as eligible. Six citations were not retrieved because we could not find the full text. We retrieved and screened the full text of the remaining 71 citations. After full text screening, we excluded 57 articles for the following reasons: outcome of interest not measured (30 studies), review articles (12 studies), outcome is not drug related (three studies), different intervention (intrathecal injection) (8 studies), central nervous system lesions (two studies), renal insufficiency (one study), hypothesis (one study) (Figure 1).

14 papers were identified fulfilling our inclusion criteria and these are summarized in Table 1. Therefore, our systematic review included the following: seven cohort studies, one case series, five case reports, and one RCT.

We summarize the characteristics and findings of included studies as follows

3.1. Bone pain, joint pain, musculoskeletal system pain, central torso pain and legs or arm pain

Four cohort studies and four case reports assessed this outcome. One case series by Semelka et al. examined and reported four patients who developed symptomatology within hours to four weeks of having received an intravenous administration of GBCA. Both at the time of clinical evaluation and at the time of GBCA exposure, all patients exhibited normal renal function. Two patients were exposed one time, one patient exposed four times, and one patient was exposed six times to GBCAs. The youngest

patient was 29 years old and the oldest one was 58 years old. Two patients were assessed in an early stage, at two months and at three months, and two patients were assessed in a late stage, at seven years and at eight years after the last GBCA administration. Three patients developed symptoms within 24 hours of GBCA exposure, while the fourth developed symptoms after two to three weeks of exposure. At least one month following the GBCA-enhanced MRI, all four patients showed detectable quantities of gadolinium in their blood serum, urine, hair, and/or skin. Moreover, all four patients had central torso pain as well as peripheral arm and leg pain, which were still present at the time of clinical evaluation (Semelka, Commander, Jay, Burke, & Ramalho, 2016).

Similar symptomatology was reported by two studies of patients recruited from two online gadolinium toxicity support groups. The two anonymous online surveys were conducted by the same research group; the nine-question survey asked about general symptoms, while the 18-question survey asked more detailed questions about symptoms.

50 participants completed the first nine-question survey by Burke et al., describing their complaints to gadolinium exposure. An average of 4.2 doses (range between one and 23 contrast-enhanced MRIs) of intravenous GBCAs had been administered by all 50 patients. All 50 patients self-reported normal renal function. Different tests and methods to detect gadolinium in various tissues after exposure to GBCAs were undergone by 45 patients including: 31 patients had urine test, five patients had blood test, four patients had hair test, three patients had skin test, one patient had thyroid test, and one patient had breast biopsy test. 66 percent (33 patients), 32 percent (16 patients), and two percent of patients (1 patient) reported onset of

symptoms immediately, within six weeks, and six months following GBCA exposure, respectively. Moreover, 78 percent of patients (38 patients) reported bone and/or joint pain, which are two of the most common complaints (Burke et al., 2016).

A total of 42 participants completed the second 18-question survey by Semelka et al., describing clinical features assumed to be associated with gadolinium toxicity, following intravenous administration of GBCAs. 14 men, 27 women and one did not specify with an age ranged from 28 to 69 years responded to this survey. All 42 patients reported normal renal function. One patient had a history of kidney dysfunction long time preceding his/her MRI. However, this patient had normal renal function at the time of his/her MRI. Testing the urine of 41 participants and the thyroid tissue of one participant evidenced the presence of gadolinium at least one month following GBCA administration. Moreover, eight patients had elevated gadolinium in blood, two patients in skin, two patients in hair, one patient in scalp, and one patient in thyroid tissue (Semelka, Ramalho, Vakharia, et al., 2016).

The symptoms started after multiple administrations of GBCAs in 21 participants and after a first-time exposure in 21 participants as well. Pain lasted for less than three months (considered as acute pain) and pain lasted at least for three months and persisted to the time of the survey (considered as chronic pain) were assessed in the 42 patients. For less than three months, six, nine, and seven patients reported central pain, peripheral pain, and bone pain, respectively. Beyond three months and to the time of the survey, 15, 26, and 26 patients reported central pain, peripheral pain and bone pain, respectively. Different types of pain were described often by the same patient. 25 patients, 15 central and 10 peripheral, described their pain as sharp or as “pins and needles”. Furthermore, 15 patients, 10 central and five peripheral, described their pain

as intense burning. With time, 20 patients experienced shifting of pain from central to peripheral, and the description of pain changed to an intense burning in all 10 patients who had peripheral limb pain from the beginning. In general, at the time of the survey, 74 percent of patients (31 patients) still had pain described as residual pain. In addition, bone pain, both as acute and chronic, was reported in total of 33 patients (78.6 percent), which is consistent with the results of Burke et al.'s survey (78 percent bone pain) (Semelka, Ramalho, Vakharia, et al., 2016).

A third study published in 2019 by Parillo et al. investigated the incidence of symptoms reported by Semelka et al. (Semelka, Commander, et al., 2016; Semelka, Ramalho, Vakharia, et al., 2016) and Burke et al. (Burke et al., 2016), including central torso pain, arm or leg pain, and bone pain, among others, within 24 hours following the intravenous exposure to GBCAs. This prospective cohort study included 1088 patients subdivided into two groups: 481 patients out of 1088 (44.2 percent) underwent unenhanced MRI (uMRI) (uMRI group) and 607 patients out of 1088 (55.8 percent) underwent enhanced MRI (eMRI) (eMRI group). The eMRI group is further subdivided into two groups: 241 patients out of 607 (39.7%) administered gadodiamide (Omniscan) (eMRI gadodiamide group) and 366 patients out of 607 (60.3%) administered gadoterate meglumine (Dotarem) (gadoterate meglumine group). The same structured survey was given to each patient before and 24 hours after the MRI scan so that only new onset symptoms after the MRI scan can be extracted and analyzed and symptoms present before MRI can be excluded. The age of patients in the uMRI group, eMRI gadodiamide group, and eMRI gadoterate meglumine group ranged from 17 to 88, 18 to 86, and 17 to 90, respectively (Parillo et al., 2019).

Three patients (1.2 percent) in the eMRI gadodiamide group and three patients (0.8 percent) in the eMRI gadoterate meglumine group reported central torso pain, giving a total of six patients (1.0 percent) in the eMRI group compared to two patients (0.4 percent) in the uMRI group. One patient (0.4 percent) in the eMRI gadodiamide group and four patients (1.1 percent) in the eMRI gadoterate meglumine group reported legs or arm pain, giving a total of five patients (0.8 percent) in the eMRI group compared to one patient (0.2 percent) in the uMRI group. Zero patients in the eMRI gadodiamide group and one patient (0.3 percent) in the eMRI gadoterate meglumine group reported bone pain, giving a total of one patient (0.2 percent) in the eMRI group compared to one patient (0.2 percent) in the uMRI group. For central torso pain and legs or arm pain, the percentage of reported cases in the eMRI is greater than that in the uMRI; however, for bone pain, the percentages are equal (Parillo et al., 2019).

The percentages of patients reported central torso pain and legs or arm pain, 1.0 percent and 0.8 percent, following exposure to GBCAs are much lower than the percentages reported by Semelka et al. for central and peripheral pain lasted for less than three months, 14.3 percent and 21.4 percent. Furthermore, the percentage of patients reporting bone pain was 0.2 percent in both eMRI and uMRI, contradicting the very high percentages of bone pain reported in Burke et al. and Semelka et al. studies, 78 percent and 78.6 percent respectively.

A previous study published in 2014 by Azzouz et al. investigated the prevalence of late and very late adverse reactions in patients who underwent eMRI and uMRI. A total of 669 patients underwent MRI scan: 253 patients administered gadoterate meglumine representing the eMRI group, and 416 patients served as MRI control group (uMRI). The age of patients in the eMRI group and uMRI group ranged from 18 to 96

years and from 23 to 89 years, respectively. To document the late adverse events (LAEs) and very late adverse events (VLAEs), the patients were contacted three days and one month, respectively, after MRI examination, using the same questionnaire. Three days after MRI examination, three percent of patients (eight patients out of 253) in the eMRI group reported musculoskeletal system pain (bone or joint or muscle pain) and same percentage was reported in the uMRI group (12 patients out of 416). Similarly, one month after MRI examination, both eMRI group and uMRI group reported the same percentage (five percent) of patients who developed musculoskeletal system pain (eMRI: nine patients and uMRI: 16 patients) (Azzouz, Rømsing, & Thomsen, 2014).

The percentages of musculoskeletal system pain reported in the late and very late periods are equal in both eMRI and uMRI groups. This result is consistent with the findings of Parillo et al. regarding bone pain, questioning the association between GBCA administration and the development of bone pain or musculoskeletal pain in general. However, comparing groups exposed to GBCAs, it is found that the percentages documented in this study (three percent and five percent) are higher than the percentage reported for bone pain in Parillo et al. study (0.2 percent). At the same time, these percentages are much lower than those reported by Burke et al. (78 percent) and Semelka et al. (78.6 percent) for bone/joint pain.

Finally, beside the musculoskeletal system pain including muscle pain assessed by Azzouz et al., a case report by Prieto-García et al. described a fatal anaphylaxis including complaint of myalgia (muscle pain) by gadolinium. A 64 year old female with no previous exposure to GBCAs and with no history of drug allergy, asthma, or atopy

complained of myalgia two minutes following intravenous administration of gadobenate dimeglumine (MultiHance) (Prieto-García et al., 2017).

In 1993, two case reports documented arthralgia (joint pain) development after exposure to GBCAs. Wexler and Spencer reported a case of a 23 years old female patient with no history of drug allergy or anaphylaxis and with no previous reaction to any contrast who developed generalized arthralgia (joint pain) few hours after intravenous injection of gadopentetate dimeglumine during MRI examination. Arthralgia was transient and mainly affected her knees, elbows and wrists as she felt moderate pain while moving her major joints, especially the elbows (Wexler & Spencer, 1993). A second report by Takebayashi et al. described arthralgia development, among other symptoms, in a 29 years old female patient who had injected intravenously with gadopentetate dimeglumine, even though she had no previous reaction to contrast agents and had no allergy to certain drugs (Takebayashi et al., 1993).

3.2. General pain

This outcome was assessed by two cohort studies and one case report. An open-label (non-blinded), prospective post-marketing surveillance study published in 1995 by Nelson et al. investigated the safety of gadopentetate dimeglumine and reported pain- acute general pain- as one of the symptoms complained by patients after eMRI. 15,496 patients with an average age ranged from less than one year to 101 years had intravenous injection of 0.1 mmol/kg gadopentetate meglumine. 45.5 percent and 28.0 percent of this cohort were exposed previously to iodinated contrast agents and GBCAs, respectively. Moreover, 24.9 percent had a history of allergy and 5.4 percent had a history of asthma. Onset of symptoms occurred within 30 minutes and more than one

hour after administration were reported. 21 patients out of 15,496 (0.14 percent) complained of pain (Nelson, Gifford, Lauber-Huber, Gross, & Lasser, 1995).

A study published in 2019 by Young et al. investigated the onset of chronic pain, among other outcomes, as an effect of presumed toxicity to gadoteric acid (Dotarem). This study included a total of 37,813 and 1,265 contrast-enhanced and unenhanced scans performed on a cohort of 21,770 adult patients and 698 pediatric patients, respectively. 22,325 of scans performed on adults and 572 performed on pediatrics were contrast-enhanced. 14 percent and nine percent of the contrast-enhanced scans were performed on renally insufficient adults and pediatrics, respectively. In the adult cohort, all patients described onset of chronic pain had normal renal function at the time of exposure to gadoteric acid. A total of 10 cases (0.026 percent) reported chronic pain onset: seven cases (0.019 percent) were contrast-enhanced scans and three were unenhanced scans (0.007 percent). The rate of chronic pain onset in contrast-enhanced scans was not significantly higher than that in unenhanced scans ($p = 0.777$). Similarly, in the pediatric cohort, the rate of chronic pain onset did not differ significantly between contrast-enhanced and unenhanced scans (Young, Matthew, & Houston, 2019).

A case report published by Lattanzio and Imbesi in 2020 tried to link gadolinium deposition to fibromyalgia, a chronic generalized pain. A 30 year-old female developed gadolinium toxicity related symptoms and signs including pain after repeated exposure to GBCA, Gadovist. This patient complained of osteoarticular lumbar pain, hip pain, onset of pain at the right shoulder and trapezium, pain at knees, and severe exacerbation of lumbar aches, among many other symptoms. The symptoms started and developed in

a subsequent manner following multiple administrations of GBCAs. Finally, her diagnosis with fibromyalgia was confirmed (Lattanzio & Imbesi, 2020).

3.3. Burning sensation

One RCT**,** one cohort study and one case report assessed this outcome. In a study published by Bosch et al. in 2008, one of the objectives was to report adverse reactions including burning sensation experienced by patients after exposure to different doses of the GBCA gadofosveset. This study included 185 patients who were randomized into two groups: a group received 0.03 mmol/kg and a group received 0.05 mmol/kg of gadofosveset for MR angiography. 96 patients of an age ranged from 43 to 91 years administered 0.03 mmol/kg of gadofosveset and 89 patients of an age ranged from 42 to 88 years administered 0.05 mmol/kg. After exposure to gadofosveset, patients were monitored for 72 to 96 hours to account for adverse reactions. In the 0.03 mmol/kg group, there is no report of burning sensation as a common adverse reaction associated with gadofosveset. However, four percent of adverse reactions in the 0.05 mmol/kg group were burning sensation (Bosch et al., 2008).

A study published by Rapp et al. in 2005 aimed to determine the safety of a GBCA, gadofosveset, reported burning sensation as one of the adverse reactions associated with gadofosveset administration in MR angiography (MRA). This study included a total of 274 patients injected intravenously with 0.03 mmol/kg gadofosveset. Patients were monitored for 72 to 96 hours after their exposure to gadofosveset. Eight patients reported eight incidences of burning sensation (2.9 percent), and this symptom were judged to be most likely related to gadofosveset (Rapp et al., 2005).

At 0.03 mmol/kg dose, Bosch et al. did not report burning sensation as one of adverse reactions to gadofosveset, while Rapp et al. (in category III) reported 2.9 percent of incidences to be burning sensation at the same dose. In addition, the rate of burning sensation at 0.05 mmol/kg dose is higher than that at 0.03 mmol/kg dose.

Moreover, a case report published by Boehm et al. in 2018 reporting burning sensation, among other symptoms, as an adverse reaction to gadopentetate dimeglumine (Magnevist), supports the findings of Rapp et al. study. A 39 year-old female who got exposed to GBCAs two times and tolerated them very well, complained of burning sensation in her mouth following third exposure to GBCAs (Boehm, Hungerbühler, & Heverhagen, 2018).

3.4. Risk of Bias Assessment

The risk of bias of the seven observational studies and the RCT is illustrated and detailed by providing evidence for each domain in tables 2 and 3 respectively.
The risk of bias is high in the seven observational studies. Four observational studies were at high risk of bias across all domains (Nelson et al., 1995) (Burke et al., 2016) (Semelka, Ramalho, Vakharia, et al., 2016) (Parillo et al., 2019). All studies have a high risk of bias in the comparability domain as there are three studies without control groups (Burke et al., 2016) (Semelka, Ramalho, Vakharia, et al., 2016) (Rapp et al., 2005) and the rest did not match intervention groups and control groups and did not adjust for confounders. However, the study by Young et al. has low risk of bias in the selection and outcome domains (Young et al., 2019). The RCT has a high risk of bias in blinding of participants and personnel (performance bias) domain and blinding of

outcome assessment (detection bias) since it is an open-label study, whereas the other domains have a low risk of bias (Bosch et al., 2008).

3.5. Certainty of Evidence Assessment

Using GRADE, the certainty of evidence was assessed for the pain outcome categorized into five different types: bone, joint and musculoskeletal system pain, central torso and leg or arm pain, general pain, burning sensation (table 4), and burning sensation (high dose versus low dose) (table 5). The certainty of evidence of the first four outcomes is very low mainly because of the observational studies and case reports (study design), because of the very serious risk of bias and because of the serious imprecision. For the last outcome, it has a low certainty of evidence mainly because of serious risk of bias and serious imprecision.

CHAPTER 4

DISCUSSION

Gadolinium deposits in the brain and different tissues as evidenced by many studies (Kuno et al., 2017; R. J. McDonald, McDonald, Dai, et al., 2017; Zhang et al., 2017). Although there have not been any documented histopathological changes and signs due to gadolinium up till now, it can be neurotoxic. Pain is reported as one of the symptomatology associated with gadolinium toxicity in patients with normal renal function. Central torso pain, arm or leg pain, bone pain, joint pain, generalized pain, chronic pain, fibromyalgia, myalgia, musculoskeletal system pain, and burning sensation have been reported in the literature, among other symptoms, and believed to be associated with gadolinium exposure. However, findings among studies are inconsistent.

4.1. Summary of Findings

Bone/joint/musculoskeletal system pain: As a result of gadolinium toxicity, Burke et al and Semelka et al. found consistent results, 78 percent and 78.6 percent of patients complained of bone/joint pain, respectively (Burke et al., 2016) (Semelka, Ramalho, Vakharia, et al., 2016). In addition, two patients reported arthralgia following GBCA administration (Takebayashi et al., 1993; Wexler & Spencer, 1993), and one patient reported myalgia (Prieto-García et al., 2017). On the other hand, in both eMRI and uMRI, Parillo et al. reported 0.2 percent bone pain (Parillo et al., 2019) and Azzouz et al. reported three percent musculoskeletal system pain as LAE and five percent as VLAE (Azzouz et al., 2014).

Central torso and peripheral arm or leg pain: Due to gadolinium toxicity, Semelka et al. found that 14 percent and 21 percent of patients reported central torso pain and peripheral arm or leg pain lasted for less than three months, respectively. And 35 percent and 62 percent of patients reported central torso pain and arm or leg pain lasted beyond three months and persisted to the time of the survey, respectively (Semelka, Ramalho, Vakharia, et al., 2016). Moreover, Semelka et al. reported four patients complained of central torso pain and peripheral arm and leg pain (Semelka, Commander, et al., 2016). On the contrary, Parillo et al. found that after 24 hours one percent and 0.8 percent of patients complained of central torso pain and peripheral arm or leg pain in the eMRI compared to 0.4 percent and 0.2 percent in the uMRI, respectively (Parillo et al., 2019).

General pain: Nelson et al. found that 0.14 percent of patients complained of general pain within 30 min and more than one hour (acute) after GBCA injection (Nelson et al., 1995). Young el al. found that 0.019 percent and 0.007 percent of cases reported chronic pain in contrast-enhanced and unenhanced scans, respectively (Young et al., 2019). Furthermore, a case diagnosed with fibromyalgia after repeated exposure to GBCAs was documented (Lattanzio & Imbesi, 2020).

Burning sensation: Rapp et al. found that 2.9 percent of patients monitored for 72 to 96 hours after intravenous injection of 0.03 mmol/kg GBCA complained of burning sensation (Rapp et al., 2005). In contrast, Bosch et al. reported no burning sensation at 0.03 mmol/kg dose but reported four percent burning sensation at 0.05 mmol/kg dose (Bosch et al., 2008). In addition, burning sensation in a patient's mouth was reported after intravenous gadolinium injection (Boehm et al., 2018).

4.2. Interpretation of Findings

There is contradiction in the findings of the cohort studies. The findings of Burke et al. and Semelka et al. were consistent; however, they contradict Parillo et al. and Azzouz et al. findings. This discrepancy in results could be due to many factors. The two studies of Burke et al. and Semelka et al. are surveys; they are subjective self-report studies that may have validity problems. They depend on participants' integrity, knowledge and descriptions, as important details might be forgotten, and frequency and severity of symptoms might be either over-reported or under-reported by patients in order to worsen or reduce their condition. However, linking pain outcome, among other symptoms, to GBCAs injection relied on investigators' judgment in Parillo et al. and Rapp et al. studies, which is less uncertain that patients' judgment. Moreover, there is no evidence that respondents reported only new onset symptoms following GBCA administration. On the other hand, to ensure that only new onset symptoms after MRI will be extracted and analyzed, Parillo et al. gave the same structured survey to each patient before and 24 hours after the MRI scan. Furthermore, participants from online gadolinium toxicity support groups volunteered to complete the two surveys, so there is selection bias. Moreover, Burke et al. and Semelka et al. had no access to gadolinium retention testing results and to the MRI examinations' clinical indications, respectively. Thus, some respondents might not have gadolinium retention and even if gadolinium levels were documented, there is no standardized accepted gadolinium level to identify certain values as normal or abnormal. Studies and case reports did not include examination of biological samples to document gadolinium levels or quantify gadolinium deposition in tissues. In addition, there might be health conditions, other

than gadolinium toxicity, causing pain development. However, a common pattern of symptomatology was observed among respondents of the two surveys.

It is known that studies with no comparators or control groups are at high risk of bias. Burke et al. and Semelka et al. did not compare their findings to a control group of patients who did not develop symptoms after multiple exposures to GBCAs or a control group of patients who underwent uMRI and developed similar symptomatology. On the other hand, there were control groups in Parillo et al., Azzouz et al., and Young et al. studies; they compared contrast eMRI groups to uMRI groups (control). Pain was reported in both contrast eMRI and uMRI, suggesting that GBCAs may not be always the cause of the developed pain. Higher percentages of central torso pain, peripheral arm or leg pain, and chronic pain were reported in the contrast eMRI groups compared to uMRI groups, but the difference was not statistically significant. Additionally, the same percentages of bone pain and musculoskeletal system pain were reported by Parillo et al. and Azzouz et al. in contrast eMRI and uMRI groups, respectively, questioning the possible relationship between GBCA exposure and bone pain or musculoskeletal system pain development in general.

No matching between eMRI and uMRI groups in Parillo et al., Azzouz et al., and Young et al. studies, which does not ensure ideal comparison. However, due to practical and ethical reasons, randomized controlled trials (RCTs) and prospective randomization are not feasible. For instance, if it is necessary to use eMRI to diagnose a patient's certain disease or condition, it would be unethical to randomize this patient to have uMRI, and vice versa. Moreover, it is not practical and unethical to randomize a patient with renal insufficiency or who had a history of adverse reactions to GBCAs into eMRI.

Inconsistency of findings might be a consequence of the difference in the symptom assessment time span among studies. Some studies had a longer time span for symptom assessment. Semelka et al. reported four patients who had persisted symptomatology two months, three months, seven years, and eight years after GBCA exposure (Semelka, Commander, et al., 2016). Moreover, respondents reported onset of symptoms immediately, within six weeks, and six months, onset from one to 365 days, and onset within three days and within one month after GBCA administration (Burke et al., 2016) (Semelka, Ramalho, Vakharia, et al., 2016) (Azzouz et al., 2014). On the other hand, some studies had a shorter time span for symptom assessment. Symptoms were assessed with 30 min and beyond one hour, within 24 hours, and within 72 to 96 hours following GBCA administration (Nelson et al., 1995) (Parillo et al., 2019) (Rapp et al., 2005) (Bosch et al., 2008). Although 95 percent of GBCA is eliminated by excretion in the urine within 24 hours after injection, and most of the cases reported symptoms within 24 hours following GBCA injection (I. Krefting, 2017), not assessing symptoms beyond 24 hours might underestimate the prevalence and the persistence of LAEs and VLAEs including pain. At the same time, the more the time passes, the more and more it is difficult and effortful for the patients or the investigators to associate new symptoms or complaints to GBCA administration, and the more the uncertainty level increases.

As the number of symptoms (related to pain for example) listed in a questionnaire to choose from increases, the likelihood of reporting these symptoms will increase. For example, in the questionnaire delivered by Semelka et al. and Parillo et al., central torso pain, peripheral arm or legs pain, and bone pain were listed among other symptoms, and they were reported by patients. However, patients reported bone/joint

pain and musculoskeletal system pain, but not central torso pain and peripheral arm and legs pain, in the questionnaires delivered by Burke et al. and Azzouz et al., respectively, in which they listed bone/joint pain and musculoskeletal system pain only. Furthermore, the type of interview has an impact on the frequency of reported symptoms and complaints including pain (Thomsen, 1997). In addition, the more the patients are knowledgeable about gadolinium safety, the more the attention on symptoms, and thus the more they are reported. To illustrate, participants in Burke et al. and Semelka et al. studies believe that they had suffered from gadolinium toxicity and were informed of the purpose of the studies. On the contrary, participants were not informed about gadolinium safety in Parillo et al. study so that over-attention on symptoms can be avoided.

In general, patients with normal renal function are seen by a variety of doctors, including generalists and specialists, who ask their patients to undergo eMRI using GBCAs as a contrast media in order to diagnose certain diseases. As a result, the chances of any one-physician group to see a group of patients with common types of pain and who had administered GBCAs are very low or none.

4.3. Limitations and Strengths

This systematic review has a number of limitations. Six studies were case reports, and four cohort studies had no comparators or control groups out of 14 studies identified as eligible. They are at higher risk of bias compared to RCTs and cohort studies with control groups. Moreover, meta-analysis was not conducted because only one RCT was retrieved and because of the high risk of bias in almost all 10 studies.

Data derived from Rapp et al. and Bosch et al. studies included only patients who have been diagnosed with or are suspected of having peripheral vascular disease.

On the contrary, this systematic review has many strengths. It is the first to assess the effect of GBCA administration and deposition on pain development in patients with normal renal function. It fills a gap of knowledge regarding the safety of GBCAs and the possible consequences associated with gadolinium retention in the central nervous system. Moreover, this systematic review throws light on the availability and the quality of the studies that reported pain following GBCA exposure. In addition, the search methodology was quite thorough, encompassing five international databases, in addition to two Grey literature databases.

4.4. Implications for Practice

Although pain is not an over-reported symptom associated with intravenous gadolinium injection and retention in patients with normal function, it is essential for medical practitioners to be careful and cautious when using GBCAs. Prior to GBCA administration, patients should be informed about the safety profile of GBCAs, and an informed consent should become standard when gadolinium eMRI is ordered. And thorough recording of administered GBCA, dosage and exposure frequency as well as adverse reaction, symptoms including pain should be documented and maintained at institutions to improve patient safety. Moreover, for patients receiving multiple doses of GBCAs, practitioners should follow-up for persistence of symptoms and for gadolinium retention. Because GBCA eMRI might not provide increased clinical utility and might expose patients to unneeded risk, discretion should be exerted by practitioners when ordering it.

4.5. Implications for Research

When the intervention is the administration of GBCAs, RCTs and prospective randomization are not possible because of practical and ethical reasons. However, designing prospective studies with control groups that account for immediate, late (over weeks) and very late adverse reactions (over months) and that account for persistence of symptomatology in patients with normal renal function is needed. These studies must ensure that the symptoms reported are exhibited post GBCA exposure and must adjust for confounders. Moreover, testing for gadolinium level along with histological autopsy examinations and evaluating possible increase in T1 signal at different brain structures is needed for patients enrolled in the studies so that association of symptoms to gadolinium administration will be evidenced and less biased. In addition, when assessing gadolinium toxicity, a reference value for gadolinium level in the blood should be taken into consideration in future studies to identify the toxic range of gadolinium level.

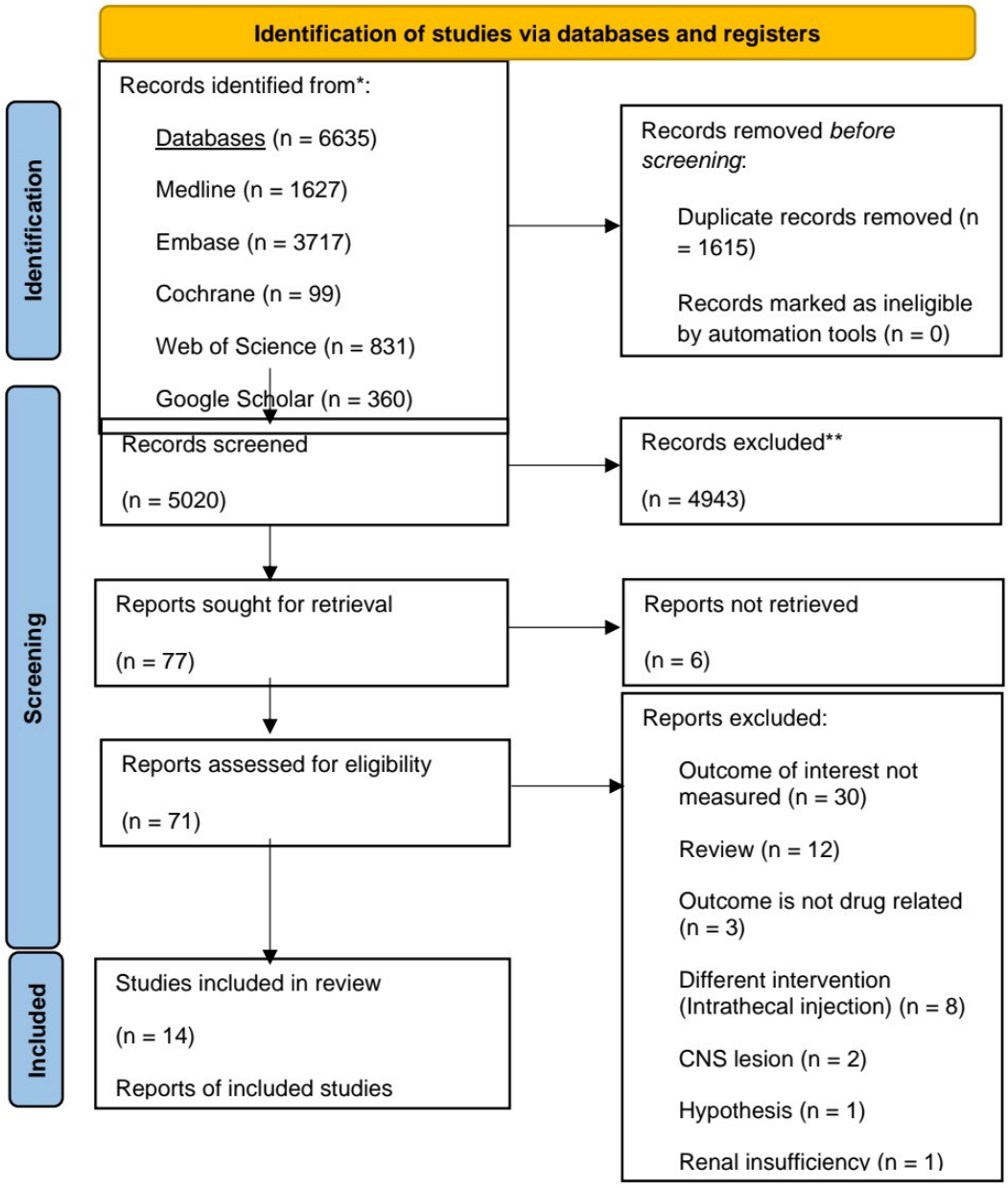

Figure 1 Flow diagram of the Different Phases of Systematic Review

Table 1 Included Studies and Extracted Data

Study	Methods	Total Number	Age	Sex	Setting	Interventions	Control	Outcomes	Results
Azzouz et al., 2014)	Prospective study	669 patients: Contrast-enhanced MRI group (n = 253), MRI control group (n = 416)	eMRI: mean age, 53.2 years; range, 18–96 uMRI: mean age 56.8 years; range 23–89	eMRI: male n = 104 female n = 149, uMRI: male n = 148 female n = 268	Single-center study conducted from September 2010 to December 2012, Department of Diagnostic Radiology, Copenhagen University Hospital Herlev, Herlev, Denmark	Gadoteric acid 279.3 mg/ml (Dotarem) was injected for MRI examinations of head, spine, chest, abdomen, pelvis, extremity and whole body	Enhanced and unenhanced MRI	Musculoskeletal system pain, Pain in groin, back pain	LAEs (after 3 days): musculoskeletal system pain (eMRI n = 8 and uMRI n = 12). VLAEs (after 1 month): musculoskeletal system pain (eMRI n = 9 and uMRI n = 16)
Boehm et al., 2018	Case report	n = 1 patient	39 years old	Female n = 1	Department of Diagnostic, Interventional and Pediatric Radiology, Inselspital, Bern University Hospital, University of Bern, Switzerland	Received gadopentetate dimeglumine (third exposure to GBCAs)	N/A	Allergy reaction with urticaria on the trunk and the lower arms accompanied by itching, prickling, heat feeling within the pharynx, burning sensation in her mouth	Burning sensation n = 1

Bosch et al., 2008	Open-label multicenter crossover study	n = 185 patients	Mean age, 67.8 years; range, 42–91 years	Male n = 135 Female n = 50	Between April 2002 and February 2003	Randomized in a group receiving 0.03 mmol/kg and a group receiving 0.05 mmol/kg of gadofosveset for MR angiography of the pedal arteries	Comparing 2 different doses (0.03 and 0.05 mmol/kg)	In the 0.05-mmol/kg dose group, the most common treatment-related AEs were nausea, burning sensation, and paresthesia (4% each) and pruritus and vasodilatation (3% each)	Burning sensation 4% (out of 89 patients)
Burke et al. (2016)	Online survey	n = 50 patients	N/A	N/A	The survey was posted using an online survey program (SurveyMonkey.com, Palo Alto, CA). The survey consisted of 9 open and closed questions and was open for responses for a total of two months	Intravenous gadolinium contrast with an average of 4.2 doses (range 1-23)	N/A	Bone/joint pain, Head/neck (headache, vision change, and hearing change), Flu-like symptoms, Skin changes, Digestive symptoms (nausea, vomiting, diarrhea), Chest symptoms (difficulty breathing), Generalized whole body symptoms, Other	Bone/joint pain n = 38

Lattanzio & Imbesi, 2020	Case report	n = 1 patient	30 years old	Female n = 1	Neurological unit	Over the course of the following 5 years, she underwent 15 CE-MRI	N/A	Refer to table 1 (Symptoms) Fibromyalgia (Chronic pain)	n = 1
Nelson et al. (1995)	Open-label (nonblinded), prospective postmarketing surveillance study	n = 15496 patients	Age range, < 1 year to 101 years; mean age, 48.3 years)	Male n = 7309 Female n = 8168	April-September 1992 at 207 MR imaging sites in the United States.	Each patient received a single intravenous administration of 0.1 mmol/ kg gadopentetate dimeglumine	N/A	Nausea, Headache, Dizziness, Injection site reaction, Paresthesia, Nausea/vomiting, Pain, Asthenia, Rash, Vasodilatation, Urticaria	Pain n = 21
Parillo et al. (2019)	Prospective cohort study	n = 1088 patients. 44.2% (481/1088) were uMRI scan and 55.8% (607/1088) were eMRI. Among eMRI, 241/607 (39.7%) patients were tested for symptoms after gadodiamide and 366/607 (60.3%) after gadoterate meglumine	eMRI Gadodiamide (n = 241): 60 ± 15 years (18–86), eMRI Gadoterate Meglumine (n = 366): 57 ± 15 years (17–90), uMRI (n = 481): 55 ± 16 (17–88)	Male n = 506 Female n = 582	From the Departmental Faculty of Medicine and Surgery, Università Campus Bio-Medico di Roma, Rome, Italy between March 1, 2017, and March 31, 2018	Enhanced magnetic resonance imaging (eMRI) with intravenous administration of gadodiamide or gadoterate meglumine	Control group undergoing unenhanced MRI (uMRI), Comparison between the eMRI group	Gadolinium deposition disease (GDD)-like symptoms within 24 hours after eMRI: central torso pain, arm or leg pain, bone pain, headache, skin redness (any site of the body), fatigue, and mental confusion	Central torso pain, arm or leg pain, bone pain: eMRI Gadodiamide + Gadoterate Meglumine (n = 607): n = 12 (6 + 5 + 1)/ uMRI (n = 481): n = 4 (2 + 1 + 1)

Prieto-García et al., 2017	Case report	n = 1 patient	64 years old	Female n = 1	Hospital General Universitario Gregorio Marañón, Madrid, Spain.	Intravenous gadobenate dimeglumine (20 mL) (MultiHance) was administered	N/A	Malaise and myalgia	myalgia n = 1
Rapp et al. (2005)	Open label, multicenter phase III trial	n = 274 patients	Mean age, 65.8 years; range, 33.0–87.9	Male n = 190 Female n = 84	Patients were enrolled in the study between June 1999 and September 2001 in 37 centers (U.S.).	Each patient received 0.03 mmol/kg gadofosveset diluted to 30 mL for hand injection or 15 mL for power injection. Per protocol, the dose was administered over a 30-second span via a catheter in the antecubital vein.	N/A	The related adverse events that occurred with the greatest frequency were feeling hot (12 incidents in 12 patients [4.4%]), nausea (10 incidents in 10 patients [3.6%]), headache (nine incidents in nine patients [3.3%]), and burning sensation (eight incidents in eight patients [2.9%]).	Burning sensation n = 8 (2.9%)

Semelka, Commander, et al., 2016	Case report	n = 4 patients	P2mo: 29 years old P3mo: 43 years old P7yr: 58 years old P8yr: 55 years old	P2mo: Female P3mo: Female P7yr: Female P8yr: Female	Departments of Radiology, and Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC; and Department of Radiology, Hospital Garcia de Orta, Almada, Portugal.	4 subjects who reported development of new disease features within hours to 4 weeks of having received an intravenous administration of GBCA.	N/A	Central torso pain, peripheral arm and leg pain, clouded mentation, and distal arm and leg skin thickening and rubbery subcutaneous tissue	Central torso pain and peripheral arm and leg pain n=4
Semelka, Ramalho, Vakharia, et al., 2016	Online survey (prospective study)	n = 42 patients	age: 28-69 years old	Male n = 14 Female n = 27 not specified n = 1	The survey was posted online and consisted of 18 questions that were completed between November 21 and November 30, 2015	GBCA administration (enhanced MRI)	N/A	Central pain, peripheral pain, headache, bone pain, other pain location, residual pain	Central pain (n = 15), peripheral pain (n = 26), bone pain (n = 26), other pain location (n = 25), residual pain (n = 31)
Takebayashi et al., 1993	Case report	n = 1 patient	29 years old	Female n = 1	Yokohama City University Yokohama 236, Japan	Gadopentetate dimeglumine (0.1 mmol/kg body weight) was given IV via a 24-gauge Teflon sheath catheter.	N/A	The patient again had vomiting, in addition to chest discomfort, arthralgia, and abdominal pain.	Arthralgia (joint pain) n = 1

Wexler & Spencer, 1993	Case report	n = 1 patient	23 years old	Female n = 1	Diagnostic Imaging Department, Luton and Dunstable Hospital NHS Trust, Lewsey Road, Luton LU4 0DZ	Intravenous Gd-DTPA 0.2 ml/kg	N/A	Developed a symmetrical polyarthralgia principally affecting her wrists, elbows and knees (moderate pain on movement of the major joints,especially the elbows)	Arthralgia (joint pain) n = 1
Young et al. (2019)	Retrospective study	n = 37,813 contrast and non-contrast scans (21,770 adult patients)/ n = 1,265 scans (698 pediatric patients)	Adults: 1/2, 53.3 ± 15.4 years; stage 3, 69.6 ± 11.6 years; stage 4, 73.1 ± 12.7 years), in the stage 5 (60.5 ± 15.3 years)/ Pediatrics: normal, 11.6 ± 5.4 years; insufficient, 9.7 ± 6.5 years; normal, 9.6 ± 6.5 years; insufficient, 7.6 ± 5.7)	Adults: Female 58.2% (across stages)/ Pediatrics: female 49.0 % (normal and insufficient groups)	Locally from 2004–2016	Administration of gadoteric acid	Controls (those who underwent non-contrast scans)	Chronic pain	n = 7 (contrast-enhanced MRI) n = 3 (non-contrast MRI)

Table 2 New Castle- Ottawa Quality Assessment Scale.

Study	**Selection**				**Comparability**	**Outcome**		
	Representativeness of exposed cohort	Selection of the non-exposed cohort from same source as exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Comparability of cohorts	Assessment of outcome	Follow-up long enough for outcome to occur	Adequacy of follow- up
Azzouz et al. (2014)	It was a single-center study conducted over a period of 2 years and 6 months/ Copenhagen University Hospital Herlev, Herlev, Denmark	Yes (1)	The patients were referred to a CT or MRI examination as part of their work-up of their symptoms and signs (1)	Unclear	There were significant differences between the MRI- and CT-enhanced groups and control groups with regard to age and weight. In the enhanced MRI group, 81% of the patients underwent head and abdomen scans, while 63% patients in the MRI control group had spine and extremity scans.	Patients self-report	Yes (1)	669 out of 749 completed 3-day follow up and 532 out of 749 completed 1-month follow up (1)

Parillo et al. (2019)	Participants were consecutive patients admitted to their department between March 1, 2017, and March 31, 2018 and received eMRI with gadodiamide or gadoterate meglumine or uMRI as indicated by their clinical condition	Yes (1)	The participants underwent a structured questionnaire by phone call before and 24 hours after the MRI scan	Yes (1)	The distribution of MRI examinations was different between the eMRI and uMRI groups. Lack of clear statement about the adjustment for confounders (age, sex, etc.)	Participant self-report	Assessment beyond 24 hours and up to 7 days was not conducted (limitations) No statement	No statement
Young et al. (2019)	MRI scans performed locally from 2004–2016/ Clinical Radiology, NHS Tayside, Ninewells Hospital and Medical School, Dundee, UK (Performed at one institution)	Yes (1)	Local electronic patient data were used to identify and compile patient timelines. Patient data for those who had undergone solely gadoteric acid-enhanced scans were included into the study cohort (1)	Yes (1)	The average age at scan of all patients was significantly different between renal function categories. Age tended to increase with increasing RI	Through health data linkage, the anonymized patient data from 39,078 MRI scans, performed locally between 2004 and 2016, was linked with patient-specific electronic health records. (1)	Yes (1)	Following these patients via their health records for an average of 6 years (this study is not patient-consented) (1)

Nelson et al. (1995)	207 MR imaging sites in the United States. The majority of patients were white (82%).		Case report form	Unclear	There were no statistically significant differences between comparable patient groups in the rate or type of adverse reactions observed (P > .05). There was no statistically significant difference in the rate of adverse reactions observed between patients of different races or between pediatric patients 2-18 years of age, adult patients, and patients younger than 2 years of age.	If the patient did not voluntarily report an adverse reaction, the MR technologist, nurse, or physician directly questioned the patient to detect any possible adverse reaction. The patient was asked how he or she was feeling or if he or she felt any different after the MR examination. Investigators were asked to provide a diagnosis of a condition after injection and MR imaging in each patient in the study. (1)	Yes (1)	Only 27.6% (n = 4,278) of the patients were contacted directly or received a return telephone call from the MR imaging center 24 hours after the procedure. Those patients who did not receive a telephone call from the MR imaging center were not considered part of the follow-up group.
Burke et al. (2016)	No description of the derivation of the cohort		50 respondents completed the nine-question survey	Unclear		Participant self-report	Immediately, Within 6 weeks, 6 weeks to 6 months, after 6 months Yes (1)	No statement

Semelka, Ramalho, Vakharia, et al., 2016	Participants were recruited from two online gadolinium toxicity support groups		42 respondents completed the 18-question online survey	Yes (1)		Participant self-report	Yes (1)	No statement
Rapp et al. (2005)	Patients were enrolled in the study between June 1999 and September 2001 in 37 centers (USA)		Each patient received 0.03 mmol/kg gadofosveset diluted to 30 mL for hand injection or 15 mL for power injection (1)	Yes (1)		Safety was assessed by reviewing medical history and monitoring the following parameters: physical examination, vital signs, pulse oximetry, electrocardiograms, and results of clinical laboratory tests (including hematologic analysis, clinical chemistry, coagulation, anaphylaxis panel, and urinalysis) (1)	All patients were monitored for at least 72 hours, and some patients were monitored for as many as 96 hours after administration of gadofosveset Yes (1)	No statement

Table 3 Cochrane Risk of Bias Tool

Study	Random sequence generation	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting? (reporting bias)	Other bias
Bosch et al. (2008)	Patients received either 0.03 or 0.05 mmol/kg according to a predetermined randomization scheme (low risk)	Predetermined randomization scheme (low risk)	Open-label multicenter crossover study/ a third blinded reader/ three blinded readers (high risk)	All readers of MR angiograms were blinded to patient information/ All image readers were blinded to clinical information about the patients and therefore provided an assessment of the diagnostic imaging procedure alone/ Two independent readers blinded to patient information aside from the images interpreted the radiographs (high risk)	One patient reported one AE that was severe and led to the patient's withdrawal from the study, but the AE was not considered treatment related (low risk)	The ethical committees of each institution participating in the study approved the protocol, and each enrolled patient gave signed written informed consent (low risk)	Low risk

Question: Gadolinium Based Contrast Agent Intravenous Injection compared to No Gadolinium Based Contrast Agent intravenous injection for Patients with normal renal function and with no nervous system lesions

Table 4 Certainty of Evidence Following the GRADE Method (Four Outcomes).

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Central torso and arm or leg pain									
3	observational studies	very serious [a]	very serious [b]	not serious	serious [c]	none	Semelka, Ramalho, Vakharia et al.: less than 3 months (14% for central pain and 21% for arm or leg pain) and beyond 3 months (35% and 62%)/ Semelka, Commander, et al.: 4 case reports/ Parillo et al. (1% and 0.8% eMRI vs 0.4% and 0.2% uMRI for central pain and arm or leg pain respectively)	⊕◯◯◯ VERY LOW	
Bone, joint and musculoskeletal system pain									
7	observational studies	very serious [d]	very serious [e]	not serious	serious [f]	none	Burke et al. and Semelka, Ramalho, Vakharia et al.: 78% and 78.6% respectively (bone/joint pain)/ Takebayashi et al., Wexler and Spencer, Prieto-Garcia et al.: case reports/ Parillo et al.: 0.2% (bone pain)/ Azzouz et al.: 3% LAE and 5% VLAE musculoskeletal system pain)	⊕◯◯◯ VERY LOW	
General pain									
3	observational studies	very serious [g]	not serious	not serious	serious [h]	none	Nelson et al.: 0.14% (acute pain)/ Young et al.: 0.019% and 0.007% for eMRI and uMRI respectively (chronic pain)/ Lattanzio & Imbesi: case report	⊕◯◯◯ VERY LOW	
Burning sensation									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
2	observational studies	very serious [i]	not serious	not serious	serious [j]	none	Rapp et al.: 2.9% (0.03 mmol/kg) (burning sensation)/ Boehm et al.: case report	⨁◯◯◯ VERY LOW	

Explanations

a. Case reports (1 study), no comparative or control group (two studies), and follow-up time

b. Large difference in the percentage of reporting the same outcome.

c. No comparative test (2 studies) and no effect estimate recorded

d. Case reports (3 studies), surveys, no comparator or control group (two studies), and follow-up time

e. Large difference in the percentage of reporting the same outcome

f. No comparative test (5 studies) and no effect estimate recorded

g. Case reports (1 study), follow-up time

h. Low number of events, no comparative test (3 studies) and no effect estimate recorded

i. Case reports (1 study), no control group (1 study)

j. Low number of events, no comparative test (2 studies) and no effect estimate recorded

Question: 0.05 mmol/kg dose intravenous injection compared to 0.03 mmol/kg dose intravenous injection for Patients with normal renal function and with no nervous system lesions

Table 5 Certainty of Evidence Following the GRADE Method (One Outcome).

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Burning sensation (high dose versus low dose)									
1	randomized trials	serious [a]	not serious	not serious	serious [b]	none	Bosch et al.: 4% (0.05mmol/kg) and 0% (0.03mmol/kg) (burning sensation)	⊕⊕◯◯ LOW	

Explanations

a. open label

b. low number of events and no comparative test and no effect estimate recorded

APPENDIX 1

PRISMA CHECKLIST

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	

Section and Topic	Item #	Checklist item	Location where item is reported
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	

Section and Topic	Item #	Checklist item	Location where item is reported
syntheses	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

APPENDIX 2

SEARCH STRATEGIES

Medline search:

1 exp pain/ (403272)
2 Schnitzler syndrome/ or exp burns/ or dyspareunia/ or dysuria/ or exp migraine disorders/ or trigeminal neuralgia/ or hyperalgesia/ or erythromelalgia/ or exp compartment syndrome/ or fibromyalgia/ or intermittent claudication/ or Persian Gulf syndrome/ or Polymyalgia Rheumatica/ or carpal tunnel syndrome/ or cauda equina syndrome/ or cubital tunnel syndrome/ or tarsal tunnel syndrome/ or exp Thoracic Outlet Syndrome/ or vulvodynia/ (145277)
3 (pain* or (physical adj3 suffering?) or ache? or aching or arthralgia* or (angina adj3 (stable or unstable or pector?s)) or toothache? or tooth-ache? or headache? or head-ache? or glossalgia? or earache? or ear-ache? or (((slit adj ventricle) or (piriformis adj muscle) or (failed adj back adj surgery)) adj syndrome?) or (renal adj colic) or mastodynia? or metatarsalgia? or (Morton* adj neuroma*) or myalgia? or neuralgia? or sciatica? or (phantom adj limb) or dysmenor?hea? or Polyarthralgia? or Arthritis or Joint disease? or backache? or back-ache? or (((Post adj operative) or postoperative) adj Complication?) or Sciatica or lumbago or (((pre adj cordial) or precordial) adj catch?) or "texidor twinge" or stenocardia? or otalgia? or odontalgia? or glossodynia? or glossopyroses or glossopyrosis or hemicrania or migraine or cephalalgia?or cephalgia? or cephalodynia? or "Cerebrospinal Fluid Shunt?" or Ventriculostomy or mammalgia? or mastalgia? or Metatarsus or "muscle soreness" or "symphysis pubis dysfunction" or cervicalgia? or cervicodynia? or neckache? or neck-ache? or neurodynia? or "Herpes Zoster" or Perineum or pseudomelia? or pseudo-melia? or "Urinary Calculi").mp. (1644110)
4 ("abdominal angina" or allodynia or "application site pain" or "breast tenderness" or cystalgia or "chronic daily" or "hemicrania continua" or "heavy-headedness" or "temporal arteritis" or "hypoalgesia" or "burning feet syndrome" or algodystrophy or "posttraumatic osteoporosis" or "sympathetic dystrophy" or ischialg* or "meralgia paresthetica" or "piriformis syndrome" or "acute scrotum" or "sore throat" or "biliary colic" or "kidney colic" or "Schnitzler syndrome" or burn* or dyspareunia or dysuria or "migraine disorders" or "trigeminal autonomic cephalalgias" or "paroxysmal hemicrania" or "SUNCT syndrome" or "trigeminal neuralgia" or hyperalgesia or erythromelalgia or "compartment syndrome" or "fibromyalgia" or "intermittent claudication" or "Persian Gulf syndrome" or "Polymyalgia Rheumatica" or "carpal tunnel syndrome" or "cauda equina syndrome" or "cubital tunnel syndrome" or "tarsal tunnel syndrome" or "Thoracic Outlet Syndrome" or vulvodynia).mp. (233927)
5 1 or 2 or 3 or 4 (1810715)
6 Gadolinium DTPA/ (12133)
7 ((Gadolinium or gd) adj2 (DTPA or diethylenetriaminepenta)).mp. (14234)
8 ((Gadolinium or gd) adj2 ((acetic adj acid) or (based adj contrast adj agent?))).mp. (1642)
9 (((gadopentet* or gadobenate) adj1 (dimeglumine or acid?)) or Magnevist or "k2i13dr72l" or "rh248g8v27" or Gadodiamide).mp. (3595)
10 (Optimark or Multihance or (gadofesveset adj trisodium) or ablavar or vasovist or (gadoxetate adj disodium) or Eovist or primovist or gadoteridol or prohance or gadobutrol or gadavist or (gadoterate adj meglumine) or Dotarem).mp. (2739)
11 ("mp 1177" or "mp1177").mp. (2)

12 (methylamide or omniscan or "s 041" or "teslapaque").mp. (1199)
13 ("b 19036 7" or "b 190367" or "b190367").mp. (0)
14 ("gadovist" or "gadolinium 10 (2, 3 dihydroxy 1 hydroxymethylpropyl) 1").mp. (113)
15 ("gadoxetic acid" or "gadolinium ethoxybenzyl DTPA" or "gadolinium EOB DTPA" or "gadolinium ethoxybenzyl diethylenetriamine pentaacet" or "gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid" or gadoxetate or "gadoxetic acid disodium").mp. (1722)
16 ("gadolinium 10 (2 hydroxypropyl) 1, 4, 7, 10 tetraazacyclodo" or "gadolinium HP DO3A" or artirem or clariscan or "meglumine gadoterate" or "p 449" or "p449" or "sq 32692").mp. (120)
17 ("dotagit" or "dotamulti" or "dotaspin" or "gadolinium 1, 4, 7, 10 tetraazacyclododecane 1, 4, 7, gadolinium DOTA meglumine").mp. (0)
18 ("Gadolinium pentetate meglumine" or "magnograf").mp. (1)
19 (angiomark or "gadofosveset sodium" or "ms 325" or "ms 32520" or "ms325" or "zk 236018" or "ms32520" or "zk 236018" or "zk236018").mp. (96)
20 or/6-19 (19330)
21 Gadolinium/ (11978)
22 exp Chelating Agents/ (146133)
23 Contrast Media/ (88438)
24 21 and (22 or 23) (7278)
25 (("au0v1lm3jt" or Gadolinium or "7440-54-2") and (chelat* or (contrast adj (medi* or agent?)))).mp. (20605)
26 5 and (20 or 24 or 25) (1627)

Embase search:

#48 #24 AND (#40 OR #43 OR #44 OR #47)

#47 #45 AND #46 6243

#46 'chelat*':ti,ab,kw OR 'contrast medi*':ti,ab,kw OR 'contrast agent?':ti,ab,kw

#45 'au0v1lm3jt':ti,ab,kw OR 'gadolinium':ti,ab,kw OR '7440-54-2':ti,ab,kw

#44 'gadolinium chelate'/exp

#43 #41 AND #42

#42 'contrast medium'/exp

#41 'gadolinium'/de

#40 #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39

#39 'angiomark':ti,ab,kw OR 'gadofosveset sodium':ti,ab,kw OR 'ms 325':ti,ab,kw OR 'ms 32520':ti,ab,kw OR 'ms325':ti,ab,kw OR 'ms32520':ti,ab,kw OR 'zk 236018':ti,ab,kw OR 'zk236018':ti,ab,kw

#38 'gadolinium pentetate meglumine':ti,ab,kw OR 'magnograf':ti,ab,kw

#37 'dotagit':ti,ab,kw OR 'dotamulti':ti,ab,kw OR 'dotaspin':ti,ab,kw OR 'gadolinium 1, 4, 7, 10 tetraazacyclododecane 1, 4, 7, gadolinium dota meglumine':ti,ab,kw

#36 'gadolinium 10 (2 hydroxypropyl) 1, 4, 7, 10 tetraazacyclodo':ti,ab,kw OR 'gadolinium hp do3a':ti,ab,kw OR 'artirem':ti,ab,kw OR 'clariscan':ti,ab,kw OR 'meglumine gadoterate':ti,ab,kw OR 'p 449':ti,ab,kw OR 'p449':ti,ab,kw OR 'sq 32692':ti,ab,kw

#35 'gadoxetic acid':ti,ab,kw OR 'gadolinium ethoxybenzyl dtpa':ti,ab,kw OR 'gadolinium eob dtpa':ti,ab,kw OR 'gadolinium ethoxybenzyl diethylenetriamine pentaacet':ti,ab,kw OR 'gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid':ti,ab,kw OR 'gadoxetate':ti,ab,kw OR 'gadoxetic acid disodium':ti,ab,kw

#34 'gadovist':ti,ab,kw OR 'gadolinium 10 (2, 3 dihydroxy 1 hydroxymethylpropyl) 1':ti,ab,kw

#33 'b 19036 7':ti,ab,kw OR 'b 190367':ti,ab,kw OR 'b190367':ti,ab,kw

#32 'methylamide':ti,ab,kw OR 'omniscan':ti,ab,kw OR 's 041':ti,ab,kw OR 'teslapaque':ti,ab,kw

#31 'mp 117':ti,ab,kw OR 'mp1177':ti,ab,kw

#30 'optimark':ti,ab,kw OR 'multihance':ti,ab,kw OR 'gadofesveset trisodium':ti,ab,kw OR 'ablavar':ti,ab,kw OR 'vasovist':ti,ab,kw OR 'gadoxetate disodium':ti,ab,kw OR 'eovist':ti,ab,kw OR 'primovist':ti,ab,kw OR 'gadoteridol':ti,ab,kw OR 'prohance':ti,ab,kw OR 'gadobutrol':ti,ab,kw OR 'gadavist':ti,ab,kw OR 'gadoterate meglumine':ti,ab,kw OR 'dotarem':ti,ab,kw

#29 (((gadopentet* OR gadobenate) NEAR/1 (dimeglumine OR acid?)):ti,ab,kw) OR 'magnevist':ti,ab,kw OR 'k2i13dr72l':ti,ab,kw OR 'rh248g8v27':ti,ab,kw OR 'gadodiamide':ti,ab,kw

#28 ((gadolinium OR gd) NEAR/2 ('acetic acid' OR 'based contrast agent?')):ti,ab,kw

#27 ((gadolinium OR gd) NEAR/2 (dtpa OR diethylenetriaminepenta)):ti,ab,kw

#26 'gadolinium dtpa':ti,ab,kw

#25 'gadoversetamide'/exp OR 'gadodiamide'/exp OR 'gadobenate dimeglumine'/exp OR 'gadobutrol'/exp OR 'gadoxetic acid'/exp OR 'gadoterate meglumine'/exp OR 'gadolinium pentetate meglumine'/exp OR 'gadofosveset'/exp

#24 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23

#23 'abdominal angina':ti,ab,kw OR allodynia:ti,ab,kw OR 'application site pain':ti,ab,kw OR 'breast tenderness':ti,ab,kw OR cystalgia:ti,ab,kw OR 'chronic daily':ti,ab,kw OR 'hemicrania continua':ti,ab,kw OR 'heavy-headedness':ti,ab,kw OR 'temporal arteritis':ti,ab,kw OR 'hypoalgesia':ti,ab,kw OR 'burning feet syndrome':ti,ab,kw OR 'algodystrophy':ti,ab,kw OR 'posttraumatic osteoporosis':ti,ab,kw OR 'sympathetic dystrophy':ti,ab,kw OR 'ischialg*':ti,ab,kw OR 'meralgia paresthetica':ti,ab,kw OR 'piriformis syndrome':ti,ab,kw OR 'acute scrotum':ti,ab,kw OR 'sore throat':ti,ab,kw OR 'biliary colic':ti,ab,kw OR 'kidney colic':ti,ab,kw OR 'schnitzler syndrome':ti,ab,kw OR 'burn*':ti,ab,kw OR 'dyspareunia':ti,ab,kw OR 'dysuria':ti,ab,kw OR 'migraine disorders':ti,ab,kw OR 'trigeminal autonomic cephalalgias':ti,ab,kw OR 'paroxysmal hemicrania':ti,ab,kw OR 'sunct syndrome':ti,ab,kw OR 'trigeminal neuralgia':ti,ab,kw OR

'hyperalgesia':ti,ab,kw OR 'erythromelalgia':ti,ab,kw OR 'compartment syndrome':ti,ab,kw OR 'fibromyalgia':ti,ab,kw OR 'intermittent claudication':ti,ab,kw OR 'persian gulf syndrome':ti,ab,kw OR 'polymyalgia rheumatica':ti,ab,kw OR 'carpal tunnel syndrome':ti,ab,kw OR 'cauda equina syndrome':ti,ab,kw OR 'cubital tunnel syndrome':ti,ab,kw OR 'tarsal tunnel syndrome':ti,ab,kw OR 'thoracic outlet syndrome':ti,ab,kw OR 'vulvodynia':ti,ab,kw

#22 'urinary calculi':ti,ab,kw

#21 ‘pseudo next melia$’:ti,ab,kw

#20 ‘pseudomelia$’:ti,ab,kw

#19 'perineum':ti,ab,kw

#18 'herpes zoster':ti,ab,kw

#17 ‘neurodynia$’:ti,ab,kw

#16 ‘neck next ache$’:ti,ab,kw

#15 ‘neckache$’:ti,ab,kw

#14 ‘mammalgia$’:ti,ab,kw OR ‘mastalgia$’:ti,ab,kw OR 'metatarsus':ti,ab,kw OR 'muscle soreness':ti,ab,kw OR 'symphysis pubis dysfunction':ti,ab,kw OR ‘cervicalgia$’:ti,ab,kw OR ‘cervicodynia$’:ti,ab,kw

#13 'hemicrania':ti,ab,kw OR 'migraine':ti,ab,kw OR ‘cephalalgia$’:ti,ab,kw OR ‘cephalgia$’:ti,ab,kw OR ‘cephalodynia$’:ti,ab,kw OR ‘cerebrospinal fluid shunt$’:ti,ab,kw OR 'ventriculostomy':ti,ab,kw

#12 'texidor twinge':ti,ab,kw OR ‘stenocardia$’:ti,ab,kw OR ‘otalgia$’:ti,ab,kw OR ‘odontalgia$’:ti,ab,kw OR ‘glossodynia$’:ti,ab,kw OR 'glossopyroses':ti,ab,kw OR 'glossopyrosis':ti,ab,kw

#11 'sciatica':ti,ab,kw OR 'lumbago':ti,ab,kw OR 'pre-cordial catch$':ti,ab,kw OR 'precordial catch$':ti,ab,kw

#10 'post operative complication$':ti,ab,kw OR 'postoperative complication$':ti,ab,kw

#9 'mastodynia$':ti,ab,kw OR 'metatarsalgia$':ti,ab,kw OR 'morton* neuroma*':ti,ab,kw OR 'myalgia$':ti,ab,kw OR 'neuralgia$':ti,ab,kw OR 'sciatica$':ti,ab,kw OR 'phantom limb':ti,ab,kw OR 'dysmenorhea':ti,ab,kw OR 'polyarthralgia$':ti,ab,kw OR 'arthritis':ti,ab,kw OR 'joint disease$':ti,ab,kw OR 'backache$':ti,ab,kw OR 'back-ache$':ti,ab,kw

#8 'slit ventricle syndrome':ti,ab,kw OR 'piriformis muscle syndrome':ti,ab,kw OR 'failed back surgery syndrome':ti,ab,kw

#7 'renal colic':ti,ab,kw

#6 'toothache$':ti,ab,kw OR 'tooth-ache$':ti,ab,kw OR 'headache$':ti,ab,kw OR 'head-ache$':ti,ab,kw OR 'glossalgia$':ti,ab,kw OR 'earache$':ti,ab,kw OR 'ear-ache$':ti,ab,kw

#5 (angina NEAR/3 (stable OR unstable OR pector$s)):ti,ab,kw

#4 ache$:ti,ab,kw OR aching:ti,ab,kw OR arthralgia*:ti,ab,kw

#3 pain*:ti,ab,kw OR ((physical NEAR/3 suffering$):ti,ab,kw)

#2 earache:ti,ab,kw OR glossalgia:ti,ab,kw OR mastodynia:ti,ab,kw OR 'piriformis muscle syndrome':ti,ab,kw

#1 'pain'/exp OR 'acute abdomen'/exp OR 'angina pectoris'/exp OR 'unstable angina pectoris'/exp OR 'phantom limb'/exp OR 'myalgia'/exp OR 'stable angina pectoris'/exp OR 'morton neuroma'/exp OR 'dysmenorrhea'/exp

Cochrane search:

#1

#2 MeSH descriptor: [Pain] explode all trees

#3 MeSH descriptor: [Burns] explode all trees

#4 MeSH descriptor: [Dyspareunia] this term only

#5 MeSH descriptor: [Dysuria] this term only

#6 MeSH descriptor: [Migraine Disorders] explode all trees

#7 MeSH descriptor: [Trigeminal Neuralgia] this term only

#8 MeSH descriptor: [Hyperalgesia] this term only

#9 MeSH descriptor: [Schnitzler Syndrome] this term only

#10 MeSH descriptor: [Erythromelalgia] this term only

#11 MeSH descriptor: [Compartment Syndromes] explode all trees

#12 MeSH descriptor: [Fibromyalgia] this term only

#13 MeSH descriptor: [Intermittent Claudication] this term only

#14 MeSH descriptor: [Persian Gulf Syndrome] this term only

#15 MeSH descriptor: [Polymyalgia Rheumatica] this term only

#16 MeSH descriptor: [Carpal Tunnel Syndrome] this term only

#17 MeSH descriptor: [Cauda Equina Syndrome] this term only

#18 MeSH descriptor: [Cubital Tunnel Syndrome] this term only

#19 MeSH descriptor: [Tarsal Tunnel Syndrome] this term only

#20 MeSH descriptor: [Thoracic Outlet Syndrome] explode all trees

#21 MeSH descriptor: [Vulvodynia] this term only

#22 ((pain* or (physical NEAR/3 suffering?) or ache? or aching or arthralgia* or (angina NEAR/3 (stable or unstable or pector?s)) or toothache? or tooth-ache? or headache? or head-ache? or glossalgia? or earache? or ear-ache? or (((slit adj ventricle) or (piriformis adj muscle) or (failed adj back adj surgery)) adj syndrome?) or (renal adj colic) or mastodynia? or metatarsalgia? or (Morton* adj neuroma*) or myalgia? or neuralgia? or sciatica? or (phantom adj limb) or dysmenor?hea? or Polyarthralgia? or Arthritis or Joint disease? or backache? or back-ache? or (((Post adj operative) or postoperative) adj Complication?) or Sciatica or lumbago or (((pre adj cordial) or precordial) adj catch?) or "texidor twinge" or stenocardia? or otalgia? or odontalgia? or glossodynia? or glossopyroses or glossopyrosis or hemicrania or migraine or cephalalgia?or cephalgia? or cephalodynia? or "Cerebrospinal Fluid Shunt?" or Ventriculostomy or mammalgia? or mastalgia? or Metatarsus or "muscle soreness" or "symphysis pubis dysfunction" or cervicalgia? or cervicodynia? or neckache? or neck-ache? or neurodynia? or "Herpes Zoster" or Perineum or pseudomelia? or pseudo-melia? or "Urinary Calculi")):ti,ab,kw

#23 (("abdominal angina" or allodynia or "application site pain" or "breast tenderness" or cystalgia or "chronic daily" or "hemicrania continua" or "heavy-headedness" or "temporal arteritis" or "hypoalgesia" or "burning feet syndrome" or algodystrophy or "posttraumatic osteoporosis" or "sympathetic dystrophy" or ischialg* or "meralgia paresthetica" or "piriformis syndrome" or "acute scrotum" or "sore throat" or "biliary colic" or "kidney colic" or "Schnitzler syndrome" or burn* or dyspareunia or dysuria or "migraine disorders" or "trigeminal autonomic cephalalgias" or "paroxysmal hemicrania" or "SUNCT syndrome" or "trigeminal neuralgia" or hyperalgesia or erythromelalgia or "compartment syndrome" or "fibromyalgiaâ€ • or â€œintermittent claudication" or "Persian Gulf syndrome" or "Polymyalgia Rheumatica" or "carpal tunnel syndrome" or "cauda equina syndrome" or "cubital tunnel syndrome" or "tarsal tunnel syndrome" or "Thoracic Outlet Syndrome" or vulvodynia)):ti,ab,kw

#24 {OR #1-#23}

#25 MeSH descriptor: [Gadolinium DTPA] this term only

#26 (((Gadolinium or gd) NEAR/2 (DTPA or diethylenetriaminepenta))):ti,ab,kw

#27 (((Gadolinium or gd) NEAR/2 ((acetic NEXT acid) or (based NEXT contrast NEXT agent?)))):ti,ab,kw

#28 ((((gadopentet* or gadobenate) NEAR/1 (dimeglumine or acid?)) or Magnevist or "k2i13dr72l" or "rh248g8v27" or Gadodiamide)):ti,ab,kw

#29 ((Optimark or Multihance or (gadofesveset NEXT trisodium) or ablavar or vasovist or (gadoxetate NEXT disodium) or Eovist or primovist or gadoteridol or prohance or gadobutrol or gadavist or (gadoterate NEXT meglumine) or Dotarem)):ti,ab,kw

#30 (("mp 1177" or "mp1177")):ti,ab,kw

#31 ((methylamide or omniscan or "s 041" or "teslapaque")):ti,ab,kw

#32 (("b 19036 7" or "b 190367" or "b190367")):ti,ab,kw

#33 (("gadovist" or "gadolinium 10 (2, 3 dihydroxy 1 hydroxymethylpropyl) 1")):ti,ab,kw

#34 (("gadoxetic acid" or "gadolinium ethoxybenzyl DTPA" or "gadolinium EOB DTPA" or "gadolinium ethoxybenzyl diethylenetriamine pentaacet" or "gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid" or gadoxetate or "gadoxetic acid disodium")):ti,ab,kw

#35 (("gadolinium 10 (2 hydroxypropyl) 1, 4, 7, 10 tetraazacyclodo" or "gadolinium HP DO3A" or artirem or clariscan or "meglumine gadoterate" or "p 449" or "p449" or "sq 32692")):ti,ab,kw

#36 (("dotagit" or "dotamulti" or "dotaspin" or "gadolinium 1, 4, 7, 10 tetraazacyclododecane 1, 4, 7, gadolinium DOTA meglumine")):ti,ab,kw

#37 (("Gadolinium pentetate meglumine" or "magnograf")):ti,ab,kw

#38 ((angiomark or "gadofosveset sodium" or "ms 325" or "ms 32520" or "ms325" or "zk 236018" or "ms32520" or "zk 236018" or "zk236018")):ti,ab,kw

#39 {OR #25-#38}

#40 MeSH descriptor: [Gadolinium] this term only

#41 MeSH descriptor: [Chelating Agents] explode all trees

#42 MeSH descriptor: [Contrast Media] this term only

#43 #40 AND (#41 or #42)

#44 ((("au0v1lm3jt" or Gadolinium or "7440-54-2") and (chelat* or (contrast adj (medi* or agent?)))):ti,ab,kw

#45 #24 and (#39 or #43 or #44)

Web of Science search:

26 #5 AND (#20 OR #24 OR #25)

25 TS=(("au0v1lm3jt" OR Gadolinium OR "7440-54-2") AND (chelat* OR ("contrast medi*" OR "contrast agent$")))

24 #21 AND (#22 OR #23)

23 TS="Contrast Media"

22 TS="Chelating Agents"

21 TS=Gadolinium

20 #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6

19 TS=(angiomark OR "gadofosveset sodium" OR "ms 325" OR "ms 32520" OR "ms325" OR "zk 236018" OR "ms32520" OR "zk 236018" OR "zk236018")

18 TS=("Gadolinium pentetate meglumine" OR "magnograf")

17 TS=("dotagit" OR "dotamulti" OR "dotaspin" OR "gadolinium 1, 4, 7, 10 tetraazacyclododecane 1, 4, 7, gadolinium DOTA meglumine")

16 TS=("gadolinium 10 (2 hydroxypropyl) 1, 4, 7, 10 tetraazacyclodo" OR "gadolinium HP DO3A" OR artirem OR clariscan OR "meglumine gadoterate" OR "p 449" OR "p449" OR "sq 32692")

15 TS=("gadoxetic acid" OR "gadolinium ethoxybenzyl DTPA" OR "gadolinium EOB DTPA" OR "gadolinium ethoxybenzyl diethylenetriamine pentaacet" OR "gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid" OR gadoxetate OR "gadoxetic acid disodium")

14 TS=("gadovist" OR "gadolinium 10 (2, 3 dihydroxy 1 hydroxymethylpropyl) 1")

13 TS=("b 19036 7" OR "b 190367" OR "b190367")

12 TS=(methylamide OR omniscan OR "s 041" OR "teslapaque")

11 TS=("mp 1177" OR "mp1177")

10 TS=(Optimark OR Multihance OR ("gadofesveset trisodium") OR ablavar OR vasovist OR ("gadoxetate disodium") OR Eovist OR primovist OR gadoteridol OR prohance OR gadobutrol OR gadavist OR ("gadoterate meglumine") OR Dotarem)

9 TS=(((gadopentet* OR gadobenate) NEAR/1 (dimeglumine OR acid$)) OR Magnevist OR "k2i13dr72l" OR "rh248g8v27" OR Gadodiamide)

8 TS=((Gadolinium OR gd) NEAR/2 (("acetic acid") OR ("based contrast agent$")))

7 TS=((Gadolinium OR gd) NEAR/2 (DTPA or diethylenetriaminepenta))

6 TS="Gadolinium DTPA"

5 #4 OR #3 OR #2 OR #1

4 TS=("abdominal angina" OR allodynia OR "application site pain" OR "breast tenderness" OR cystalgia OR "chronic daily" OR "hemicrania continua" OR "heavy-headedness" OR "temporal arteritis" OR "hypoalgesia" OR "burning feet syndrome" OR algodystrophy OR "posttraumatic osteoporosis" OR "sympathetic dystrophy" OR ischialg* OR "meralgia paresthetica" OR "piriformis syndrome" OR "acute scrotum" OR "sore throat" OR "biliary colic" OR "kidney colic" OR "Schnitzler syndrome" OR burn* OR dyspareunia OR dysuria OR "migraine disorders" OR "trigeminal autonomic cephalalgias" OR "paroxysmal hemicrania" OR "SUNCT syndrome" OR "trigeminal neuralgia" OR hyperalgesia or erythromelalgia OR "compartment syndrome" OR "fibromyalgia" OR "intermittent claudication" OR "Persian Gulf syndrome" OR "Polymyalgia Rheumatica" OR "carpal tunnel syndrome" OR "cauda equina syndrome" OR "cubital tunnel syndrome" OR "tarsal tunnel syndrome" OR "Thoracic Outlet Syndrome" OR vulvodynia)

3 TS=(pain* OR (physical NEAR/3 suffering$) OR ache$ OR aching OR arthralgia* OR (angina NEAR/3 (stable OR unstable OR pector$s)) OR toothache$ OR tooth-ache$ OR headache$ OR head-ache$ OR glossalgia$ OR earache$ OR ear-ache$ OR "slit ventricle Syndrome" OR "piriformis muscle syndrome" OR "failed back surgery syndrome" OR "renal colic" OR mastodynia$ OR metatarsalgia$ OR "Morton* neuroma*" OR myalgia$ OR neuralgia$ OR sciatica$ OR "phantom limb" OR dysmenor?hea$ OR Polyarthralgia$ OR Arthritis OR "Joint disease$" OR backache$ OR back-ache$ OR "Post operative complications" OR "postoperative Complication$"OR "post-operative complications" OR Sciatica OR lumbago OR "pre-cordial catch$" OR "precordial catch$" OR "pre cordial catch$" OR "texidor twinge" OR stenocardia$ OR otalgia$ OR odontalgia$ OR glossodynia$ OR glossopyroses OR glossopyrosis OR hemicrania OR migraine OR cephalalgia$ OR cephalgia$ OR cephalodynia$ OR "Cerebrospinal Fluid Shunt$" OR Ventriculostomy OR mammalgia$ OR mastalgia$ OR Metatarsus OR "muscle soreness" OR "symphysis pubis dysfunction" OR cervicalgia$ OR cervicodynia$ OR neckache$ OR neck-ache$ OR neurodynia$ OR "Herpes Zoster" OR Perineum OR pseudomelia$ OR pseudo-melia$ OR "Urinary Calculi")

2 TS=("Schnitzler syndrome" OR burns OR dyspareunia OR dysuria OR "migraine disorders" OR "trigeminal neuralgia" OR hyperalgesia OR erythromelalgia OR "compartment syndrome" OR fibromyalgia or "intermittent claudication" OR "Persian Gulf syndrome" OR "Polymyalgia

Rheumatica" OR "carpal tunnel syndrome" OR "cauda equina syndrome" OR "cubital tunnel syndrome" OR "tarsal tunnel syndrome" OR "Thoracic Outlet Syndrome" OR vulvodynia)

#1 TS=Pain

Google Scholar search:

intitle:"Gadolinium-based contrast agents"|"Gadolinium DTPA"|"Gadolinium diethylenetriaminepenta"|"gd DTPA"|"Magnevist"|"Optimark"|"Omniscan"|"Gadoxetic acid"|"gadovist"|"magnevist"|"gadodiamide"|"gadobutrol "|"gadoxetate" intitle:pain

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