U.S. FOOD & DRUG ADMINISTRATION

Integrating Sentinel into Routine Regulatory Drug Review: A Snapshot of the First Year

Contrast and Non-Contrast Magnetic Resonance Imaging (MRI) and Risk for Same Day Seizure

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Contrast MRI

- Gadolinium is a rare earth metal with paramagnetic properties which is widely used to enhance magnetic resonance imaging (MRI) for visualization of internal body structures and blood vessels.

- The gadolinium ion is bound to a proprietary ligand to minimize toxicity in gadolinium based contrast agents (GBCA)

- Review of FAERS identified 183 case reports of seizure within one hour of a contrast MRI [*Phelan K, 2014*].
  - 12 of these reports had no identifiable confounding risk factors

Current Evidence

- Preclinical studies in dogs found a dose-dependent increase in seizure risk with GBCA in the presence of a dysfunctional blood brain barrier [Muldoon, 2015]

- Intraventricular injection of GBCA in rats caused acute neurotoxicity [Ray, 1996]

- Intrathecal injection of GBCA can cause seizures. [Kapoor, 2010; Safriel, 2006].

Study Objective

- Our study aims to quantify the relative risk of same-day seizure requiring transfer to the emergency department (ED) or inpatient admission among patients receiving ambulatory MRI with and without gadolinium contrast.

Cohort of Outpatient MRIs

Inclusion Criteria

- Outpatient Contrast or Non-Contrast MRI
- Extremity or Non-Extremity MRI (i.e. No head MRIs)
- Jan 2008 through Nov 2016
- 2 years of age or older
- 183 days with prescription and medical coverage prior to the index MRI

Exclusion Criteria*

- Recent MRI
- Same day head MRI or head CT
- Seizure or epilepsy
- Antiepileptic drug use
- Myocardial infarction or Stroke
- Syncope
- Brain tumors
- Alzheimer's disease
- Autism spectrum disorder
- Overdose with illegal or legal drugs
- Head injury
- Kidney Disease
- Drug Dependency
- Brain Compression

*Baseline period for exclusion is 183 days prior to index date

Exposure Definition

- Extremity MRI (e.g., upper or lower extremity joint or non-joint imaging)
- Non-extremity MRI (e.g., cervical, thoracic, and lumbar spine, chest, abdomen, and pelvic imaging).
- MR angiography (MRA; extremity and non-extremity)

Self-Controlled Risk Interval Design

- Relative Risk (RR) for seizure calculated, comparing seizure risk on the day of MRI versus the daily adjusted seizure risk in the following 6 weeks
  - Conducted independently for contrast and non-contrast MRI
  - A relative risk ratio for seizure with gadolinium was produced, comparing the contrast MRI versus non-contrast MRI.
  - Stratifications of extremity and non-extremity MRI locations
  - Subset analysis of Magnetic Resonance Angiography (MRA)

Seizure Outcome Ascertainment

- Emergency Department seizure on day of outpatient MRI
  - Epilepsy: 345, 345.X, 345.XX, A subset of G40 ICD10 codes
  - Convulsions: 780.3, 780.3X, R56.00, R56.01, R56.9
  - PPV: 83.6% to 99.3% [Thyagarajan; Jette; Shui; Klien]

- Hospital Admission on day of outpatient MRI
  - Primary Discharge Diagnosis of Epilepsy or Convulsion
  - PPV: 79.1% to 97.7% [Thyagarajan; Jette; Shui; Klien]

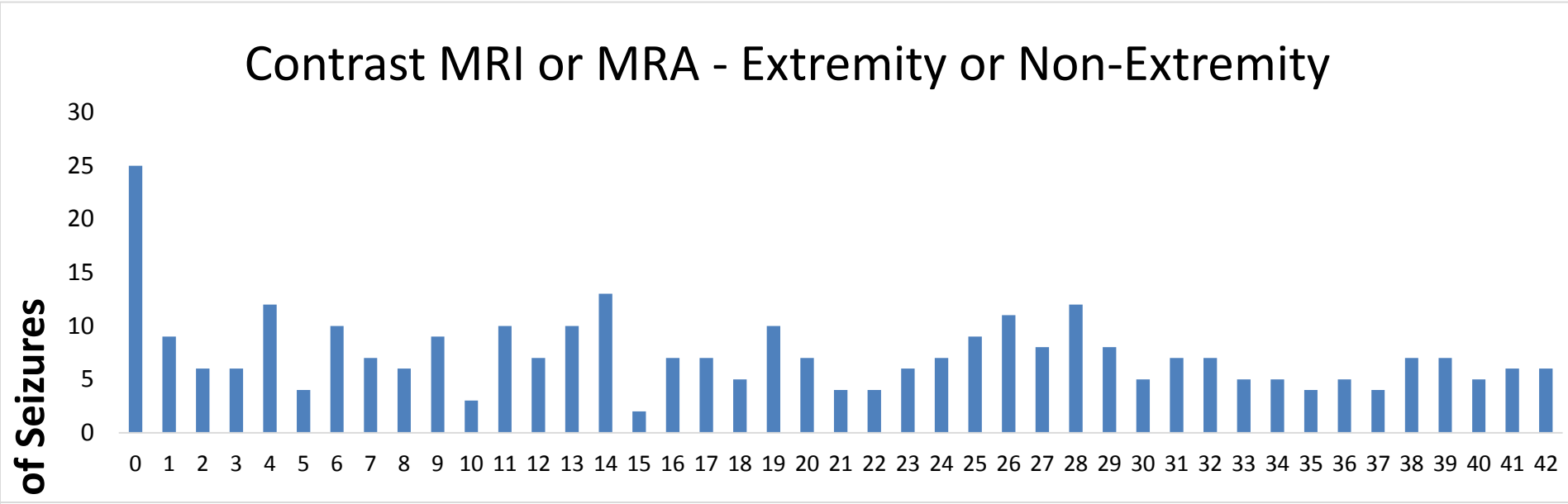
- The sensitivity for seizure coding is unknown.
  - We would expect relatively high rates of presentation to the Emergency Department for a first time convulsive seizure in a non-epileptic

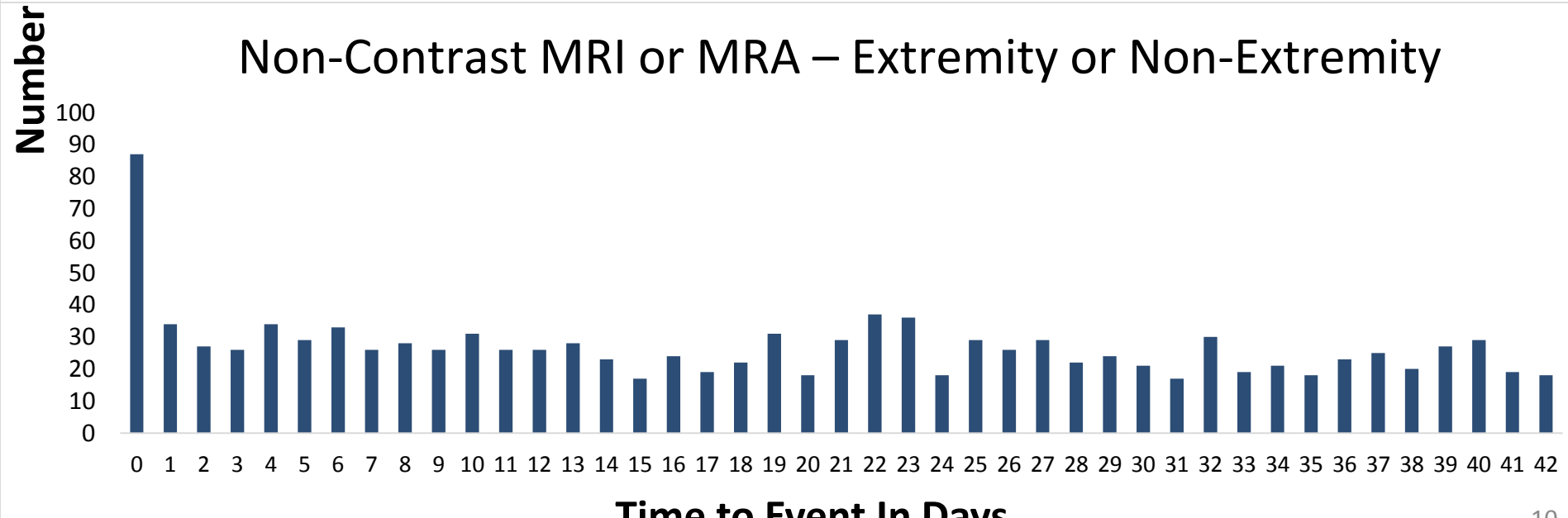
Relative Risk for Seizure with MRI

	Exposure Cohort		*Analysis Cohort*		
	No. of Patients	No. MRIs	No. Risk Window Seizures	No. Control Window Seizures	Relative Risk (95% CI)
Contrast MRI	1,708,779	1,991,158	25	292	3.49 (2.32, 5.25)
Non-Extremity MRI	1,210,037	1,445,364	21	225	3.85 (2.46, 6.03)
Extremity MRI	507,944	535,838	4	66	2.35 (0.86, 6.47)
MRA only	57,705	63,919	3	10	12.60 (3.27, 45.78)
Non-Contrast MRI	6,714,901	7,955,932	87	1,065	3.35 (2.69, 4.16)

Relative Risk Ratio attributable to gadolinium contrast was 1.04 (95%CI: 0.62-1.61)

Frequency of Seizure Events by Day





Results

- Both contrast and non-contrast MRI were associated with an approximate three-fold increased risk for seizure on the day of MRI procedure compared to the following 6 week control window

- Absolute risk is very low; 1 seizure per 79,646 MRI procedures, regardless of contrast

- Gadolinium contrast was not associated with increased seizure risk above that observed with the MRI procedure

- Our study found a higher frequency of seizure with contrast MRA
  - It could be a chance finding due to the smaller number of total seizures (n=13) or it could reflect a dose response relationship.

MRI and Seizure Risk

- Among 9.9 million MRI procedures, some patients are likely to be more susceptible to adverse effects of magnetic fields.
  - Increased susceptibility could occur from factors such as medications, anxiety during the MRI procedure, and acoustic noise from the MRI
  - The absolute risk in our study was one seizure per 79,646 MRI.
  - Even if our study outcome has a sensitivity of 70%, the absolute risk is one seizure per 63,300 MRI.

Limitations

- The exposure and outcome were required to occur in different facilities to identify progression of care from outpatient exposure to emergent treatment.
  - We felt the reverse was unlikely to occur, where patients presenting to emergent care with a new-onset seizure would later that same day undergo an outpatient extremity or non-extremity MRI for a non-neurological condition.
- Our study also does not assess the long term effect of gadolinium deposition in the brain [*McDonald 2015; Kanda 2015*].
- The sensitivity of the seizure algorithm in this study is unknown

Conclusions

- We found increased seizure risk on the same day for both contrast and non-contrast MRI with no differential risk associated with administration of GBCA.

- Given the widespread use of MR imaging and the current trend towards introducing MRI scanners with stronger magnetic fields, questions of potential neurologic side effects warrant more attention.

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Acknowledgments

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Questions?