

## Research Protocol

### Title:

Comparing the effect of venous and non-venous routes of prehospital midazolam on emergency room and inpatient seizure recurrence

### Objective:

To compare the efficacy of prehospital intravenous, intranasal, and intramuscular midazolam on emergency room and inpatient seizure recurrence

### Background:

Benzodiazepines are the guideline recommended first-line treatment option for acute convulsive seizures and status epilepticus.<sup>1</sup> The focus of recent literature has centered on examining various routes of benzodiazepine administration for the cessation of seizures. Multiple clinical trials have confirmed the non-inferiority of intramuscular midazolam to intravenous benzodiazepines in the prehospital setting.<sup>2-4</sup> Studies showing reduced time to seizure cessation, based on route, have led to a complete transformation in the treatment of prehospital status epilepticus.<sup>5</sup>

The efficacy and safety of intramuscular midazolam was firmly established in the RAMPART trial, which has moved novel routes of administration, such as intranasal, to the forefront of prehospital treatment algorithms.<sup>3</sup> Intranasal administration of medications takes advantage of the highly vascularized nasal mucosa, bypasses first pass metabolism, and is absorbed in close proximity to the blood-brain barrier.<sup>6</sup> Its low cost and favorable pharmacokinetic profile have made intranasal midazolam increasingly common in the prehospital setting for indications such as agitated delirium and acute convulsive seizures despite the lack of clinical evidence comparing it to the intramuscular route.<sup>5</sup> Most of the studies to date compare intranasal midazolam to rectal diazepam showing superiority of the intranasal route for the cessation of seizure.<sup>3</sup> When compared to other non-venous routes of benzodiazepine administration, intranasal midazolam is well tolerated and easy to administer. The only study to date comparing the efficacy and safety of intramuscular and intranasal midazolam is a meta-analysis of various non-venous routes.<sup>7</sup> This review has gaps in evidence and variability in study design that limit the clinical application of their conclusions. Research is underway to compare prehospital efficacy of different routes of midazolam administration. However, in order to bridge the gap between prehospital and inpatient treatment of status epilepticus, the proposed study will be the first to directly compare the efficacy and safety of prehospital intravenous, intranasal, and intramuscular midazolam on recurrence of seizure in the emergency department.

### Methods:

This study will be submitted to the institutional review board for approval.

**Study Design:** Retrospective, observational cohort study

**Study Period:** January 1, 2016 – July 31, 2020

**Study Setting:** Huntington Hospital's Emergency Department; Pasadena, California

### **Inclusion Criteria:**

1. Adult and pediatric patients >28 days of age
2. Midazolam administered intravenously, intranasally, and/or intramuscularly
3. Administration in the prehospital setting
4. Indicated for the treatment of active seizure
5. Transport destination: Huntington Memorial Hospital

**Exclusion Criteria:**

1. Midazolam administered for an indication other than active seizure
2. Neonates  $\leq 28$  days of age
3. Pregnant females
4. Patients in police custody
5. Prehospital medication administration record incomplete

**Data Collection:**

The following will be collected from the electronic and paper records to characterize the study population as listed in the data collection sheet:

- Emergency Medical Service (EMS) Electronic Patient Care Record (EPCR): All information documented under the following sections of the EPCR will be collected: incident information, patient assessment, Glasgow Coma Scores (GCS), patient information, comments, complaints, impression, vitals, medication, reassessment, care transferred to, therapies, mucosal atomizer device use
- Emergency and Inpatient Clinical Course: Financial identification number (FIN), age, gender, weight, pregnancy status, date and time of discharge from emergency room, date and time of admission to hospital, date and time of intubation, date and time of extubation, date and time of admission to the intensive care unit (ICU), date and time of discharge to the ICU, diagnosis/etiology of seizure, date and time of discharge, disposition at discharge, vitals and oxygen saturation up to 30 minutes of admission to the ER, ER and inpatient antiepileptic medication administration information, home antiepileptic medications, documented recurrence of seizure, documented adverse reaction to benzodiazepine administration, GCS documented by receiving physician

**Research Outcomes****Primary:**

1. Recurrence of seizure within 30 minutes of emergency department arrival

**Secondary:**

1. Need for rescue antiepileptic therapy administration
2. Adverse drug reactions
3. Rates of intubation
4. Rates of ICU admission

**Study Definitions:**

1. Status Epilepticus
  - a. More than 30 minutes of continuous seizure activity or  $\geq 2$  sequential seizures without recovery of consciousness between seizures
  - b. Patients found by paramedics to be in active seizure will be included given uncertainty of prehospital seizure duration upon arrival
2. Active Seizures:
  - a. Tonic and/or clonic activity
  - b. Focal seizure with altered level of consciousness
  - c. Eye deviation, clenched jaw, lip smacking or focal twitching qualify as subtle signs of seizure
3. Cessation of seizure
  - a. Positive cessation is identified as a "+" signifying "improvement" which is documented in the results section of the electronic patient medical record after the initial administration of midazolam
  - b. Negative cessation is identified by a "-" or an "n" signifying "deterioration" and "no change" per EMS guidelines, respectively
4. Recurrence of seizure
  - a. Documentation of repeated midazolam administration by paramedics prior to hospital arrival
  - b. Documentation of recurrent seizure in the comment history dictated by transporting paramedic

- c. Documentation of benzodiazepine administration for status epilepticus within 30 minutes of arrival to the emergency department
- 5. Rescue antiepileptic therapy
  - a. Administration of medication with antiepileptic properties for the cessation of active seizure after initial midazolam administration within 30 minutes of arrival to the ER
- 6. Adverse drug reaction
  - a. Hypotension:
    - i. Adults:
      - 1. Systolic blood pressure (SBP) < 90mm Hg
    - ii. Pediatrics:
      - 1. Infants (1 to 3 months): SBP <60 mm Hg
      - 2. Infants and children (4 months to 4 years): SBP <70 mm Hg
      - 3. Children (5 to 9 years): SBP <80 mm Hg
      - 4. Adolescents (10-17 years): SBP <90 mm Hg
  - b. Bradycardia:
    - i. Adults: Heart rate <60 beats per minute
    - ii. Pediatrics:
      - 1. Infants (1 to 10 months): <100 beats per minute
      - 2. Infants and children (11 months to 3 years): <90 beats per minute
      - 3. Children (4 to 5 years): <80 beats per minute
      - 4. Children (6 to 9 years): <70 beats per minute
      - 5. Adolescents (10-17 years): <60 beats per minute
  - c. Respiratory depression:
    - i. Adults: <12 breaths per minute
    - ii. Pediatrics:
      - 1. Infants (1 to 18 months): <25 breaths per minute
      - 2. Infants and children (19 months to 4 years): <20 breaths per minute
      - 3. Children (5 to 12 years): <15 breaths per minute
      - 4. Adolescents (13-17 years): <12 breaths per minute
  - d. Oxygen Desaturation:
    - i. Oxygen saturation <94%
  - e. Cardiac arrest requiring adult or pediatric advanced cardiac life support
  - f. Allergic reaction
    - i. Flushing, pruritis, urticaria, angioedema, nausea, vomiting, laryngeal edema, shortness of breath, respiratory arrest, wheezing, disseminated intravascular coagulation within 20 minutes of medication administration

**Statistical Analysis:**

Chi-squared, Student's t, and Mann Whitney U tests will be used to assess continuous data. Fisher's exact test will be applied to categorical data. Additional statistical analysis may be appropriately applied after data collection is complete.

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**References:**

1. Glauser T, Shinnar S, Gloss D, et al. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society. *Epilepsy Currents*, Vol. 16, No. 1 (January/February) 2016 pp. 48–61.
2. Holsti M, Sill B, Firth S, et al. Prehospital Intranasal Midazolam for the Treatment of Pediatric Seizures. *Pediatric Emergency Care*. March 2007. Vol 23; N0 3.
3. Rainbow J, Browne GJ, Lam LT. Controlling seizures in the prehospital setting: diazepam or midazolam. *J Paediatr Child Health*. 2002;38: 582–586.
4. Silbergleit, R, Durkalski V, Lowenstein D, et al. Intramuscular versus Intravenous Therapy for Prehospital Status Epilepticus. *N Engl J Med*. February 2012. 366;7.
5. Department of Health Services Los Angeles County: Prehospital Care Manual. Accessed Aug 2020. <https://dhs.lacounty.gov/more-dhs/departments/ems/resources/prehospital-care-manual-2/>
6. Wolfe T and Braude D. Intranasal Medication Delivery for Children: A Brief Review and Update. *Pediatrics* 2010; 126; 532.
7. Arya R, Kothari H, Zhang Z, et al. Efficacy of nonvenous medications for acute convulsive seizures. *Neurology*. 2015;85:1859–1868
8. Kleinman ME, Chameides L, Schexnayder SM, Samson RA, Hazinski MF, Atkins DL, et al. Pediatric advanced life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Pediatrics*. 2010;126(5):e1361–99. doi: 10.1542/peds.2010-2972D.
9. Glauser TA. Designing practical evidence-based treatment plans for children with prolonged seizures and status epilepticus. *J Child Neurol*. 2007;22(suppl 5):38S–46S.
10. Haybarger E, Young A, Giovannitti J. Benzodiazepine Allergy With Anesthesia Administration: A Review of Current Literature. *Anesth Prog* 63:160–167 2016.
11. Kapur, J, Elm J, Chamberlain J, et al. Randomized Trial of Three Anticonvulsant Medications for Status Epilepticus. *N Engl J Med*. November 2019. 381;22.