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COMPARATIVE EFFICACY AND SAFETY OF INTRAMUSCULAR MIDAZOLAM VERSUS INTRAVENOUS LORAZEPAM IN PREHOSPITAL MANAGEMENT OF STATUS EPILEPTICUS: EVIDENCE FROM RAMPART TRIAL

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ABSTRACT

Background: Status Epilepticus (SE) is a life-threatening neurological emergency that requires immediate treatment. Intravenous (IV) lorazepam is a standard first-line therapy, but IV access is often delayed in Prehospital settings. Intramuscular (IM) Midazolam offers a potential alternative due to its ease of administration. **Objective:** To evaluate and compare the effectiveness of IM midazolam and IV lorazepam in terminating seizures in patients with status epilepticus in a Prehospital setting.

KEYWORDS: *Status epilepticus (SE), Intramuscular (IM) midazolam, Intravenous (IV) Lorazepam, Emergency Medical Services (EMS), seizure treatment, neurological emergencies.*

INTRODUCTION

Epilepsy is a chronic neurological disorder affecting approximately 50 million individuals worldwide, making it one of the most common neurological conditions globally. It is characterized by recurrent, unprovoked seizures resulting from abnormal, excessive neuronal discharges in the brain. Among the various seizure types, generalized tonic-clonic seizures –firmly referred to as "grand mal" seizures-

are particularly dangerous due to their intense motor involvement and potential to escalate into status epilepticus (SE)if not promptly controlled.

Status epilepticus is defined as a seizure lasting longer than five minutes or recurrent seizures without recovery between episodes. It is a life-threatening neurological emergency associated with increased risks of neuronal injury, long-term cognitive impairment, systemic complications, and mortality. The longer a seizure continues, the more difficult it becomes to terminate and the greater the potential for permanent damage. Therefore, early and effective intervention in the Prehospital setting is critical to improving outcomes.

Benzodiazepines are the standard first-line treatment for seizures due to their rapid anticonvulsant effects via potentiation of GABA-A receptor-mediated inhibitory neurotransmission. Intravenous (IV) lorazepam has traditionally been the preferred agent in hospital settings due to its proven efficacy and relatively long duration of action. However, IV administration is often challenging or delayed in Prehospital care, particularly when patients are actively seizing, combative, or in transit. This delay can compromise seizure control and patient safety.

In contrast, intramuscular (IM) midazolam, a short–acting benzodiazepine with high lipid solubility, offers an alternative route of administration that is both practical and rapid. it can be administered without the need for venous access, potentially shortening the time to treatment. Midazolam is also available in auto-injector and intranasal forms, making it especially attractive for emergency medical services (EMS) and out–of–hospital interventions.

The RAMPART (rapid anticonvulsant medication prior to arrival trial) was a pivotal study designed to address the critical question of whether IM midazolam is non-inferior or possibly superior to IV lorazepam in controlling seizures during Prehospital care. Considering the growing need for time-efficient, field-appropriate interventions, comparing these two medications is vital to guiding evidence-based emergency treatment protocols for status epilepticus.

This study aims to analyze and compare the efficacy and safety of (IM) midazolam versus IV lorazepam in real-world, Prehospital settings by examining data from the Rampart trial. Through this, the study seeks to offer insight into optimizing seizure management strategies

and improving clinical outcomes in patients presenting with status epilepticus outside the hospital environment.

METHODS

The RAMPART (rapid anticonvulsant medication prior to arrival trial) was a tightly controlled, multicenter, randomized, double-blind, non-inferiority clinical trial comparing the effectiveness of intramuscular (IM) midazolam with intravenous (IV) lorazepam in pre-hospital treatment of status epilepticus.

This trial design was chosen with deliberate intent to answer an urgent need in emergency neuro care: whether a faster –administered (IM) benzodiazepine would provide seizure control comparable to the proven IV formulation, particularly in time-critical, Prehospital settings when iv access is difficult or delayed .given tolerability of (IM) administration and pharmacokinetics benefits of (IM) midazolam, the study employed a non-inferiority trial design with a pre-specified margin of 10% absolute difference in effect, a cut-off value selected from previous clinical experience, expert opinion, and statically consideration to be a clinically relevant cut-point.

Performed under actual emergency conditions, the trial requested the exception from informed consent (EFIC) provision of U.S. FDA regulation 21 CFR (50.24 t)o reflect both the emergency conditions of se and the ethical necessity of timely intervention (EFIC)procedures were taken up with care, from extensive community consultation to public disclosure across all the regions involved.

PARTICIPANTS

Participants eligible to be registered in the Rampart study were patients with an ongoing generalized convulsive seizure lasting five or more minutes, with unbroken seizure activity documented at the time of (EMS) arrival. Adults and children were eligible if they had met the prior clinical criteria and field operational requirements. Seizures were diagnosed based on paramedic clinical judgment from witnessed convulsive motor activity, consistent with generalized tonic-clonic seizures.

EXCLUSION CRITERIA

Children estimated to be less than 13 kg, based on limitations in reliable dosing available and safety factors related to young paediatric patients. History of hypersensitivity or

contraindications to benzodiazepines. Seizures that the paramedics have assessed to be of non-convulsive origin (e.g., absence, focal non-motor).Presence of trauma or other medical illness that would break the continuity of safe administration of the protocol (e.g., hypotension necessitating alternative immediate intervention)

Pre-enrolment into the trial (same episode) or scenarios in which protocol-adherent treatment was not available (e.g., study kit not available)

In children, weight estimation was derived from the use of a brose low-type tape based on length, allowing for precise assignment to the correct tier of dosing within the field. The system maintained operational usability with dosing safety within a broad age and weight range. All subjects were enrolled under exception from informed consent (EFIC) as per federal regulations (21 CFR 50.24) because of the emergent nature of status epilepticus and infeasibility of prospectively obtaining consent. Community consultation and public disclosure were done thoroughly before trial initiation in every participating EMS region, and educational materials were distributed via many avenues to inform the public and enable opt-outs.

The recruitment was accomplished by more than 4300 trained paramedics who served in 33 NETT network EMS emergencies, among a representative geographic and demographic United States population. A uniform training protocol was adopted by all the EMS agencies for utilizing inclusion/exclusion criteria and intervention protocols equally.

Demographic and clinical information, sex, estimated weight, seizure onset time (if available), type of seizure, and deduced seizure etiology were ascertained in Prehospital care and augmented by data abstracted from inpatient and emergency department records. This population had a broad age range, varied races, and different underlying seizure etiologies.

INTERVENTION

Patients were randomly assigned 1:1, by estimated weight. Participants weighing ≥ 40 kg were randomized to receive either

10 mg IM midazolam +IV placebo, or

IM placebo +4mg IV lorazepam

Paediatric patients less than 40 kg were given either.

5 mg IM midazolam, or 2mg IV lorazepam,

With double–blinding ensured by matching placebo controls.

Randomization sequences were pre-determined and programmed in tamper-evident study drug kits with coordinated internal timers and voice-activated audio recorders to record real-time timestamps of critical events. Paramedics were required to deliver verbal time at predetermined times, such as the time of medication administration, attempts at IV access, seizure termination, and ED arrival, in order to facilitate objective quantification of clinical endpoints.

When IV access had not been obtained within 10 minutes in either arm, rescue was allowed by paramedics per protocol to gain Intraosseous (IO) access. When convulsions did not end 10 minutes after intervention, rescue treatment was initiated per local EMS protocol. In contrast, where seizures did cease before IV drug administration in the IM arm, the study drug was not administered, and the protocol considered the intervention to be completed.

All procedures were conducted in complete compliance with ethical standards governing emergency research. The trial was conducted under an investigational new drug (IND) application, and IRB approval was obtained at each site.

The main efficacy outcome was clinical seizure termination upon ED arrival without the requirement of rescue therapy during EMS transport.

OUTCOMES

The RAMPART trial was systematic and randomized to compare the therapeutic efficacy and safety of intramuscular (IM) versus intravenous (IV) lorazepam or midazolam for Prehospital status epilepticus treatment. The outcomes framework was divided into primary efficacy, safety, and secondary outcomes, each of which was previously specified to assess key clinical and operations measures pertaining to emergency treatment of seizures lasting in the field.

PRIMARY EFFICACY OUTCOME

The primary efficacy measure was clinical resolution of apparent convulsive seizure activity at presentation to the (ED) after a single protocol–determined dose of study drug was given by (EMS) personnel. Central to the measure was the requirement that resolution of seizure activity be accomplished without the necessity of a rescue dose [i.e., second dose of a benzodiazepine] before (ED) presentation.

This result was defined as a binary variable ----seizure activity stopped or present----- according to the clinical opinion of the emergency physician on duty at the time of arrival. Inter–observer variation was minimized by the utilization of standardized clinical assessment methods.

The trial utilized a non-inferiority design, which aimed to compare whether (IM) midazolam was not significantly less effective than (IV) lorazepam. The non-inferiority margin was pre-specified as a 10 absolute difference in the proportion of subjects attaining seizure cessation before (ED) arrival. It was chosen by consensus with experts and clinical acumen and is the boundary beyond which any differential efficacy found would be extremely unlikely to be harmful to patients or affect decision-making.

Sample size and power calculation were set on the basis of an expected rate of seizure termination of around 70% in the IV lorazepam arm based on historical and pilot estimates. The non-inferiority analysis was selected based on the pragmatic benefits of (IM) delivery in Prehospital treatment, especially when intravenous access is not readily available or not timely during an ongoing convulsive seizure.

SAFETY OUTCOMES

Safety endpoints were monitored closely during the trial to enable comparison of the risk profile between treatment arms. Pre-specified safety endpoints included Incidence of acute endotracheal intubation (as airway instrumentation involving placement of a breathing tube either in the field or in the ED) and Recurrence of seizure after initial clinical suppression. Both the safety events were decided upon (EMS) records and (ED) clinical records. Data collection procedures involved clear time-stamping and source tagging to ensure that the data were accurate. These endpoints were chosen to determine potential adverse effects due to prolonged sedation or failure to suppress seizures, including respiratory depression or lack of therapeutic response.

Aside from these main safety procedures, frequent analyses were conducted to identify differences between treatment groups in intubation incidence and recurrence of seizures, thus providing a greater understanding of the safety profile between interventions.

SECONDARY OUTCOMES

In addition to the primary and safety endpoints, a range of secondary outcomes was measured as adjunct to these. These outcomes were chosen to observe treatment-related differences in clinical effectiveness, resource utilization, and the longer-term effects of patient management.

Time-course secondary outcomes were:

Time from EMS arrival on scene to cessation of observed seizure, and Time from the initiation of study drug administration to seizure cessation. To measure these outcomes accurately, EMS staff employed an instrumented logger device that automatically recorded important time points, such as vehicle arrival and drug administration.

STATISTICAL ANALYSIS

The main aim of the RAMPART trial was to find out whether intramuscular (IM) midazolam was non-inferior to intravenous (IV) lorazepam in the pre-hospital management of status epilepticus. The main outcome measure was the number of participants whose seizure was stopped before arrival in the emergency department without rescue treatment. To measure this, a non-inferiority design was used with a pre-specified non-inferiority margin of 10 percentage points.

The non-inferiority hypothesis was evaluated using a one-sided Z-test for the difference in proportions between the two treatment groups (IM midazolam and IV lorazepam). The null hypothesis was that IM midazolam was inferior to IV lorazepam by more than the non-inferiority margin. Although not prospectively designed within trial design, a one-sided superiority test was then performed on an alpha (PF 0.025), after non-inferiority had been demonstrated. The post-hoc analysis was performed to ascertain whether IM midazolam was statistically superior at ending seizures in the out-of-hospital environment.

Secondary outcomes were assessed utilizing two-sided hypothesis tests with a type I error rate of 0.005. These comprised time to end of convulsion (from both study box opening and drug dose administration), rates of acute seizure recurrence, hospital and ICU stay frequency and length, and serious adverse event occurrence, including endotracheal intubation. Independent-samples t-tests based on approximate normality were applied in testing differences between continuous variables, like mean hospital stay duration.

Sample size calculation was for an independent proportions two—group non-inferiority trial. Assuming 70%success for the IV lorazepam arm, as in previous studies, and a non-inferiority margin of 10%, 890 patients (445per arm) would have 90%power to establish non-inferiority at one-sided alpha=0.025.To accommodate this possible unintentional repeat enrolment and other protocol contingencies, the 15% inflation in the sample size resulted in a target of 1024 patients, and confirmed repeat enrolment was excluded from the primary analysis dataset.

All primary outcomes were analyzed on an intention-to-treat (IIT) basis, which included all patients who were randomized and on study medications. Aside from ensuring the solidity of findings, secondary analysis per-protocol was performed excluding patients with pre-specified protocol violations, i.e., Poor dose management, inclusion/exclusion criteria breach, or faulty drug delivery. Sensitivity analyses based on both ITT and per-protocol patients were performed to ensure the validity of the observed treatment effect.

REPORT

PRIMARY OUTCOME

Of the 893 patients who were randomized and treated, seizure termination without rescue therapy on presentation to the emergency department was seen in 73.4% (329of 448)of intramuscular midazolam subjects versus 63.4%(282of445) of intravenous lorazepam subjects. The absolute difference in outcome was 10.1% Points (95%Cl, 4.0 to 16.1), greater than the preset non-inferiority margin of -10 %points and therefore also the requirements for both non-inferiority and superiority ($P<0.001$ for both). This indicates that IM midazolam was not just as, but likely superior to IV lorazepam in the prevention of seizures upon arrival at the emergency department without the requirement of further benzodiazepine treatment.

Additionally, the percentage of patients arriving at the ED without persistent convulsion, with or without rescue therapy, was greater in the IM group (83.9%) than in the IV group (76.2%).

A noteworthy difference existed in the rate of failure to administer the study medication. In the IV group, 31 patients (7.0%) received no study drug due to unsuccessful attempts at vascular access. In the IM group, only 5 patients (1.1%) did not receive the assigned drug, primarily due to auto-injector failure or application failure. This operational advantage likely contributed to the superior efficacy of the IM group.

SECONDARY OUTCOMES

Time to treatment and seizure cessation

The time from opening the study box until drug administration was shorter for the IM group (1.2 minutes) than for the IV group (4.8 minutes)

Time to cease seizure was shorter for the IV group (1.6 minutes) compared with the IM group (3.3 minutes).

Whereas the onset time was more sluggish in each group, total time to seizure suppression following the opening of the study box was not substantially different between groups but demonstrated the pragmatic benefit of faster administration in the IM group.

CONCLUSION

This study indicates that* intramuscular (IM) midazolam is at least as safe and effective as *intravenous (IV) lorazepam for stopping seizures in the Prehospital setting for subjects in status epilepticus*.

This represents an absolute difference of 10 % points, demonstrating that IM midazolam was *non-inferior and even superior to IV lorazepam ($p<0.001$ for both non-inferiority and superiority)

The study concludes that intramuscular (IM) midazolam is at least as safe and effective as intravenous (IV) lorazepam for the Prehospital treatment of status epilepticus. IM administration resulted in faster initiation of treatment due to ease of delivery, despite a slightly slower onset of action.

Overall time to seizure cessation was similar between groups, with IM midazolam demonstrating superior efficacy in seizure control upon emergency department arrival. Safety outcomes, including rates of intubation and seizure recurrence, were comparable between the two groups. Given its reliability, rapid administration, and logistical advantages, IM midazolam is a practical first-line option for use by emergency medical services in the Prehospital setting.

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