The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 16, 2012 VOL. 366 NO. 7

Intramuscular versus Intravenous Therapy for Prehospital Status Epilepticus

Robert Silbergleit, M.D., Valerie Durkalski, Ph.D., Daniel Lowenstein, M.D., Robin Conwit, M.D., Arthur Pancioli, M.D., Yuko Palesch, Ph.D., and William Barsan, M.D., for the NETT Investigators*

ABSTRACT

BACKGROUND

Early termination of prolonged seizures with intravenous administration of benzodiazepines improves outcomes. For faster and more reliable administration, paramedics increasingly use an intramuscular route.

METHODS

This double-blind, randomized, noninferiority trial compared the efficacy of intramuscular midazolam with that of intravenous lorazepam for children and adults in status epilepticus treated by paramedics. Subjects whose convulsions had persisted for more than 5 minutes and who were still convulsing after paramedics arrived were given the study medication by either intramuscular autoinjector or intravenous infusion. The primary outcome was absence of seizures at the time of arrival in the emergency department without the need for rescue therapy. Secondary outcomes included endotracheal intubation, recurrent seizures, and timing of treatment relative to the cessation of convulsive seizures. This trial tested the hypothesis that intramuscular midazolam was noninferior to intravenous lorazepam by a margin of 10 percentage points.

RESULTS

At the time of arrival in the emergency department, seizures were absent without rescue therapy in 329 of 448 subjects (73.4%) in the intramuscular-midazolam group and in 282 of 445 (63.4%) in the intravenous-lorazepam group (absolute difference, 10 percentage points; 95% confidence interval, 4.0 to 16.1; $P<0.001$ for both noninferiority and superiority). The two treatment groups were similar with respect to need for endotracheal intubation (14.1% of subjects with intramuscular midazolam and 14.4% with intravenous lorazepam) and recurrence of seizures (11.4% and 10.6%, respectively). Among subjects whose seizures ceased before arrival in the emergency department, the median times to active treatment were 1.2 minutes in the intramuscular-midazolam group and 4.8 minutes in the intravenous-lorazepam group, with corresponding median times from active treatment to cessation of convulsions of 3.3 minutes and 1.6 minutes. Adverse-event rates were similar in the two groups.

CONCLUSIONS

For subjects in status epilepticus, intramuscular midazolam is at least as safe and effective as intravenous lorazepam for prehospital seizure cessation. (Funded by the National Institute of Neurological Disorders and Stroke and others; ClinicalTrials.gov number, NCT00809146.)

From the Department of Emergency Medicine, University of Michigan, Ann Arbor (R.S., W.B.); the Department of Medicine, Division of Biostatistics and Epidemiology, Medical University of South Carolina, Charleston (V.D., Y.P.); the Department of Neurology, University of California, San Francisco, San Francisco (D.L.); the National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD (R.C.); and the Department of Emergency Medicine, University of Cincinnati, Cincinnati (A.P.). Address reprint requests to Dr. Silbergleit at the Department of Emergency Medicine, Suite 3100, 24 Frank Lloyd Wright Dr., Ann Arbor, MI 48105, or at robert.silbergleit@umich.edu.

*The Neurological Emergencies Treatment Trials (NETT) investigators are listed in the Supplementary Appendix, available at NEJM.org.

This article (10.1056/NEJMoa1107494) was updated on February 16, 2012.

N Engl J Med 2012;366:591-600.

Early termination of prolonged epileptic seizures in response to intravenous administration of benzodiazepines by paramedics in the prehospital setting is associated with better patient outcomes. The randomized, controlled Prehospital Treatment of Status Epilepticus (PHTSE) trial (ClinicalTrials.gov number, NCT00004297) compared diazepam, lorazepam, and placebo given intravenously by paramedics to treat subjects with prolonged convulsive seizures.[1] The trial showed that both these benzodiazepines were an effective prehospital treatment for seizures, as compared with placebo. The proportion of subjects whose seizures were terminated at the time of arrival in the emergency department was 59.1% in the group receiving intravenous lorazepam, 42.6% in the group receiving intravenous diazepam, and 21.1% in the group receiving intravenous placebo.

Many emergency medical services (EMS) systems, however, have begun to use intramuscular midazolam rather than an intravenous agent, largely because intramuscular administration is faster and is consistently achievable.[2] This practice has become increasingly common despite the lack of clinical-trial data regarding the efficacy and safety of intramuscular midazolam. Although intravenous lorazepam is the preferred treatment for patients with seizures in the emergency department (and was the most effective treatment in the PHTSE trial), it is rarely used by paramedics in the prehospital setting because of the potential difficulty with intravenous administration, as well as the short shelf-life of lorazepam when it is not refrigerated.[3] EMS medical directors need a practical alternative that is at least as safe and effective as intravenous lorazepam. We therefore performed a noninferiority study to determine whether intramuscular midazolam is as effective as intravenous lorazepam, with a similar degree of safety, for terminating status epilepticus seizures before arrival at the hospital.

Methods

Study Design

The Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) was a randomized, double-blind, phase 3, noninferiority clinical trial. It was designed and conducted by the Neurological Emergencies Treatment Trials (NETT) network, a multidisciplinary clinical trials infrastructure funded by the National Institute of Neurological Disorders and Stroke (NINDS). The investigators were responsible for all elements of the trial, including design, data collection, and analysis. The authors wrote the manuscript and vouch for the data and analysis. The trial was performed under an Investigational New Drug application with the Food and Drug Administration (FDA). Autoinjectors with active medication and placebo were purchased by the Department of Defense and provided to the NINDS through a cooperative agreement. The Department of Defense had no role in the design of the study, accrual or analysis of data, or preparation of the manuscript. The study was conducted in accordance with the protocol, which is available with the full text of this article at NEJM.org.

RAMPART involved 4314 paramedics, 33 EMS agencies, and 79 receiving hospitals across the United States. Paramedics received continuing medical education in the management of seizures and other neurologic emergencies, as well as supplemental training in human subjects research and protections and in the study protocol, with refresher protocol training provided throughout the trial.

The trial met the exception from informed-consent requirements for emergency research under the FDA code of regulations 21 CFR 50.24.[4] Institutional review boards for all entities engaged in this research reviewed local community consultation activity, according to the regulations regarding the exception from informed consent, and provided approval. Subjects or their legally authorized representatives were notified about enrollment in the trial by the study team as soon as possible, usually while the subject was still in the emergency department, and provided written informed consent to allow continued data collection until follow-up was completed.

Study Subjects

The intended study population included children with an estimated body weight of 13 kg or more and adults requiring treatment with benzodiazepines for status epilepticus in the prehospital setting. Subjects were enrolled if they were having convulsive seizures at the time of treatment by paramedics and were reported by reliable witnesses to have been continuously convulsing for longer than 5 minutes or if they were having convulsive seizures at the time of treatment after having in-

termittent seizures without regaining consciousness for longer than 5 minutes.

Subjects were excluded for the following reasons: the acute precipitant of the seizures was major trauma, hypoglycemia, cardiac arrest, or a heart rate of less than 40 beats per minute (since these conditions require alternative treatments); they had a known allergy to midazolam or lorazepam; they were known to be pregnant or a prisoner; they were being treated as part of another study; or, preemptively, they opted out of this study by wearing a medical-alert tag marked "RAMPART declined."

STUDY INTERVENTION

When they arrived at the scene, the study paramedics rapidly performed an initial assessment and stabilized subjects who were in status epilepticus, according to their local EMS protocols. For subjects who met the eligibility criteria, the paramedics began the study procedure by opening an instrumented box containing a study drug kit. Each kit contained two color-coded, shrink-wrapped study-drug bundles, one for each dose tier; each bundle consisted of one intramuscular autoinjector (Investigational Midazolam Autoinjector [Meridian Medical Technologies]) and one prefilled intravenous syringe (Carpuject System [Hospira]). All adults and those children with an estimated body weight of more than 40 kg received either 10 mg of intramuscular midazolam followed by intravenous placebo or intramuscular placebo followed by 4 mg of intravenous lorazepam. In children with an estimated weight of 13 to 40 kg, the active treatment was 5 mg of intramuscular midazolam or 2 mg of intravenous lorazepam. Blinding and simple randomization with equal numbers of subjects assigned to the two study groups were achieved with the use of a double-dummy strategy, in which each kit was randomly assigned at the central pharmacy to contain either the active intramuscular drug with intravenous placebo or intramuscular placebo with the active intravenous drug. All subjects were treated with the intramuscular autoinjector, after which venous access was immediately achieved and treatment was administered by means of intravenous syringe. Subjects were considered to be enrolled in the trial when the intramuscular autoinjector was applied, regardless of whether the intramuscular dose was successfully delivered.

A voice recorder was activated by opening the study box. Paramedics were instructed to record oral statements when intramuscular treatment was administered, when intravenous access was obtained, when the intravenous study drug was administered, when any rescue treatments were given, and when convulsions were observed to stop. Each statement was time-stamped by the study box's internal clock. Paramedics also stated whether the subject was convulsing on arrival at the emergency department.

When it was difficult to obtain intravenous access, paramedics were instructed to continue attempts for at least 10 minutes, but they were permitted to use intraosseous access at any time in lieu of intravenous access. For the purposes of this trial, intraosseous access to the vascular space was considered equivalent to intravenous access. Rescue therapy, as dictated by local EMS protocol, was recommended for use in subjects who were still convulsing 10 minutes after the last study medication was administered. If there was a delay in obtaining intravenous access and the subject stopped having seizures before the intravenous study drug could be given, the intravenous study medication was not used. If convulsions resumed later during EMS transport, rescue therapy (according to the local protocol) was to be given.

STUDY OUTCOMES

The primary outcome was termination of seizures before arrival in the emergency department without the need for the paramedics to provide rescue therapy. Subjects did not reach the primary outcome if they were having seizures on arrival in the emergency department or if they received rescue medication before arrival. Termination of seizures on arrival was determined according to the clinical judgment of the attending emergency physician and was based on examination of the subjects, their clinical course, and results of any routine diagnostic testing (Section 6.1 of the protocol). This outcome measure was previously used in the PHTSE trial.[1,5]

Key secondary outcome measures included the time from study-box opening to termination of convulsions and the time from initiation of active-drug administration to termination of convulsions (among subjects in whom convulsions ceased before arrival in the emergency department), the frequency and duration of hospitalization and of admissions to the intensive care unit, and the frequencies of acute endotracheal intubation and acute seizure recurrence. Acute endotracheal in-

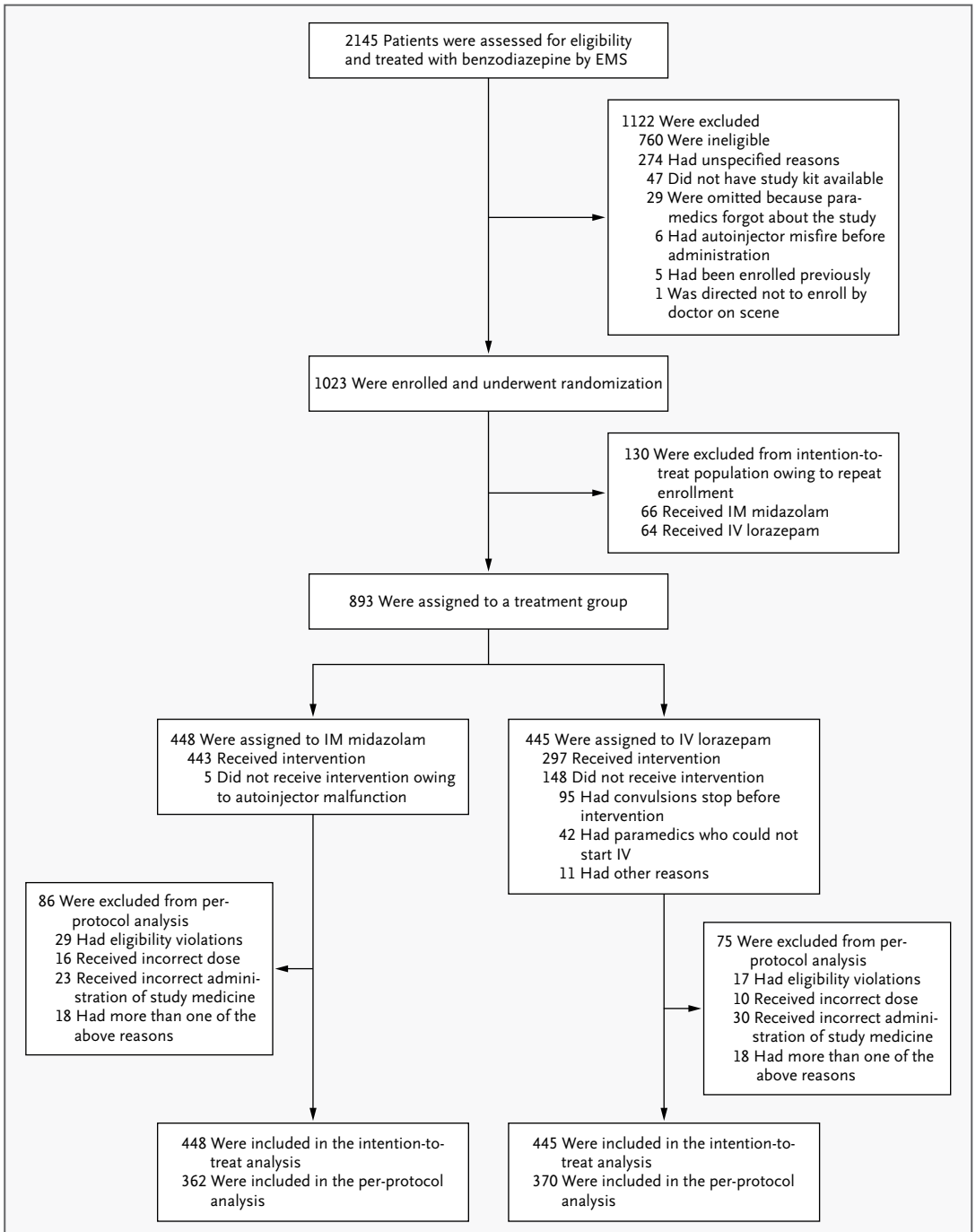

Figure 1. Screening, Enrollment, Randomization, and Inclusion in Intention-to-Treat and Per-Protocol Analyses.

The number of patients who were assessed and enrolled includes any repeat assessments and enrollments for those who presented to emergency medical services (EMS) with status epilepticus more than once. The number assigned to treatment in the intention-to-treat analysis includes every patient who was enrolled in the study but only the initial enrollment for those enrolled more than once. Randomization was defined as occurring when an autoinjector was applied to the subject. "Misfire" refers to instances when the autoinjector was inadvertently triggered before it could be applied to the subject. "Malfunction" refers to instances when the autoinjector was applied but the drug was not administered because of operator error or mechanical failure. IM denotes intramuscular, and IV intravenous.

tubation was defined as intubation performed or attempted by EMS personnel or performed within 30 minutes after arrival in the emergency department. Acute seizure recurrence was defined as any further convulsive or electrographic seizures that required additional antiepileptic medications during the first 12 hours of hospitalization in subjects who did not have seizures on arrival in the emergency department. Serious adverse events were recorded through the end of the study for every subject (see Table A2 in the Supplementary Appendix, available at NEJM.org).

STATISTICAL ANALYSIS

The primary objective of the study was to show that the proportion of subjects whose seizures were terminated before arrival in the emergency department (without the use of rescue medications) in the intramuscular midazolam group was not inferior to that in the intravenous lorazepam group by more than a prespecified amount (the noninferiority margin). The null hypothesis of inferiority was tested with the use of a one-sided z statistic.[6] The primary analysis was followed by a one-sided test (conditional on the finding of noninferiority) for superiority at a significance level of 0.025, although this was not prespecified in the protocol. On the basis of published studies of similar patient populations, and accounting for differences in the dose of lorazepam and in the definition of efficacy, we estimated that after an initial dose of intravenous lorazepam had been administered, seizures would be terminated in 70% of subjects before arrival in the emergency department. Sample size was estimated on the basis of the comparison of independent proportions, with two planned interim analyses for futility with respect to the primary outcome; 90% power to show the noninferiority of intramuscular midazolam; a noninferiority margin of 10 percentage points; and a one-sided test with the probability of a type I error of 0.025. The maximum sample size required for randomization was 890 subjects (445 per treatment group). Because some patients have recurring episodes of status epilepticus, the total sample size was inflated by 15% (1024 subjects) to account for inadvertent repeated enrollment of the same subjects. (Repeated enrollments of the same subject were not analyzed.) Secondary outcomes were compared in a superiority framework with the use of a two-sided test with the

Table 1. Characteristics of the Subjects at Baseline.*

Characteristic	IM Midazolam (N=448)	IV Lorazepam (N=445)
Age		
Mean (range) — yr	43±22 (0–102)	44±22 (1–94)
Age group — no. (%)		
0–5 yr	32 (7)	29 (7)
6–10 yr	15 (3)	20 (4)
11–20 yr	28 (6)	21 (5)
21–40 yr	114 (25)	112 (25)
41–60 yr	169 (38)	169 (38)
≥61 yr	90 (20)	94 (21)
Male sex — no. (%)	250 (56)	238 (53)
Race — no. (%)†		
Black	229 (51)	224 (50)
White	165 (37)	183 (41)
Other, mixed, or unknown	54 (12)	38 (9)
Ethnic group — no. (%)†		
Non-Hispanic	310 (69)	290 (65)
Hispanic	49 (11)	57 (13)
Unknown	89 (20)	98 (22)
Dose tier — no. (%)‡		
Low	62 (14)	59 (13)
High	386 (86)	386 (87)
History of epilepsy — no. (%)		
Yes	293 (65)	295 (66)
No	111 (25)	103 (23)
Not documented	44 (10)	47 (11)
Final diagnosis — no. (%)		
Status epilepticus	404 (90)	399 (90)
Nonepileptic spell	31 (7)	32 (7)
Undetermined	13 (3)	14 (3)
Precipitating cause of status epilepticus — no. (%)		
Noncompliance with or discontinuation of anticonvulsant therapy	137 (31)	141 (32)
Idiopathic or breakthrough status epilepticus	121 (27)	121 (27)
Coexisting condition that lowered seizure threshold	33 (7)	29 (7)

* Plus–minus values are means ±SD. There were no significant differences between the two groups with respect to baseline characteristics.
† Race and ethnic group were reported by the investigators. More detailed data for race are provided in Table A3 in the Supplementary Appendix.
‡ The high-dose tier included children whose estimated body weight was above 40 kg and all adults, and active treatment consisted of either 10 mg of intramuscular (IM) midazolam or 4 mg of intravenous (IV) lorazepam. The low-dose tier included children whose estimated body weight was 13 to 40 kg, and active treatment consisted of either 5 mg of IM midazolam or 2 mg of IV lorazepam.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.