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.)

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

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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. 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. 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. 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 vouched 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. 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-
study box. Paramedics were instructed to record
tramuscular dose was successfully delivered.
injector was applied, regardless of whether the in-
enrolled in the trial when the intramuscular auto-
travenous syringe. Subjects were considered to be
treated with the intramuscular autoinjector, after
we were known to be pregnant or a
prisoner; they were being treated as part of an-
other 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 paramed-
ics 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 instru-
ment 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 (In-
vestigational Midazolam Autoinjector [Meridian
Medical Technologies]) and one prefilled intrave-
nous syringe (Carpject 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 es-
timated weight of 13 to 40 kg, the active treatment
was 5 mg of intramuscular midazolam or 2 mg of
intravenous lorazepam. Blinding and simple ran-
domization with equal numbers of subjects as-
signed 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 pharma-
cy 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 in-
travenous syringe. Subjects were considered to be
enrolled in the trial when the intramuscular auto-
injector was applied, regardless of whether the in-
tramuscular 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 ob-
tained, when the intravenous study drug was ad-
ministered, when any rescue treatments were giv-
en, 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 ac-
cess, paramedics were instructed to continue at-
ttempts for at least 10 minutes, but they were per-
mitted 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. Res-
cue 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 (accord-
ting to the local protocol) was to be given.

STUDY OUTCOMES
The primary outcome was termination of seizures
before arrival in the emergency department with-
out the need for the paramedics to provide rescue
therapy. Subjects did not reach the primary out-
come 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 diagno-
sic testing (Section 6.1 of the protocol). This out-
come 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 be-
fore arrival in the emergency department), the
frequency and duration of hospitalization and of
admissions to the intensive care unit, and the fre-
cuencies 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>
<thead>
<tr>
<th>Characteristic</th>
<th>IM Midazolam (N = 448)</th>
<th>IV Lorazepam (N = 445)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean (range) — yr</td>
<td>43±22 (0–102)</td>
</tr>
<tr>
<td>Age group — no. (%)</td>
<td>0–5 yr</td>
<td>32 (7)</td>
</tr>
<tr>
<td></td>
<td>6–10 yr</td>
<td>15 (3)</td>
</tr>
<tr>
<td></td>
<td>11–20 yr</td>
<td>28 (6)</td>
</tr>
<tr>
<td></td>
<td>21–40 yr</td>
<td>114 (25)</td>
</tr>
<tr>
<td></td>
<td>41–60 yr</td>
<td>169 (38)</td>
</tr>
<tr>
<td></td>
<td>≥61 yr</td>
<td>90 (20)</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>250 (56)</td>
<td>238 (53)</td>
</tr>
<tr>
<td>Race — no. (%)†</td>
<td>Black</td>
<td>229 (51)</td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>165 (37)</td>
</tr>
<tr>
<td></td>
<td>Other, mixed, or unknown</td>
<td>54 (12)</td>
</tr>
<tr>
<td>Ethnic group — no. (%)†</td>
<td>Non-Hispanic</td>
<td>310 (69)</td>
</tr>
<tr>
<td></td>
<td>Hispanic</td>
<td>49 (11)</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>89 (20)</td>
</tr>
<tr>
<td>Dose tier — no. (%)‡</td>
<td>Low</td>
<td>62 (14)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>386 (86)</td>
</tr>
<tr>
<td>History of epilepsy — no. (%)</td>
<td>Yes</td>
<td>293 (65)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>111 (25)</td>
</tr>
<tr>
<td></td>
<td>Not documented</td>
<td>44 (10)</td>
</tr>
<tr>
<td>Final diagnosis — no. (%)</td>
<td>Status epilepticus</td>
<td>404 (90)</td>
</tr>
<tr>
<td></td>
<td>Nonepileptic spell</td>
<td>31 (7)</td>
</tr>
<tr>
<td></td>
<td>Undetermined</td>
<td>13 (3)</td>
</tr>
<tr>
<td>Precipitating cause of status epilepticus — no. (%)</td>
<td>Noncompliance with or discontinuation of anticonvulsant therapy</td>
<td>137 (31)</td>
</tr>
<tr>
<td></td>
<td>Idiopathic or breakthrough status epilepticus</td>
<td>121 (27)</td>
</tr>
<tr>
<td></td>
<td>Coexisting condition that lowered seizure threshold</td>
<td>33 (7)</td>
</tr>
</tbody>
</table>

* 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.
probability of a type I error of less than 0.05. All analyses were conducted with the intention-to-treat population defined as all subjects randomly assigned to a study medication. A sensitivity analysis was conducted with the per-protocol population, which excluded subjects with any of the following three predefined protocol deviations: eligibility violation, incorrect dose of study medication, or incorrect administration.

### Results

#### Subjects and Enrollment

Between June 15, 2009, and January 14, 2011, a total of 893 subjects were enrolled (with a total of 1023 enrollments and a reenrollment rate of 13%) (Fig. 1). The two treatment groups were well balanced with respect to demographic and clinical characteristics.

#### Table 2. Primary and Secondary Outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intention-to-Treat Analysis† (N = 893)</th>
<th>Per-Protocol Analysis‡ (N = 732)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IM Midazolam (N = 448)</td>
<td>IV Lorazepam (N = 445)</td>
</tr>
<tr>
<td></td>
<td>IM Midazolam (N = 362)</td>
<td>IV Lorazepam (N = 370)</td>
</tr>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizures terminated, no rescue therapy given</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of subjects</td>
<td>329</td>
<td>282</td>
</tr>
<tr>
<td>% of subjects (95% CI)</td>
<td>73.4 (69.3–77.5)</td>
<td>63.4 (58.9–67.9)</td>
</tr>
<tr>
<td>Treatment failed — no. of subjects (%)</td>
<td>119 (26.6)</td>
<td>163 (36.6)</td>
</tr>
<tr>
<td>Seizures not terminated, no rescue therapy given</td>
<td>50 (11.2)</td>
<td>64 (14.4)</td>
</tr>
<tr>
<td>Seizures not terminated, rescue therapy given</td>
<td>22 (4.9)</td>
<td>42 (9.4)</td>
</tr>
<tr>
<td>Seizures terminated, rescue therapy given</td>
<td>47 (10.5)</td>
<td>57 (12.8)</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endotracheal intubation within 30 min after ED arrival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of subjects — %</td>
<td>63 (14.1)</td>
<td>64 (14.4)</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>0.98 (0.70–1.34)</td>
<td>1.02 (0.71–1.45)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of subjects — %</td>
<td>258 (57.6)</td>
<td>292 (65.6)</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>0.88 (0.79–0.98)</td>
<td>0.86 (0.77–0.96)</td>
</tr>
<tr>
<td>ICU admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of subjects — %</td>
<td>128 (28.6)</td>
<td>161 (36.2)</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>0.79 (0.65–0.95)</td>
<td>0.76 (0.61–0.93)</td>
</tr>
<tr>
<td>Recurrent seizure within 12 hr after ED arrival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of subjects — %</td>
<td>51 (11.4)</td>
<td>47 (10.6)</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>1.08 (0.74–1.56)</td>
<td>0.97 (0.63–1.48)</td>
</tr>
<tr>
<td>Hypotension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of subjects — %</td>
<td>12 (2.7)</td>
<td>13 (2.9)</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>0.92 (0.42–1.98)</td>
<td>0.57 (0.19–1.67)</td>
</tr>
</tbody>
</table>

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**Figure 2.** Primary Outcome According to Treatment Group.

$P_{IM} - P_{IV}$ represents the absolute difference in the primary outcome between the proportion of subjects treated with IM midazolam and the proportion treated with IV lorazepam (i.e., the proportion of subjects who did not have seizures on arrival in the emergency department and who did not receive rescue medication). CI denotes confidence interval.
characteristics, dose tier, presence or absence of a history of epilepsy, accuracy of the diagnosis of status epilepticus (vs. a discharge diagnosis of a non-epileptic spell), and the diagnosis of the underlying cause of status epilepticus (Table 1). The overall number of subjects who were black reflected the proportion of blacks in the subject population from which the sample was drawn.

**PRIMARY OUTCOME**

Seizures were absent without rescue therapy on arrival in the emergency department in 329 of 448 subjects assigned to active treatment with intramuscular midazolam (73.4%) and in 282 of 445 assigned to active treatment with intravenous lorazepam (63.4%) (difference, 10 percentage points; 95% confidence interval [CI], 4.0 to 16.1; \( P<0.001 \) for noninferiority and \( P<0.001 \) for superiority) (Fig. 2). The primary results were similar in the per-protocol analysis. Table 2 shows the number of subjects who were having seizures at the time of arrival in the emergency department and the number who needed rescue medication. Subjects randomly assigned to the intramuscular group were less likely to be having seizures on arrival in the emergency department (regardless of the use or nonuse of rescue therapy) than were those randomly assigned to the intravenous group (proportion of subjects without seizures, 83.9% vs. 76.2%; difference, 7.7 percentage points; 95% CI, 2.5 to 12.9). Inability to start an intravenous infusion was anticipated to be a common reason for failure of intravenous therapy. Among subjects in the intravenous group who did not reach the primary outcome, 31 never received the intravenous study medication because of failure to obtain vascular access, whereas only 5 in the entire intramuscular group did not receive the intramuscular study medication owing to malfunction or misapplication of the autoinjector.

**SECONDARY AND SAFETY OUTCOMES**

The secondary and safety outcomes were consistent with the primary outcome and reinforced the
finding that intramuscular midazolam was non-inferior to intravenous lorazepam. The frequencies of endotracheal intubation, recurrent seizures, and other predefined safety outcomes were similar in the two study groups (Table 2). Among subjects admitted to the hospital, the lengths of stay in the intensive care unit and in the hospital did not differ significantly between the groups, but the proportion of subjects admitted was significantly lower (and the proportion discharged from the emergency department was significantly higher) in the intramuscular group than in the intravenous group (P = 0.01).

Figure 3 shows the temporal data (the times from administration of active treatment to cessation of convulsions, from box opening to cessation of convulsions, and from box opening to administration of active treatment) for the 317 subjects in the intention-to-treat analysis who met the primary outcome and for whom times of active treatment and of cessation of convulsions were recorded. The median time to administration of active treatment was significantly shorter by the intramuscular route than by the intravenous route (1.2 vs. 4.8 minutes), but the onset of action (i.e., termination of convulsions) occurred sooner after intravenous administration than after intramuscular administration (1.6 vs. 3.3 minutes). The overall interval until termination of convulsions was similar in the two treatment groups.

**DISCUSSION**

This double-blind, randomized trial showed that prehospital treatment with intramuscular midazolam was at least as effective as intravenous lorazepam in subjects in status epilepticus (P<0.001 for noninferiority and for superiority). Establishing intravenous access in patients who are having seizures in the prehospital environment can be challenging and time-consuming. Since intramuscular treatments can be given more quickly and reliably than intravenous treatments and have noninferior efficacy, our data support the use of the former route of administration by EMS personnel.

The use by EMS systems of intramuscular midazolam for status epilepticus has been increasing because small studies have indicated its efficacy and because this drug is rapidly absorbed intramuscularly. According to a meta-analysis of small trials, the use of nonintravenous midazolam in the hospital setting compared favorably with intravenous diazepam in the emergency treatment of status epilepticus. Furthermore, unlike lorazepam, midazolam does not have the problem of poor stability when not refrigerated. Midazolam can be administered by other nonintravenous routes as well, but the intramuscular route is more consistently effective than the intranasal or buccal routes because the drug cannot be blown or spat out by the convulsing patient.
In this noninferiority study, we used lorazepam as an active control. Inclusion of a placebo group would have been unethical, since PHTSE showed unambiguously that benzodiazepines are superior to no treatment in subjects in status epilepticus in the prehospital setting. The clinically important question is whether intramuscular midazolam works well enough for patients in status epilepticus to routinely forgo the intravenous route in order to improve the ease and speed of treatment administered by EMS personnel. The active control drug, the noninferiority margin, the trial setting, and the analysis plan were carefully chosen to avoid the known potential pitfalls and limitations of noninferiority studies.

The doses of midazolam and lorazepam used in this trial are consistent with the most effective doses for the treatment of status epilepticus that are reported in the literature. Although these initial doses are higher than the ones used by many EMS systems and emergency physicians, they are the same as those approved for this indication and are in line with those used by epileptologists. Use of an autoinjector maximized the speed and ease of intramuscular delivery (with a nominal latency period of about 20 seconds for opening the autoinjector and administering the medication) and reduced delays in initiating intravenous access.

The relationships among benzodiazepine dose, respiratory depression, and subsequent need for endotracheal intubation are poorly characterized, but higher doses of benzodiazepines may actually reduce the number of airway interventions. Our data are consistent with the finding that endotracheal intubation is more commonly a sequela of continued seizures than it is an adverse effect of sedation from benzodiazepines.

With regard to the mechanism of drug action, our temporal data are consistent with what would be expected: the intramuscular route delivers the medication more rapidly after the paramedics’ arrival at the scene than the intravenous route, but its onset of action is more rapid after intravenous administration than after intramuscular administration. The time saved by using the intramuscular route appears to more than offset the delay in the drug’s onset of action. It is interesting to speculate that a difference of just a few minutes with the earlier administration in the intramuscular group may have been enough to drive the slight superiority of the intramuscular route with respect to outcome. However, it is also possible that the difference in outcome between the two treatment groups reflects differences in the efficacy of the agents used rather than in the route of administration. Because this is a pragmatic clinical trial designed to inform EMS clinical practice rather than to elucidate mechanism, the effect of agent and route cannot be meaningfully separated in analyzing these data. Similarly, an autoinjector was used in this study to optimize the speed and efficiency of intramuscular delivery, but it is not possible to determine the importance of using this tool for intramuscular injections, as compared with conventional intramuscular injections.

Our data are consistent with a finding of statistical superiority of intramuscular midazolam. Regardless of whether it is noninferior or superior, this trial supports the clinical decision to use the more pragmatic intramuscular approach in the prehospital treatment of status epilepticus.

In conclusion, intramuscular midazolam is noninferior to intravenous lorazepam in stopping seizures before arrival in the emergency department in patients with status epilepticus treated by paramedics. Intramuscular midazolam is also as safe as intravenous lorazepam. The group of subjects treated with intramuscular midazolam had a higher rate of discharge from the emergency department than the group treated with intravenous lorazepam and had similar or lower rates of recurrent seizures and endotracheal intubation. The intramuscular administration of midazolam by EMS is a practical, safe, and effective alternative to the intravenous route for treating prolonged convulsive seizures in the prehospital setting.

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