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Critical appraisal of “Silbergleit R, Durkalski V, Lowenstein D, Conwit R, Pancioli A, Palesch Y, Barsan W, NETT Investigators. Intramuscular versus intravenous therapy for prehospital status epilepticus. *N Engl J Med*. 2012 Feb 16;366(7):591–600”

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ABSTRACT

Background: Intravenous benzodiazepines have been shown to be effective in management of status epilepticus, but due to ease of administration intramuscular route is being frequently used in prehospital care without documented evidence.

Methods: A double-blinded randomised clinical trial aiming to demonstrate that intramuscular midazolam is at least as effective as intravenous lorazepam (non-inferiority design). The non-inferiority margin was set at 10 percentage points below that of intravenous lorazepam's effect. Children and adults found in status epilepticus were included in the study and the interventions given serially by an intramuscular autoinjector followed by intravenous infusion. Double dummy strategy was followed so that each subject received either intramuscular midazolam or intravenous lorazepam along with a placebo. These subjects were followed thereafter for cessation of seizures on arrival to hospital (primary outcome) without the need for rescue therapy. Secondary outcomes included requirement of endotracheal intubation, recurrence of seizures, and timing of treatment relative to the cessation of convulsions.

Results: After screening and exclusion 893 subjects were assigned to interventions, 448 in the intramuscular midazolam group and 445 in the intravenous lorazepam group. Of the 448 of the former group 443 actually received the intervention while the intervention could be given in only 297 in the later group, 329 of 448 subjects (73.4%) in the intramuscular midazolam group and 282 of 445 (63.4%) in the intravenous lorazepam group (absolute difference, 10 percentage points; 95% confidence interval, 4.0–16.1; $P < 0.001$ for both non-inferiority and superiority) had no seizures on arrival to the emergency without the need for rescue therapy. There was no difference between the two intervention groups with regards to the need of endotracheal intubation or recurrence of seizures. the median times to administration of active treatment in the intramuscular midazolam group were 1.2 and

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4.8 min in the intravenous lorazepam group, with median times from active treatment to cessation of convulsions of 3.3 min and 1.6 min in the two groups respectively.

Conclusions: In the management of status epilepticus, intramuscular midazolam was at least as safe and effective as intravenous lorazepam for prehospital control of seizure with lesser time required for its administration.

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1. Strengths of the study

This study¹ has addressed an important area of operational research and intended to provide unequivocal evidence for the use of intramuscular midazolam instead of the more cumbersome intravenous approach by the paramedics during prehospital management of status epilepticus, doing so it has tested a very relevant and clinically useful hypothesis. The well planned and executed protocol included use of technological advancements in recording clinical events in an attempt to minimize human errors in recollection of facts which is an upcoming trend in clinical and epidemiological studies. The extent to which staff training has been described is rigorous and justifiable, given the multicentric nature of the study to ensure more uniform execution of the protocol and data collection. The outcome variables as well as the study endpoints have been adequately and clearly elaborated. The inference drawn from this study generates plausible evidence for change in practice in settings where routine care is otherwise, therefore this study has succeeded in achieving what it intended to. Lastly but importantly the study being published in the biomedical journal with highest impact factor is undoubtedly of sufficient impact to change clinical practice.

2. Limitations of the study

2.1. Methods

The 2 interventions used (iv lorazepam and im midazolam) could have been simultaneous and not sequential as it have may delayed the administration of the active agent in case it was the later intervention to be used and increased the risk of neurological morbidity. The maximum allowable time of 10 min for establishing a vascular access seems to be too long to abort a status epilepticus in contrast to Pediatric Advanced Life Support recommendation during resuscitation which is only 90 s to establish an intravenous access, the extra time provided in the protocol may have unnecessarily prolonged the time to active agent administration in a seizing individual, moreover the action following the failure of vascular access (after failure of intraosseous route) has not been described.

2.2. Sample-size calculation

Though the details of sample-size calculation have been described, the rationale behind choosing a non-inferiority

margin of 10 percentage points has not been justified adequately.

2.3. Result and analysis

The authors did not describe their experience with the voice recording system as this newly employed technology may have many shortcomings, right from mechanical faults to problems with personnel speaking out every event on time. In the analysis section, the per protocol analysis (Figure 1 of the article), the IV lorazepam group includes 148 patients who did not receive the intervention at all! Per protocol analysis classically includes only subjects who have received the intervention (non-protocol violators)² but this was not the case here, therefore the denominator in the IV Lorazepam group for the per protocol analysis should have in fact decreased from 370 to 297 (vide Table 2 of the original article) and this could have led to more favourable results. The real effect modifier in this study could have been the different chemicals used in different interventions rather than the routes of administration per se. Re-enrolment of the subjects could have been feasible if the number of seizure episodes were compared rather than the number of subjects. When matched to the modified CONSORT³ checklist this study fails to fulfill the criteria mentioned in items 7a and 7b wherein the issues of sample-size calculation, specifying the margin of equivalence along with its rationale and stopping rules following interim analysis are mentioned respectively.

Conflicts of interest

The author has none to declare.

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