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Benzodiazepines for Out-of-Hospital Status Epilepticus: Do or Do Not! There Is No Try!

Prehospital Midazolam Use and Outcomes Among Patients With Out-of-Hospital Status Epilepticus

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Objective: To examine the use of benzodiazepines and the association between low benzodiazepine dose, breakthrough seizures, and respiratory support in patients with status epilepticus. Methods: Cross-sectional analysis of adult patients with status epilepticus treated by an emergency medical services agency from 2013 to 2018. The primary outcome was treatment with a second benzodiazepine dose, an indicator for breakthrough seizure. The secondary outcome was receiving respiratory support. Midazolam was the only benzodiazepine administered. Results: Among 2494 cases of status epilepticus, mean age was 54.0 years and 1146 (46%) were female. There were 1537 patients given midazolam at any dose, yielding an administration rate of 62%. No patients received a dose and route consistent with national guidelines. Rescue therapy with a second midazolam dose was required in 282 (18%) patients. Higher midazolam doses were associated with lower odds of rescue therapy (odds ratio [OR]: 0.8, 95% CI: 0.7-0.9) and were not associated with increased respiratory support. If anything, higher doses of midazolam were associated with decreased need for respiratory support after adjustment (OR: 0.9, 95% CI: 0.8-1.0). Conclusions: An overwhelming majority of patients with status epilepticus did not receive evidence-based benzodiazepine treatment. Higher midazolam doses were associated with reduced use of rescue therapy, and there was no evidence of respiratory harm suggesting that benzodiazepines are withheld without clinical benefit. Classification of Evidence: This study provides class III evidence that for patients with status epilepticus, higher doses of midazolam led to a reduced use of rescue therapy without an increased need for ventilatory support.

Commentary

"Do or do not! There is no try!" told the venerable Yoda to young Luke Skywalker on a gloomy planet in the Dagobah system. Although it would be presumptuous to pretend to understand the complexity of the mind of an 800-year-old Jedi master, I would surmise the intent of these words was to convince his student not to be afraid to use the Force. At this point in the story, the Force was the only hope for Luke and the Rebellion to defeat the Empire and put an end to its tyranny throughout the galaxy.

Let's get back from that galaxy far away to the real world and replace 800 years of wisdom by 30 years of evidence,[1] Luke Skywalker by a paramedic in the field, the Force by parenteral benzodiazepines, and the evil Empire by the no-less evil generalized convulsive status epilepticus (GCSE). A frequent neurological emergency affecting patients across all age groups, GCSE is associated with substantial morbidity and mortality. Something we should take seriously and be ready to treat without hesitation. Early GCSE management should aim at rapid cessation of both clinical and electrical seizure activity, since appropriate and timely treatment of status epilepticus decreases the risk of complications and mortality. And there is hope. No less than 3 class I studies, on top of several class II and III studies, established parenteral benzodiazepines as an efficacious and safe first-line treatment of early convulsive SE treatment, including in the out-of-hospital setting. This evidence made its way into the most recent SE management guidelines,[1] which clearly recommend the prompt administration of intravenous (IV) lorazepam, IV diazepam, or intramuscular (IM) midazolam (level A recommendation), at the doses studied in the RCT, as initial therapy of GCSE. They also propose intranasal buccal or rectal benzodiazepines as alternatives when IV/IM administration is not available. If a first dose is not successful, then the administration of a second ("rescue") dose is recommended. Yet, overwhelming evidence and clear guidelines somehow do not translate well into clinical practice. Observational studies have found that benzodiazepines are often delayed or underdosed, when they are not simply omitted.[2-7] These deviations from guidelines are not without consequences. Delayed or insufficient treatment with benzodiazepine has been associated with lower efficacy, a longer time to seizure cessation and an increased risk of refractoriness,

leading to more intensive care unit admissions, more respiratory and hemodynamic complications, and worse outcome.[5-7]

In this study,[8] the authors examined the use of midazolam by emergency medical services (EMS) agency for treatment of out-of-hospital GCSE in a large suburban/urban setting. A total of 2494 SE cases were included. Of those, only 1537 (62%) received midazolam. Since midazolam was the only benzodiazepine available to the paramedics, it is safe to assume that the remaining patients did not receive any adequate first-line drug. Midazolam was given IV or intranasal in 85% of cases and IM in only 14% of cases. Further, two-thirds received a dose midazolam lower than 5 mg and a third a dose of 5 mg. Only 5 patients received a dose >5 mg but none received the guideline-recommended dose of 10 mg. Those with a history of epilepsy or a more pronounced alteration of consciousness were more likely to receive midazolam. Rescue therapy with a second dose was required in 282 (18%) of patients who received a first dose. In a multivariate model adjusting for confounders (level of consciousness, cardiac and respiratory status, etc), a higher first dose was associated with a lower probability of requiring recue therapy. This was the case for all modes of administration, although it was more striking for the IM route. Further, higher doses of midazolam were not associated with a higher risk of respiratory failure. On the contrary, they were associated with a decreased need for respiratory support. Although data from a single EMS agency were analyzed, potentially limiting the generalizability of the study, the findings are in line with prior observations made in other settings. There are other important limitations to this nonrandomized retrospective study based on EMS medical records. The definition of SE, used for inclusion in the study, was based on the EMS teams' clinical judgment and misdiagnoses are possible, if not likely. Reasons for administration of a rescue therapy, or lack thereof, were not explicitly reported. It was assumed to reflect the success or failure to control SE but other motives might have been involved. Important confounders, such as SE semiology, duration, etiology, and comorbidities were not accounted for. However, these limitations are unlikely to substantially alter the main conclusions of the study. All patients with out-of-hospital SE were undertreated, and undertreatment was associated with lower efficacy and increased risk of respiratory failure. As for the Force, there is no try with the administration of benzodiazepines in SE. They need to be given in full and without hesitation.

Why then does it seem so difficult to implement simple guidelines in daily practice? More importantly, what can we do to remediate this problem? Studies so far have not really addressed these questions. I would venture though that it is the result of an uneducated fear to use the drugs at their recommended dose. In my experience, paramedics and emergency physicians are reluctant to use "high" doses of benzodiazepines because of a perceived risk of drug-induced respiratory failure. Yet, this and prior studies[9] have shown that the risk associated with benzodiazepines is actually lower than the risk associated with ongoing seizures that result from under dosing. Clearly, this part of the evidence is not enough promoted. We, as neurologists and epileptologists, are rarely directly involved in the management of early SE. But it should be among our priorities to disseminate the available evidence, and to collaborate with EMS agencies, emergency and critical care physicians to develop and implement local protocols based on national and international guidelines, as well as quality improvement programs. Evidence and guidelines themselves will not be sufficient unless efforts are made to improve local adhesion.[10] Let's not lose hope, however, as examples of successful and impactful standardized protocols exist.[11,12] Trusting the Force served Luke and the Rebellion quite well in their victory over the Empire. Trusting the evidence is a necessary step in our fight against GCSE.

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