DOI: 10.4274/cayd.galenos.2025.26818
J Pediatr Emerg Intensive Care Med 2025;12(2):132-4

Letter to Editor

Editöre Mektup

Dinçer Yıldızdaş

Çukurova University Faculty of Medicine, Department of Pediatric Intensive Care Unit, Adana, Türkiye

Dear Editor,

Status epilepticus (SE) is among the most common life-threatening neurological emergencies in childhood, with an incidence of approximately 17-23 episodes per 100.000 children annually, peaking within the first five years of life.[1] SE carries a significant risk of neurological morbidity and an overall mortality rate of up to 3%.[1] We read with great interest the recently published protocol titled "2025 SE in Critically Ill Children" by Özcan et al.[2] in the Journal of Pediatric Emergency and Intensive Care Medicine. We commend the authors for their valuable contribution. Compared to previous protocols, a notable difference in the new guideline is the omission of intravenous (IV) midazolam as a first-line treatment option for SE, with IV diazepam recommended exclusively.[3] It is worth noting that if IV lorazepam were readily available in our country, this debate might have been less pronounced. Nonetheless, a national survey conducted prior to the protocol's publication could have provided a more comprehensive reflection of current practice patterns across Türkiye.

The article offers an up-to-date and comprehensive overview of SE management in critically ill children; however, several methodological aspects merit further consideration. Notably, the absence of details regarding systematic literature search strategies, database usage, and study selection criteria represents a gap in methodological transparency. Furthermore, the omission of evidence levels and recommendation strength impedes an independent evaluation of the proposed therapeutic strategies. Although references to meta-analyses and systematic reviews are made, the findings of these studies are not analyzed in depth. Practical factors-such as cost-effectiveness, feasibility, and the limitations imposed by local resources-are also insufficiently addressed, potentially affecting real-world applicability. Additionally, the lack of visual treatment algorithms limits the accessibility and ease of clinical implementation. Patient heterogeneity (e.g., preterm infants, metabolic disorders) is another critical factor inadequately discussed, creating gaps in individualized care strategies. Similarly, the application hierarchy for immunomodulatory therapies remains undefined, potentially complicating clinical decision-making. While a detailed long-term follow-up protocol is not mandatory, including a brief recommendation to refer patients to pediatric neurology or related specialties for longitudinal care would have enhanced the protocol's scientific robustness and patient safety considerations. Addressing these issues would strengthen the methodological rigor and clinical applicability of the protocol within an evidence-based framework.

A comprehensive review of the literature reveals that IV midazolam is at least as effective as diazepam, and in some cases, it may even be considered superior. According to international recommendations, if IV access is available, IV lorazepam (0.1 mg/kg, max 4 mg/dose), IV diazepam (0.2-0.3 mg/kg, max 10 mg/dose), or IV midazolam (0.1 mg/kg, max 5 mg/dose) can all be considered as first-line agents.[4] Their effects typically become apparent within 0.5 to 5 minutes. Current evidence does not strongly favor one over the others in terms of seizure control efficacy.[5,6]

Although the 2018 Cochrane review and a 2016 network meta-analysis found no clear differences in efficacy or safety among diazepam, lorazepam, and midazolam,[5,7] heterogeneity in study designs and patient populations may

Address for Correspondence/Yazışma Adresi: Prof. MD., Dinçer Yıldızdaş, Çukurova University Faculty of Medicine, Department of Pediatric Intensive Care Unit, Adana, Türkiye
E-mail: dyildizdas@gmail.com **ORCID ID:** orcid.org/0000-0003-0739-5108
Received/Geliş Tarihi: 25.04.2025 **Accepted/Kabul Tarihi:** 31.07.2025 **Epub:** 04.08.2025 **Publication Date/Yayınlanma Tarihi:** 26.08.2025
Cite this article as: Yıldızdaş D. Letter to editor. J Pediatr Emerg Intensive Care Med. 2025;12(2):132-4

affect the generalizability of these results. Furthermore, no significant difference in seizure cessation rates has been observed when comparing IV midazolam with IV diazepam or lorazepam, or IV lorazepam with the combination of IV diazepam and phenytoin.[5,8-11] However, studies have reported that fewer second doses were required when lorazepam was used compared to diazepam, although no significant difference was noted between midazolam and the other agents.[6] Importantly, IV lorazepam is associated with fewer adverse events, including respiratory depression and excessive sedation, compared to IV diazepam.[5,12]

National variations are also notable. A nationwide survey conducted by the Italian Paediatric SE group revealed that approximately 90% of physicians preferred midazolam as the first-line treatment.[13] The Canadian guidelines recommend either midazolam or lorazepam, Australian protocols favor midazolam, and Japanese protocols support the use of all three benzodiazepines.[14-16] These differences likely reflect variations in drug availability, healthcare infrastructure, and physician training across countries. Future protocols could benefit from including alternative treatment pathways that account for these factors to enhance relevance and applicability.

In conclusion, while we advocate for the inclusion of IV midazolam as a first-line treatment option based on its efficacy, safety, and route flexibility, we also underscore the importance of developing adaptable, evidence-based protocols that reflect national practice variations and evolving literature.

Keywords: Status epilepticus, children, treatment

Anahtar Kelimeler: Status epileptikus, çocuk, tedavi

Footnotes

Financial Disclosure: The author declared that this study received no financial support.

References

1. Becker LL, Gratopp A, Prager C, Elger CE, Kaindl AM. Treatment of pediatric convulsive status epilepticus. Front Neurol. 2023;14:1175370.
2. Özcan S, Yazıcı MU, Kamit F, Girgin Fİ, Özkaya PY, et al. Status epilepticus in critically ill children. J Pediatr Emerg Intensive Care Med. 2025;12:45-55.
3. Erkek N, Öztürk N, Şevketoğlu E. Status epileptikus tedavi protokolü. 2017. Erişim adresi: http://cayd.org.tr/files/status-epileptikus-tedavi-protokolu-Uw.pdf. Erişim Aralık 19,2022.
4. Singh A, Stredny CM, Loddenkemper T. Pharmacotherapy for pediatric convulsive status epilepticus. CNS Drugs. 2020;34:47-63.
5. McTague A, Martland T, Appleton R. Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. Cochrane Database Syst Rev. 2018;1:CD001905.
6. Gathwala G, Goel M, Singh J, Mittal K. Intravenous diazepam, midazolam and lorazepam in acute seizure control. Indian J Pediatr. 2012;79:327-32.
7. Zhao Z, Wang H, Wen B, Yang Z, Feng K, et al. A comparison of midazolam, lorazepam, and diazepam for the treatment of status epilepticus in children: a network meta-analysis. J Child Neurol. 2016;31:1093-107.
8. Brigo F, Nardone R, Tezzon F, Trinka E. Nonintravenous midazolam versus intravenous or rectal diazepam for the treatment of early status epilepticus: a systematic review with meta-analysis. Epilepsy Behav. 2015;49:325-36.
9. Giang DW, McBride MC. Lorazepam versus diazepam for the treatment of status epilepticus. Pediatr Neurol. 1988;4:358-61.
10. Sreenath TG, Gupta P, Sharma KK, Krishnamurthy S. Lorazepam versus diazepam-phenytoin combination in the treatment of convulsive status epilepticus in children: a randomized controlled trial. Eur J Paediatr Neurol. 2010;14:162-8.
11. Chamberlain JM, Okada P, Holsti M, Mahajan P, Brown KM, et al. Lorazepam vs diazepam for pediatric status epilepticus: a randomized clinical trial. JAMA. 2014;311:1652-60.
12. Appleton R, Sweeney A, Choonara I, Robson J, Molyneux E. Lorazepam versus diazepam in the acute treatment of epileptic seizures and status epilepticus. Dev Med Child Neurol. 1995;37:682-8.
13. Zanus C, Cannizzaro G, Danieli G, Amigoni A, Buratti S, et al. An Italian survey on the management of pediatric convulsive status epilepticus: more than just a pharmacological choice. Brain Behav. 2025;15:e70433.
14. Pediatric status epilepticus algorithm. Available at: https://cms.trekk.ca/wp-content/uploads/2023/11/2022-05-02_EIIC-Trekk_Status_Epilepticus_Algorithm_Final_Version.pdf
15. Status epilepticus management. Algorithms. Available at: https://www.apls.org.au/algorithm-status-epilepticus
16. Kikuchi K, Kuki I, Nishiyama M, Ueda Y, Matsuura R, et al. Apanese guidelines for treatment of pediatric status epilepticus - 2023. Brain Dev. 2025;47:104306.

Reply from the Authors:

To the Editor,

We sincerely thank the authors for their interest in our article. Their recognition of the importance of our work and their willingness to engage in scholarly discussion are highly appreciated. We welcome the opportunity to respond to the comments and critiques raised regarding our manuscript titled "2025 Status Epilepticus in Critically Ill Children."[1]

The authors note that intravenous diazepam was the sole agent recommended as first-line treatment in our article. However, our manuscript clearly delineates first-line treatment strategies for pediatric status epilepticus based on the availability of intravenous access. Specifically, intravenous diazepam, intramuscular midazolam, and rectal diazepam are all cited as appropriate first-line agents. As mentioned by the authors, intravenous lorazepam is not currently available in our country, and thus, was not included in the treatment recommendations.[1]

The suggestion that a national study on pediatric status epilepticus management should have preceded the development of our guideline is a valuable one. While such a study would undoubtedly provide insight into local clinical practices, the primary objective of our guideline was to evaluate the efficacy of therapeutic agents based on the international literature. As we emphasized in our article, the guideline was developed through rigorous review of global evidence, with the understanding that individual institutions may tailor their implementation according to their own resources and settings.

The Status Epilepticus in Critically Ill Children Guideline was developed under the auspices of the neurocritical care working group of the Turkish Society of Pediatric Emergency and Intensive Care Medicine. Prior to drafting the guideline, the working group conducted a comprehensive literature review using predefined keywords to identify relevant meta-analyses, guidelines, and reviews indexed in the PubMed database up to the final editorial review date of the article. Following this, the group convened weekly meetings over a two-year period to develop and refine the recommendations.

All treatment options, including those for first-line therapy, were discussed extensively and decided upon collectively. The sources referenced by the authors were among those reviewed during this process. However, current evidence continues to support the American Epilepsy Society guideline as the most reliable and evidence-based reference on this topic.[2] Notably, neither the American Epilepsy Society guideline nor the 22nd edition of Nelson Textbook of Pediatrics (March 2024) includes intravenous midazolam as a first-line treatment.[3,4] Consequently, we did not provide a dosage recommendation for intravenous midazolam within that context.

It is important to emphasize that our guideline offers recommendations, not mandates. Each healthcare institution retains the autonomy to adapt practices according to local needs and capabilities. Nonetheless, we believe that guidelines should be grounded in high-quality evidence, rather than reflect variable clinical practices. All treatments and medications included in our guideline were evaluated based on both their evidence-based efficacy and their availability in our country. None of the authors have any financial or professional conflicts of interest related to the pharmaceutical companies manufacturing these drugs.

In conclusion, the current version of the guideline represents the outcome of extensive review and deliberation by our working group. We believe it offers a sound framework for clinical practice while remaining adaptable to local conditions. As the number of pediatric emergency and intensive care specialists continues to grow in our country, we anticipate that further contributions-including clinical studies, in addition to guidelines and reviews-will enrich the global literature on pediatric status epilepticus.

Sincerely,

Serhan Özcan, Mutlu Uysal Yazıcı, Fulya Kamit, Feyza İnceköy Girgin, Pınar Yazıcı Özkaya, Çelebi Kocaoğlu, Resul Yılmaz, Eylem Ulaş Saz, Agop Çıtak

References

1. Özcan S, Uysal Yazıcı M, Kamit F, İnceköy Girgin F, Yazıcı Özkaya P, et al. Status epilepticus in critically ill children. J Pediatr Emerg Intensive Care Med. 2025;12:45-55.
2. Cao Y, Li H, Chen M, Wang P, Shi F, et al. Evaluation and systematic review of guidance documents for status epilepticus. Epilepsy Behav. 2024;150:109555.
3. Glauser T, Shinnar S, Gloss D, Alldredge B, Arya R, Bainbridge J, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the Guideline Committee of the American Epilepsy Society. Epilepsy Curr. 2016;16:48-61.
4. Nelson textbook of pediatrics. In: Kliegman RM, St Geme JW, Blum NJ, Tasker RC, Wilson KM, et al. (editors). 22nd ed. Philedelphia, Pennysilvenia:Elsevier;2024:3623-9.