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Refractory/super-refractory status epilepticus: intravenous ketamine and pragmatic algorithms

Estatus epiléptico refractario/súper refractario: ketamina intravenosa y algoritmos pragmáticos

María Manuela Maldonado Hoyos[1], Andrea Carolina Bolaños Molinares[2], Juan José Ariza López[3], María José Albarracín Ruiz[4]

[1]Departamento de Medicina, Universidad CES, Medellín, Colombia. https://orcid.org/0000-0002-1729-4530

[2]Departamento de Medicina, Universidad del Sinú, Cartagena, Colombia. https://orcid.org/0009-0005-6974-2138

[3]Departamento de Medicina, Universidad de Cartagena, Cartagena, Colombia. https://orcid.org/0009-0000-9226-9960

[4]Centro de Salud María Auxiliadora, Salamanca, Castilla y León, España. https://orcid.org/0000-0002-4165-5279

Corresponding author: María José Albarracín Ruiz. Centro de Salud María Auxiliadora, Salamanca, Castilla y León, España. Email: mjalbarracin@saludcastillayleon.es

Correspondence

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Refractory status epilepticus and the challenge of evidence-based decision-making

Refractory and super-refractory status epilepticus (RSE and SRSE) remain among the most difficult conditions encountered in neurocritical care [1]. Decisions often have to be made quickly, sometimes before the underlying etiology is fully clarified and frequently in patients whose systemic condition is already fragile [1]. Under these circumstances, treatment escalation tends to proceed in parallel with diagnostic evaluation rather than after it, and the boundary between therapeutic reasoning and empirical improvisation can become indistinct [2].

This setting exposes a tension that is rarely discussed explicitly. Evidence-based medicine has provided powerful tools for guiding clinical practice, yet those tools were largely developed in contexts where interventions can be compared under controlled conditions and outcomes unfold over weeks or months [3]. Status epilepticus does not belong to that category. In severe cases, clinicians must act while the evidence remains incomplete, drawing on physiological reasoning, accumulated experience, and partial data from heterogeneous studies [4].

Intravenous anesthetic agents have long formed the backbone of treatment in RSE and SRSE, but their limitations are well recognized, particularly with respect to hemodynamic instability and diminishing effectiveness during prolonged seizures [5]. Against this background, ketamine has gradually moved from being considered a salvage therapy to being incorporated, in many centers, into earlier stages of escalation [5]. The reasons for this shift are partly pharmacological and partly pragmatic.

Current evidence on intravenous ketamine and its limitations

A recent systematic review and meta-analysis synthesizing data from ten studies and nearly four hundred patients reported an overall seizure-termination rate of approximately 56%, with similar estimates across adult and pediatric populations [6]. These findings are consistent with earlier observational series suggesting that ketamine may achieve seizure control in a substantial proportion of patients who have not responded to conventional therapies [7].

Yet the apparent clarity of pooled estimates should not be mistaken for methodological certainty. Most of the studies included in the available literature are retrospective cohorts or case series, often conducted in single centers and involving small samples [6]. Timing of administration varies widely, dosing regimens are not standardized, and co-interventions are nearly universal. In practice, ketamine is rarely introduced as a single, isolated therapy; it is administered in the context of ongoing polypharmacy and complex supportive care [6]. Under such conditions, attributing seizure cessation to any one intervention becomes inherently difficult [6].

From the perspective of clinical epidemiology, these limitations are not trivial. Single-arm meta-analyses can provide useful descriptive information, but they cannot resolve questions of comparative effectiveness or isolate causal effects with confidence [7]. Confounding by indication, selection bias, and heterogeneity of outcome definitions remain persistent concerns. At the same time, it would be unrealistic

to dismiss this body of evidence entirely, because it represents the only systematic data available for many aspects of RSE and SRSE management. The challenge, therefore, is not whether to use such evidence, but how to interpret it with appropriate caution.

Another issue, less frequently emphasized, is the nature of the outcomes themselves. Seizure termination is an important endpoint, but it is not necessarily synonymous with neurological recovery. Long-term cognitive function, functional independence, and quality of life are seldom reported in this literature, and when they are, follow-up is often limited [6]. This gap between short-term physiological endpoints and meaningful clinical outcomes remains one of the major unresolved problems in the field.

Implications for clinical practice and future research

One way of reconciling these limitations with the realities of bedside decision-making is to reconsider what exactly is being evaluated. In severe status epilepticus, outcomes rarely depend on a single drug. They depend on a sequence of interventions implemented over time, often adjusted in response to evolving electroencephalographic findings, systemic complications, and the patient's underlying condition [4]. The effectiveness of ketamine, in this sense, cannot be fully separated from the broader therapeutic pathway in which it is used.

This perspective helps explain why many clinicians increasingly rely on pragmatic treatment algorithms rather than rigid stepwise protocols. Such algorithms are not merely simplified guidelines; they reflect a recognition that variability is intrinsic to the management of critical neurological illness [4]. Decisions about when to escalate therapy, how to balance seizure suppression against systemic risk, or when to modify sedation strategies frequently rely on judgment that cannot easily be codified in trial protocols [4].

Seen in this light, the growing use of ketamine may be understood less as the emergence of a superior pharmacological agent and more as part of a broader evolution in clinical reasoning. The drug's pharmacodynamic profile (particularly its N-methyl-D-aspartate [NMDA] receptor antagonism and relative cardiovascular stability) makes it attractive in selected scenarios, but its adoption also reflects a willingness among clinicians to integrate therapies on the basis of mechanistic plausibility and cumulative observational evidence when randomized data are lacking [8].

From a meta-research perspective, the literature on RSE and SRSE illustrates several structural weaknesses in the way evidence is generated and reported in acute neurological conditions. Definitions of outcomes vary, reporting of timing and dosing is inconsistent, and standardized data collection across centers remains limited [9-12]. These problems are not unique to ketamine; they affect much of neurocritical care research. Addressing them will require coordinated efforts to harmonize outcome measures, develop prospective multicenter registries, and explore adaptive study designs that are better suited to rapidly evolving clinical situations [9].

Randomized controlled trials, where feasible, will remain essential. However, they should probably be complemented by alternative approaches capable of capturing the complexity of real-world practice.

Registries with standardized data elements, collaborative international networks, and pragmatic trial designs may provide insights that conventional methodologies struggle to generate in this setting.

Ultimately, the role of ketamine in refractory status epilepticus may be defined not only by its efficacy but also by what its use reveals about modern clinical decision-making. In situations where evidence is incomplete yet action cannot be postponed, clinicians rely on forms of reasoning that are iterative, context-dependent, and necessarily imperfect [12]. Understanding and refining this process may prove as important as identifying new therapies.

Intravenous ketamine should therefore be viewed not as a definitive solution, but as one component within an evolving framework of pragmatic treatment strategies, strategies that attempt, often under considerable uncertainty, to reconcile the urgency of neurological emergencies with the limitations of the evidence on which they depend.

Conflicts of interest

The authors declare no conflict of interest.

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Data, Materials, and Code Availability

Not applicable.

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María Manuela Maldonado Hoyos: conceptualization, research, writing of the original draft, writing, revision and editing, approval of the final version. Andrea Carolina Bolaños Molinares: conceptualization, research, writing of the original draft, writing, revision and editing, approval of the final version. Juan José Ariza López: conceptualization, research, writing of the original draft, writing, revision and editing, approval of the final version. MJAR: conceptualization, research, writing of the original draft, writing, revision and editing, approval of the final version.

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