Supplemental Materials
(Appendices and Additional Tables)

for

Effectiveness of Ketamine as a Rescue Drug for Patients Experiencing Benzodiazepine-Resistant Status Epilepticus in the Prehospital Setting

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APPENDIX A: Palm Beach County Fire Rescue Seizure Protocol

Seizure

INFORMATION

- Consider the possible causes:
  - Meningitis
  - Fever
  - Head trauma
  - Hemorrhagic stroke
  - Drugs
  - Alcohol
  - Diabetic
  - Poisoning
- Monitoring of $EtCO_2$ shall be performed to determine the patient's respiratory status.
- Refer to the "Eclampsia" protocol (pg. 121), for pregnant patients.

ADULT

IF ACTIVELY SEIZING

- VERSED:
  - 5mg IV/IO/IN/IM
  - May repeat 1x prn, in 5 minutes if seizure reoccurs or does not subside
  - Contraindication - Hypotension
  - Precaution - Monitor for respiratory depression

IF SEIZURE DOES NOT RESPOND TO ABOVE TREATMENT

- KETAMINE with **EMS CAPTAIN approval**:
  - **Dilute**: 100mg of Ketamine in a 50mL bag of NORMAL SALINE
    - Administer IV/IO utilizing a 60 gtt set, run wide open
  - Contraindications:
    - Pregnant patients
    - Penetrating eye injury
    - Non-traumatic chest pain
  - Precautions:
    - Be prepared for advanced airway management
    - Rapid IV administration is associated with respiratory depression, apnea, and higher than usual increases in blood pressures
    - May increase schizophrenic symptoms

OR

IF UNABLE TO ESTABLISH VASCULAR ACCESS

- KETAMINE:
  - 100mg IN/IM
  - Contraindications - as noted above
  - Precautions - as noted above

Seizure

PEDIATRIC

FEBRILE SEIZURE

- ACTIVE COOLING: Remove the clothing
- **DO NOT** cover patient with a wet towel or sheet
- **DO NOT** apply ice or cold packs to the patient's body

IF ACTIVELY SEIZING

- VERSED:
  - 0.1 mg/kg IV/IO, max single dose 5mg
  - 0.2 mg/kg IN/IM, max single dose of 5mg
  - May repeat either route 1x prn, in 5 minutes if seizure reoccurs or does not subside
  - Contraindication - Hypotension
  - Precaution - Monitor for respiratory depression

IF SEIZURE DOES NOT RESPOND TO ABOVE TREATMENT (≥ 3 YEARS OLD)

- KETAMINE with **EMS CAPTAIN approval**:
  - 1mg/kg IN/IM
  - May repeat 1x prn, in 5 minutes
  - Contraindications:
    - Penetrating eye injury
  - Precautions:
    - Be prepared for advanced airway management
    - May increase schizophrenic symptoms

- **Female puberty is defined as breast development/budding and/or pubic hair/underarm hair.**
- **Male puberty is defined as underarm, pubic, chest, or facial hair.**
- **Once a child reaches puberty, use the adult guidelines**

Appendix B: Supplemental Content on Background, Setting, Methods, Results and Additional Discussion Points

Additional Comments on Background:

A many as a quarter to a half of status epilepticus (SE) patients treated in the prehospital setting continue to have convulsions despite successive dosings of benzodiazepines (1,2). In a closely-supervised *National Institutes of Health* (NIH) trial involving 33 high-performance emergency medical services (EMS) agencies, 10 mg of parenteral midazolam did not terminate convulsions in >25% (2). Extrapolating, benzodiazepine-resistant SE cases occur at least 300-400 times a month in the U.S. alone, but likely more often as many EMS systems use lower doses of midazolam or alternative drugs such as diazepam (1).

Persistent SE is not only a high-impact critical care emergency for patients, it also imposes unique risks for on-scene EMS personnel attempting to "scoop and run" with actively convulsing patients who may need to be carried down narrow, turning stairwells or extricated out of cramped quarters or crowded venues under the scrutiny of upset family members or even the public-at-large. The risks for physical harm to both patients and responders can be increased by weather conditions, traffic or other environmental/logistical threats. Uncontrolled SE-convulsions can also result in respiratory compromise with significant oxygen desaturation and additional benzodiazepine doses could impose further risks for respiratory depression (3). Also, as seizures persist, there can be significant decreases in activated post-synaptic gamma-aminobutyric acid-A receptors, the sites where benzodiazepines and many other anti-seizure medications act (3-5).

In contrast, as seizures persist, there is progressive expression of *N*-methyl-D-aspartate (NMDA) receptors indicating that NMDA receptor antagonists (e.g., ketamine) may be more suitable to terminate the SE (3,6-11). Ketamine is already carried by most EMS systems and the resulting costs, on-scene procedures and re-stocking of non-expiring alternative anti-seizure medications (e.g., valproic acid, levetiracetam, fosphenytoin) on every paramedic unit (for this relatively infrequent event) make them less feasible for the prehospital setting. Moreover, ketamine can be administered intramuscularly when intravenous (IV) or intraosseous access is difficult to achieve, particularly in actively convulsing patients.

1. Glauser T, 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(1):48-61
2. Silbergleit R, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. *N Engl J Med* 2012;366:591-600
3. Fang Y, Wang X. Ketamine for the treatment of refractory status epilepticus. *Seizure* 2015;30:14-20
4. Deeb TZ, et al. Possible alterations in GABA-A receptor signaling that underlie benzodiazepine-resistant seizures. Epilepsia 2012; 53: 79-88
5. Feng HJ, et al. Alterations of GABA-A-receptor function and allosteric modulation during development of status epilepticus. *J Neurophysiol* 2008; 99:1285-93
6. Zeiler FA, et al. NMDA antagonists for refractory seizures. *Neurocrit Care* 2014; 20: 502-513
7. Dingledine R, et al. The glutamate receptor ion channels. *Pharmacol Rev* 1999;51:7-61
8. Mazarati AM, Wasterlain CG. N-methyl-D-aspartate receptor antagonists abolish the maintenance phase of self-sustaining status epilepticus in rat. *Neurosci Lett* 1999;265:187–90
9. Rosati A, De Masi S, Guerrini R. Ketamine for refractory status epilepticus: a systematic Review. *CNS Drugs* 2018;32:997-1009.
10. Rai S, Drislane FW. Treatment of refractory and super-refractory status epilepticus. *Neurotherapeutics* 2018;15:697-712.
11. Niquet J, Lumley L, Baldwin R, Rossetti F, Schultz M, et al. Early polytherapy for benzodiazepine-refractory status epilepticus. *Epilepsy Behav* 2019;101(Pt B):106367 doi: 10.1016/j.yebeh.2019.06.01

Methods – Additional Comments on Setting and Definitions:

Setting: The study site was Palm Beach County, Florida where *Palm Beach County Fire Rescue* (PBCFR) manages the EMS responses to 9-1-1 calls across most of the county with roughly 1,500 paramedics based at 49 fire stations including 42 fire apparatus crews capable of advanced life support (ALS) and 53 ALS ambulances. There are 8 EMS paramedic captains on duty who closely supervise EMS clinical responses. A rotating team of 8 EMS medical directors respond with supervisors several times a month. On average, 230 patients are transported each day. The mean CY2023 ALS unit response interval was 6 mins 50 secs, (CY2022, 6 min 53 secs) measured from 9-1-1 call receipt to on-scene arrival (similar in prior years). Among Palm Beach County residents, 5% are <5 years old (yo), 19% <18 yo, 25% >65 years and 51% are women while 27% are foreign born and a third speak non-English languages at home. Median household income (2022) was $76,000 and 70% live in owner-occupied homes. Ethnic distributions are 52% White (WH), 18% African-American (AA), 24% Hispanic-Latino (HL), 1% Asian/Native American (AS/NA), 5% uncategorized.

Delineation of "On-Protocol" vs, "Off-Protocol" Cases: Though the posted seizure protocol (*Appendix A*) stipulated that two sequential 5 mg doses of midazolam would precede ketamine, paramedics were permitted (by training and real-time supervisor approval) to provide just one 5 mg dose if family members/medical practitioners had administered sufficient corresponding doses of benzodiazepines just prior to EMS arrival on-scene (Supplemental Content *Table 1*). Such cases were still categorized as being "on-protocol" versus those receiving ketamine directly (i.e., no midazolam from paramedics) who were

classified as “off-protocol”. Whether paramedics gave two doses (82% of cases) or one (18%), the set-up and delivery of the midazolam takes a finite period of time as do the 5 minute waiting periods for therapeutic response, each delaying ketamine administration (thus the categorization rationale). This was judged a reasonable “real-world” delineation for reporting purposes rather than creating a distinct third study group, especially with various reasons for giving only one-dose – and also because it did not change the outcomes.

Additional Results and Details

System Response: During the study, PBCFR responded to 820,899 9-1-1 medical calls with 2,098 involving paramedic treatment for seizures (1,733 adults ≥18 years of age [55% women], and 365 minors [48% girls/adolescent women]. Median age was 38 years (mean 40) with pronounced right-skewing. Ethnic distributions were 52% WH, 28% AA, 18% HL, 1% AS/NA (paralleling the general population). In contrast, ethnic distributions for the 57 adult ketamine protocol patients were disproportionately distributed: 68.4% WH, 10.5% AA, 10.5% HL (Table 1) with a 2:1 ratio of women to men including women with multiple episodes of midazolam-resistant SE. Among those <18 yo, however, 47% were HL, 27% WH, and 13% AA.

Systolic Blood Pressure (SBP), Oxygen Saturation (SpO_2) & End-Tidal CO_2 ($ETCO_2$): Among Supplemental Content-*Table 2* cases, one adult had initial monitor readings reflecting desaturation (SpO_2 = 90%,89%) after ketamine. However, this quickly corrected with passive supplemental O_2 application. In another case, a 89% reading spontaneously improved within minutes. Of the four post-ketamine cases with $ETCO_2$ abnormalities, readings had improved in two; from 76 pre-ketamine to 52 post-ketamine in one and 66 to 51 in another. A third patient had a 47 mmHg reading post-ketamine, but that patient also maintained stable vital signs and normal SpO_2 (98-100%) with awakening prior to hospital arrival. The fourth patient had a drug misuse history, presenting pre-ketamine with SpO_2 88% and $ETCO_2$ 47 mmHg and 50 mmHg post. However, repeat SBP and SpO_2 post-ketamine remained within normal limits and she received no active interventions. The one pediatric case with abnormal post-ketamine $ETCO_2$ readings was the 4-year old girl later assessed to have post-anoxic posturing. Her pre-ketamine $ETCO_2$ readings were 78, 74, 84, and 83 mmHg with SpO_2 74 and 84% improving post-ketamine to 58 mmHg ($ETCO_2$) while SpO_2 saturations were normalizing by hospital arrival. Overall, none of the 81 patients required any additional active interventions following ketamine beyond passive supplemental O_2 application and those with pre-ketamine $ETCO_2$ aberrations consistently had corrections or improvements after ketamine terminated the convulsions.

Additional Discussion Points:

Limitations of Reported Respiratory Metrics: As noted. when possible, SBP, SpO_2, and $ETCO_2$ were to be measured to help demonstrate that respiratory compromise can occur during persistent convulsions. Aberrations (low SpO_2/high $ETCO_2$) typically will self-correct with convulsion cessation absent any co-existing illness/injury (e.g., head trauma, aspiration of gastric contents) or accompanying sedation from benzodiazepines, phenobarbital or other anti-seizure medications as well as pain medication use or narcotic misuse. SpO_2/$ETCO_2$ readings were reported primarily to estimate the frequency of convulsion related (and/or sedative-related) aberrations but also to capture post-ketamine improvements (or even worsening). One caveat is that such readings in the out-of-hospital setting can be inaccurate or difficult to obtain in the presence of sustained convulsions as well as frequent rescuer and patient movements in confined spaces. False readings (particularly low SpO_2) can occur frequently due to technical/device placement issues, especially in very young children. Also, even with termination of convulsions, abnormalities can take a brief period of time before self-correcting. In this study, a single abnormal reading led to a listing in Supplemental Content-*Table 2* and there were some missing data in a percentage of cases. Therefore, the overall clinical conditions after ketamine infusion became the key indicators of any ketamine-attributable adverse effect or complication. Again, none of the 81 patients required any additional active interventions following ketamine.

Cohort Size: One perceivable limitation of this study could be the cohort size of 81 patients. However, based on available data, 81 may be considered a large “n” for this condition. For example, the closely supervised NIH RAMPART trial (involving data from 33 high-performing EMS systems providing 10 mg parenteral midazolam for status epilepticus) yielded, statistically, very favorable results, yet >25% (91 of 362) still had persistent convulsions. In retrospect, had the investigators prospectively planned to compare the current study findings (n = 56/57 on-protocol adults with termination of prehospital convulsions) vs. the RAMPART trial (271/362 terminations with 10 mg midazolam), *Fischer’s Exact* testing would have resulted in a p-value <0.00001. Comparing 67/72 combined adult and pediatric on-protocol cases (including the non-seizure cases), the p-value would have been 0.0003. Including off protocol cases (76/81), statistics would been even stronger. In addition, most “failure to terminate cases” observed in this current investigation were among children. Only ~3% of the RAMPART cases were minors versus >20% in this study.

APPENDIX C: S.T.R.O.B.E. Guidelines Checklist

Strengthening the Reporting of Observational Studies (STROBE) Guidelines

STROBE Statement—Checklist of items that should be included in ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	**1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	**1**
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	**1-2 Appendix B**
Objectives	3	State specific objectives, including any prespecified hypotheses	**2**
Methods			
Study design	4	Present key elements of study design early in the paper	**2, Appendix B**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	**2, Appendix B**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	**2, 3, Table 1, Appendix B**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	**2, Appendix B**
Data sources /measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	**2,3 Appendix B**
Bias	9	Describe any efforts to address potential sources of bias	**3,5,6 Appendix B**
Study size	10	Explain how the study size was arrived at	**Appendix B**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	**2,3, Appendix B**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding variables	**2,3,4,5 Appendix B**
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	**2,3,4,5 Appendix B**
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	

Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarize follow-up time (eg, average and total amount)	**2,4, Table 1** **Appendix B** **Suppl Table 1** **Suppl Table 2** **2,4,5**
Outcome data	15*	Report numbers of outcome events or summary measures over time	**3,4,5** **Appendix B** **Supp Table 2**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	**3,4,5** **Appendix B**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	**3,4,5** **Appendix B** **Supp Table 1** **Supp Table 2**
Discussion			
Key results	18	Summarize key results with reference to study objectives	**5,6**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	**5,6** **Appendix B**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	**5,6** **Appendix B**
Generalizability	21	Discuss the generalizability (external validity) of the study results	**5,6** **Appendix B**
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	**6**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Supplemental Table 1.

Doses and Routes of Midazolam Administration by Paramedics Prior to Supplementing Ketamine for Persistent Status Epilepticus

	Adults N=57 encounters % (n)	**Minors** (age <18 yrs) N=15 encounters % (n)
Midazolam Dose 1		
0.5 mg IM	0	6.7% (1)*
2.5 mg IM	0	6.7% (1)
2.0 mg IV	0	6.7% (1)
2.5 mg IV	1.8% (1)	0
3.0 mg IN	0	6.7% (1)
3.4 mg IM	0	6.7% (1)
5 mg IM	17.5% (10)	20.0% (3)
5 mg IN	59.7% (34)	26.7% (4)
5 mg IV	21.1% (12)	20.0% (3)
Midazolam Dose 2		
None	19.3% (11) **	13.% (2) ***
0.5 mg IM	0	6.7% (1)*
1.7 mg IO	0	6.7% (1)
2.5 mg IV	1.8% (1)	0
2.5 mg IO	1.8% (1)	0
2.5 mg IN	0	6.7% (1)
3 mg IN	0	6.7% (1)
5 mg IM	19.3% (11)	6.7% (1)
5 mg IN	22.8% (13)	26.7% (4)
5 mg IO	7.0% (4)	0
5 mg IV	28.1% (16)	26.7% (4)

* A small one-year old boy received only 0.5 mg dosings.

** Among 11 of 57 adult cases in which only one dose of midazolam was administered by paramedics, that occurred in nine cases because family members or medical facilities had provided what were judged to be adequate first doses of benzodiazepines immediately prior to EMS arrival on-scene. In two other cases, it was reported that the patient had a history of seizures not being responsive to benzodiazepines, but paramedics still gave one 5 mg dose before turning to ketamine (which did rapidly terminate the convulsions). In the one adult case in which the convulsions were rapidly terminated but a recurrence occurred later in the hospital, the patient had received 4 mg of lorazepam IV at the medical institution and 5 mg of IV midazolam from paramedics before receiving 100mg IV ketamine (which terminated the convulsions for the entire prehospital phase of care). In three other instances, lower dose midazolam (2.5 mg) was given for similar reasons (the perception that ample dosings had been provided just before paramedic arrival).

*** In two childhood/adolescent cases, paramedics provided only one dose of midazolam to an adolescent and one dose to a child for similar reasons observed in adults when family members or medical facilities had just provided what were deemed to be adequate first doses of benzodiazepines immediately prior to paramedic arrival on-scene. Ketamine terminated convulsions in both cases.

Supplemental Table 2. Systolic Blood Pressure (SBP), O_2 Saturation (SpO_2) and End-Tidal CO_2 ($ETCO_2$) Measured Before and after Prehospital Administration of Ketamine*

	Midazolam First		Direct to Ketamine
	Adults (n=57 encounters) % (n)	**Children/Adolescents** (n=15 encounters) % (n)	**8 Adult/1 Child** (n=9 encounters) % (n)
PRE-KETAMINE			
SBP <100 mmHg			
Yes	2.2% (1)	0	0
No	97.8% (45)	100% (12)	100% (4)
Missing /Unable to Document	(11)	(3)	(5)
SpO_2<90%			
Yes	16.7% (8)	7.7% (1)	0
No	83.3% (40)	92.3% (12)	100% (4)
Missing / Unable to Document	(7)	(2)	(5)
$ETCO_2$>45 mmHg			
Yes	14.9% (7)	9.1% (1)	0
No	85.1% (40)	90.9% (10)	100% (3)
Missing / Unable to Document	(10)	(4)	(6)
POST-KETAMINE			
SBP <100 mmHg			
Yes	0	0	0
No	100% (51)	100% (9)	100% (9)
Missing / Unable to Document	(6)	(6)	(0)
SpO_2 <90%			
Yes	4.2% (2)	0	0
No	95.8% (46)	100% (13)	100% (9)
Missing / Unable to Document	(9)	(2)	0
$ETCO_2$ >45 mmHg			
Yes	7.7% (4)	8.3% (1)	0
No	92.3% (48)	91.7% (11)	100% (9)

*clinical courses of cases with at least one abnormal reading post-ketamine are detailed in *Appendix B*.