Twenty Years After PHTSE

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In 1992, my friend and colleague, Brian Alldredge, then Assistant Professor of Pharmacy and Neurology at UCSF, and I were sitting at our respective desks in offices literally across the hall from one another at San Francisco General Hospital, when I said: "Hey Brian, what study should we do next in status epilepticus?" We had just submitted a manuscript to *Neurology* describing a retrospective chart review of 154 adult patients,[1] and we both quickly agreed that we should try and come up with something more impactful. This was the birth of the Prehospital Treatment of Status Epilepticus trial, affectionately known as PHTSE. We were well aware of the regular use of intravenous (IV) diazepam by the paramedics in the San Francisco Emergency Medical Services (EMS) system, but there were questions as to whether lorazepam would be more effective than diazepam, whether the diagnosis of status was sufficiently accurate, whether there were treatment-induced complications in the field, and whether a more effective strategy would be, as the paramedics would say, to "scoop and run," forgoing immediate therapy and simply getting the patient to the nearest emergency department as quickly as possible. And the more we delved into the emergency medicine literature, the more we were convinced of the importance of our study, as we discovered that a number of well-designed studies of what appeared to be intuitively appealing, obviously effective interventions, such as the use of military antishock trousers and high-volume fluid replacement for the treatment of shock, turned out to be significantly more harmful than conservative therapy.

Designing PHTSE was relatively straightforward. The literature provided very good evidence for the rationale of comparing IV diazepam (5 mg) to IV lorazepam (2 mg), and our power calculations suggested that we could enroll enough patients within our own EMS, which avoided all the complexities of a multi-institutional trial. Not surprisingly, we encountered some resistance by our institutional review board regarding the inclusion of a placebo, and we also had to carefully navigate the requirements for carrying out a trial meeting the need for exception from informed consent under the Food and Drug Administration code of regulations 21 CFR 50.24.[2] Nonetheless, together with our emergency medicine colleagues, we successfully made the case for the trial design, including the essential need to compare active therapy to rapid transport to the hospital, based on the reasons mentioned above. The reviewers of our proposal to the National Institute of Neurological Disorders and Stroke (NINDS) agreed, and we began the study in the summer of 1993. The only notable problem we encountered in executing the project was the initial and substantial reluctance of some paramedics to embrace the protocol and enroll patients, as they saw the study as a threat to their autonomy and the possibility that the results might remove their opportunity to intervene with a therapy in which they strongly believed. It took a series of individual meetings, town halls, and even joining in ambulance rides to eventually win them over, and we were able to meet our recruitment targets (with careful monitoring by a Data and Safety Monitoring Board—DSMB) and provide the results that were published in 2001.[3]

Prehospital Treatment of Status Epilepticus provided incontrovertible evidence of the effectiveness of benzodiazepine therapy for status epilepticus in adult patients in the prehospital setting. However, despite the trend in the study results favoring lorazepam over diazepam, and the increased use of lorazepam for treating status epilepticus in other clinical settings, there was the nagging problem of lorazepam having a short shelf-life when not refrigerated, which made its adoption impractical for most EMS systems. At the same time, there was an increase in use of intramuscular (IM) midazolam rather than IV agents in the prehospital setting, which set the stage for the Rapid Anticonvulsant Medication Prior to Arrival (RAMPART), a randomized, double-blind, phase 3, noninferiority trial comparing IM midazolam to IV lorazepam.[4] This proved to be a more challenging study than PHTSE due to its scale—the ability to detect a noninferiority margin of 10% with the probability of a type I error of 0.025 required a sample size of at least 890 patients, and the study population included not only adults but children with an estimated body weight of 13 kg or more.

Fortunately, and in part due to the strong rationale for RAMPART, the NINDS had committed substantial resources to creating the Neurological Emergencies Treatment Trials (NETT) network,[5] and this highly functional, multi-institutional clinical research platform (which, for RAMPART, involved 1413 paramedics, 33 EMS agencies, and 79 hospitals) enabled the successful completion of the study in less time than originally predicted. The study conclusively demonstrated IM midazolam to be at least as safe and effective as IV lorazepam, and it was recognized with the 2013 David Sackett Annual Trial of the Year Award by the Society for Clinical Trials.

The experience of RAMPART not only demonstrated the capability of the NETT infrastructure but also crystallized the professional friendships of the leadership team, so it was natural for the group to immediately begin planning for the next status epilepticus trial. Given that the use of benzodiazepines as first-line treatment in the prehospital setting was now well-established, the group turned its attention to the approximately 30% to 35% of patients who remained in status epilepticus after hospital arrival. Anecdotal experience and various surveys indicated that the approach to second-line therapy for status epilepticus varied widely across the globe and mostly included fosphenytoin (or phenytoin), valproate, or levetiracetam. Although there was consideration to study additional agents (such as lacosamide), the team ultimately chose to focus on the 3 commonly used IV drugs in a randomized, blinded, adaptive-design trial, using the NETT network as well as the Pediatric Emergency Care Applied Research Network. Similar to RAMPART, the study, although again complex logistically, was executed without any major difficulties, and enrollment was stopped by the DSMB at 384 patients (the original target was 720 patients) when the data showed that all 3 drugs were statistically similar in aborting seizures in approximately half the patients, and there was no significant difference in the incidence of adverse events.[6,7]

So, where does this leave us in 2020? I have only highlighted here the lineage of the PHTSE-RAMPART-ESETT studies, which constitute the 3 largest scale, prospective, randomized therapeutic trials of status epilepticus in the past 20 years, but there have obviously been many other clinical studies in status epilepticus looking at diagnosis and treatment in various clinical settings that have helped advance the field. Nonetheless, a number of very pressing and important questions remain unresolved. Could other interventions in the prehospital setting, such as the use of second-line agents, improve the current therapeutic success rate using benzodiazepines of approximately 70%? What is needed to improve the in-hospital success rate of 50% for patients who have not responded to sufficient doses of benzodiazepines? What is needed to enable routine electroencephalographic monitoring for status epilepticus in the emergency department, let alone prehospital? And, a question that has proved particularly enigmatic—what is the best approach to the treatment of status epilepticus refractory to second-line therapy?

I encourage anyone with an interest in these questions to consider the approach Brian Alldredge and I took now almost 30 years ago and that has been at the core of any successes we've had since. First and foremost, be a part of a team that values professional friendships built around trust, respect, and an appreciation for the remarkable power of collaboration. Second, recognize that, regardless of all efforts to keep things as simple as possible, clinical trials of this sort are complex enterprises, so be exquisitely careful and detailed in every aspect of their planning. Finally, take on questions that, if answered, could have substantial clinical impact; that is, think big.

By Daniel H. Lowenstein
Department of Neurology, University of California, San Francisco

ORCID iD

Daniel H. Lowenstein https://orcid.org/0000-0002-9546-2085

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