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Review

Plasmapheresis for refractory status epilepticus Part II: A scoping systematic review of the pediatric literature

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ABSTRACT

Background: Our goal was to perform a scoping systematic review of the literature on the use of plasmapheresis or plasma exchange (PE) for refractory status epilepticus (RSE) in children.
Methods: Articles from MEDLINE, BIOSIS, EMBASE, Global Health, Healthstar, Scopus, Cochrane Library, the International Clinical Trials Registry Platform, clinicaltrials.gov (inception to May 2016), reference lists of relevant articles, and gray literature were searched. The strength of evidence was adjudicated using both the Oxford and GRADE methodology by two independent reviewers.
Results: Twenty-two original articles were identified, with 37 pediatric patients. The mean age of the patients was 8.3 years (age median: 8.5, range: 0.6 years–17 years). Seizure response to PE therapy occurred in 9 of the 37 patients (24.3%) included in the review, with 7 patients (18.9%) displaying resolution of seizures and 2 patients (5.4%) displaying a partial reduction in seizure volume. Twenty-eight of the 37 patients (75.7%) had no response to PE therapy. No adverse events were recorded.
Conclusions: Oxford level 4, GRADE D evidence exists to suggest little to no benefit of PE in pediatric RSE. Routine application of PE for pediatric RSE cannot be recommended at this time.

1. Introduction

Immunotherapies for refractory status epilepticus (RSE) and super-refractory status epilepticus (SRSE) in the pediatric population are rarely employed [1,2]. When the treating physician decides to implement immunotherapy for RSE/SRSE, the decision is made because either the underlying etiology is believed to autoimmune related, or the standard approached to seizure control has failed and immunotherapy is being employed as a last resort. More often, immunotherapy is employed for suspected underlying autoimmune etiology to RSE/SRSE.

A variety of immunotherapies have been employed in the attempt to treat RSE/SRSE related to autoimmune pathology in the pediatric population [2–4]. These therapies include plasmapheresis or plasma exchange (PE), intravenous immunoglobulins (IVIG), corticosteroids, monoclonal antibodies, and other immunomodulating drugs. It is unclear how these various therapies may lead to seizure reduction in the setting of RSE/SRSE. The application of PE is controversial given that the filtering of harmful autoantibodies has an unknown impact across the blood brain barrier, potentially arguing for the use of steroids or other immunomodulating agents in its place.

To date, only a small number of manuscripts have appeared in the literature describing the application of PE in pediatric patients for RSE [5–27]. Given the paucity of literature available, we decided to perform an extensive review on the topic. The goal of this manuscript was to produce a scoping systematic review on the use of PE for RSE in the pediatric population, in order to determine the extent of the available literature on the topic and reported efficacy of the treatment. This article is Part II of a two-part piece on the

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impact of PE in RSE. The focus of Part I was on the impact of PE in adult RSE.

2. Materials and methods

A scoping systematic review was conducted utilizing the methods outlined in the Cochrane Handbook for Systematic Reviewers [28]. Data was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [29]. Search strategy and review questions were decided upon by the primary author (FZ) and senior author (LG). The process undertaken was identical to that seen in the companion paper on the adult response to PE, hence almost identical methods sections are seen in this manuscript and the adult companion piece.

2.1. Search question, population, inclusion and exclusion criteria

The question posed for this scoping systematic review was: What is the effectiveness of PE for RSE in pediatric patients? The definition of RSE was as per the Neurocritical Care Society guidelines on the management of SE [30]. We utilized the following sub-classification system of RSE: generalized refractory status epilepticus (GRSE) was used to refer to generalized tonic–clonic RSE, focal refractory status epilepticus (FRSE) was used to refer focal tonic–clonic RSE, multi-focal refractory status epilepticus (MFRSE) was used to refer to RSE that had a mutli-focal tonic–clonic nature, and non-convulsive refractory status epilepticus (NCRSE) was used for non-convulsive seizures that fulfilled the criteria for RSE.

All studies, prospective and retrospective of any size based on pediatric human subjects were included. The reason for an all-inclusive search was based on the small number of studies of any type identified by the primary author during a preliminary search of MEDLINE.

The primary outcome measure was electrographic seizure control, defined as: complete resolution, partial seizure reduction, and failure. This qualitative seizure response grading was used given the lack of detail around the electroencephalographic response reported within the studies found. Secondary outcome measures were patient outcome (if reported), and adverse effects to PE. Given the authors experience with systematic reviews in the area of unconventional therapies for RSE/SRSE, this qualitative seizure response grading was utilized since prior experience with literature in this area has proven that quantitative seizure response documentation to be lacking.

Inclusion criteria were: All studies including human subjects whether prospective or retrospective, all study sizes, pediatric age category only (i.e. under 18 years of age), and documented application of PE for the purpose of seizure control in the setting of RSE. Exclusion criteria were: animal and non-English studies, adult patients (i.e. age 18 years or older), any studies where the response to PE was unclear or unstated, and any studies where the application of PE was for non-specific encephalopathy symptoms and not seizure control.

2.2. Search strategy

MEDLINE, BIOSIS, EMBASE, Global Health, Healthstar, SCOPUS, and Cochrane Library from inception to May 2016 were searched using individualized search strategies for each database based on the electronic interface provided. Keywords utilized within the search were identical across all databases searched. The search strategy for MEDLINE can be seen in Appendix A of the Supplementary material; with a similar search strategy utilized for the other databases. In addition; the World Health Organizations International Clinical Trials Registry Platform and ClinicalTrials.gov were searched looking for studies planned or underway; with none identified.

Meeting proceedings for the last 5 years looking for ongoing and unpublished work based on PE for RSE were examined. The meeting proceedings of the following professional societies were searched: Canadian Neurological Sciences Federation (CNSF), American Association of Neurological Surgeons (AANS), Congress of Neurological Surgeons (CNS), European Neurosurgical Society (ENSS), World Federation of Neurological Surgeons (WFNS), American Neurology Association (ANA), American Academy of Neurology (AAN), European Federation of Neurological Science (EFNS), World Congress of Neurology (WCN), American Epilepsy Society (AES), International League Against Epilepsy (ILAE), Society of Critical Care Medicine (SCCM), Neurocritical Care Society (NCS), World Federation of Societies of Intensive and Critical Care Medicine (WFSICCM), American Society for Anesthesiologists (ASA), World Federation of Societies of Anesthesiologist (WFSA), Australian Society of Anesthesiologists, International Anesthesia Research Society (IARS), Society of Neurosurgical Anesthesiology and Critical Care (SNACC), Society for Neuroscience in Anesthesiology and Critical Care, and the Japanese Society of Neuroanesthesia and Critical Care (JSNCC).

Finally, reference lists of any review articles or systematic reviews on seizure management were reviewed for relevant studies on PE or immunotherapy application for RSE that were missed during the database and meeting proceeding search.

2.3. Study selection

Two reviewers (FZ and MM) performed a two-step review of all articles returned by our search strategies First, the reviewers independently screened all titles and abstracts of the returned articles to decide if they met the inclusion criteria. Second, full text of the chosen articles was then assessed to confirm if they met the inclusion criteria and that the primary outcome of seizure control was reported in the study. Any discrepancies between the two reviewers were resolved by a third party (LG).

2.4. Data collection

Data was extracted from the selected articles and stored in an electronic database. Data fields included: patient demographics, type of study (prospective or retrospective), number of patients, PE treatment characteristics, timing to application of PE, other immunotherapies administered, other AED were utilized prior to implementation of PE, degree of seizure control (as described previously), adverse effects, and patient outcome.

2.5. Quality of evidence assessment

Assessment of the level of evidence for each included study was conducted by a panel of two independent reviewers, utilizing the Oxford criteria [31] and the Grading of Recommendation Assessment Development and Education (GRADE) criteria [32–37] for level of evidence. We elected on utilizing two different systems to grade level of evidence given that these two systems are amongst the most commonly used. We believe this would allow a larger audience to follow our systematic approach in the setting of unfamiliarity with a particular grading system.

The Oxford criteria consists of a 5 level grading system for literature. Level 1 is split into subcategories 1a, 1b, and 1c which represent a systematic review of randomized control trials (RCT) with homogeneity, individual RCT with narrow confidence interval, and all or none studies respectively. Oxford level 2 is split into 2a, 2b, and 2c representing systematic review of cohort