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Review

Intravenous immunoglobulins for refractory status epilepticus, part I: A scoping systematic review of the adult literature

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ABSTRACT

Purpose: Our goal was to perform a scoping systematic review of the literature on the use of intravenous immunoglobulins (IVIG) for refractory status epilepticus (RSE) in adults.
Method: 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-four original articles were identified. A total of 33 adult patients were described as receiving IVIG for RSE. Seizure reduction/control with IVIG occurred in 15 of the 33 patients (45.4%), with 1 (3.0%) and 14 (42.4%) displaying partial and complete responses respectively. No adverse events were recorded.
Conclusion: Oxford level 4, GRADE D evidence exists to suggest an unclear impact of IVIG therapy in adult RSE. Routine use of IVIG in adult RSE cannot be recommended at this time.

1. Introduction

The use of intravenous immunoglobulin (IVIG) therapy within neurology has been primarily limited to autoimmune disorders, with the goal of reversing or halting progressive neurological deterioration related to the underlying immune mediated attack on the nervous system.

Occasionally, patients with autoimmune encephalitis, either formally diagnosed or suspected, will develop seizures. Such seizures can lead to refractory status epilepticus (RSE) and super refractory status epilepticus (SRSE) [1,2]. In these circumstances a variety of immunotherapies are applied as a means of both seizure control, and treatment for the underlying immune dysfunction.

Immunotherapies employed in RSE/SRSE include, but are not limited to: IVIG, plasmapheresis or plasma exchange (PE), corticosteroids, and monoclonal antibodies [1–5]. Administration of IVIG is thought to flood the system with non-reactive antibodies leading to a downregulation of inflammatory response via direct leukocyte interactions and catabolism of pathologic antibodies [6].

To date the literature on the administration of IVIG for RSE in adults is limited and widely dispersed [7–32]. Our goal was to perform a scoping systematic review of the literature on the use of IVIG for RSE in adults, in order to gain a better understanding of its current use and reported efficacy. This manuscript is part I in a two-part series of IVIG for RSE. Part II focuses on IVIG in pediatric RSE.

2. Materials and methods

A scoping systematic review using the methodology outlined in the Cochrane Handbook for Systematic Reviewers [33] was conducted. The data was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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(PRISMA) [34]. The review questions and search strategy 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 pediatric response to IVIG, hence almost identical methods sections are seen in this manuscript and the pediatric companion piece.

2.1. Search question, population, inclusion and exclusion criteria

The question posed for scoping systematic review was: what is the effectiveness of IVIG in adult RSE? Similar to our other review papers on therapies in RSE, the definition of SE, and RSE was as per the Neurocritical Care Society guidelines on the management of SE [35]. The term generalized refractory status epilepticus (GRSE) was used to refer to generalized tonic–clonic RSE. The term focal refractory status epilepticus (FRSE) was used to refer focal tonic–clonic RSE. The term multi-focal refractory status epilepticus (MFRSE) was used to refer to RSE that had a mutli-focal tonic–clonic nature. The term 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 adult 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 of the administration of IVIG.

Inclusion criteria were: All studies including human subjects whether prospective or retrospective, all study sizes, the age category adults only (i.e. age 18 years or older), the documented use of IVIG for the purpose of seizure control in the setting of RSE, and documentation of some response to IVIG administration. Exclusion criteria were: pediatric studies, animal and non-English studies, and any studies failing to describe the use of IVIG or a response to IVIG administration.

2.3. 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. 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.

As well, meeting proceedings for the last 5 years looking for ongoing and unpublished work based on IVIG 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 immunotherapy usage for RSE that were missed during the database and meeting proceeding search.

2.3. Study selection

This process was identical to other systematic reviews we have performed. Utilizing two reviewers (FZ and MM), a two-step review of all articles returned by our search strategies was performed. 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, dose of IVIG used, timing to administration of IVIG, other immunotherapies administered, how many other AED were utilized prior to implementation of IVIG therapy, 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 [36] and the Grading of Recommendation Assessment Development and Education (GRADE) criteria [37–41] 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 studies with homogeneity of data, individual cohort study or low quality RCT, and outcomes research respectively. Oxford level 3 is split into 3a and 3b representing systematic review of case-control studies with homogeneity of data and individual case-control study respectively. Oxford level 4 represents case-series and poor cohort studies. Finally, Oxford level 5 represents expert opinion.

The GRADE level of evidence is split into 4 levels: A–D. GRADE level A represents high evidence with multiple high quality studies having consistent results. GRADE level B represents moderate evidence with one high quality study, or multiple low quality studies. GRADE level C evidence represents low evidence with one or more studies with severe limitations. Finally, GRADE level D