Cochrane
Library

Cochrane Database of Systematic Reviews

Intravenous immunoglobulins for epilepsy (Review)

Geng J, Dong J, Li Y, Ni H, Jiang K, Shi LL, Wang G

Geng J, Dong J, Li Y, Ni H, Jiang K, Shi LL, Wang G.

Intravenous immunoglobulins for epilepsy.

Cochrane Database of Systematic Reviews 2017, Issue 7. Art. No.: CD008557.

DOI: 10.1002/14651858.CD008557.pub3.

www.cochranelibrary.com

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON	3
BACKGROUND	5
OBJECTIVES	5
METHODS	5
RESULTS	8
Figure 1.	9
DISCUSSION	11
AUTHORS' CONCLUSIONS	12
ACKNOWLEDGEMENTS	12
REFERENCES	12
CHARACTERISTICS OF STUDIES	14
DATA AND ANALYSES	19
Analysis 1.1. Comparison 1 IVIg versus placebo, Outcome 1 50% or greater reduction in seizure frequency for refractory epilepsy, ITT analysis.	20
Analysis 1.2. Comparison 1 IVIg versus placebo, Outcome 2 50% or greater reduction in seizure frequency for refractory epilepsy, per-protocol.	20
Analysis 1.3. Comparison 1 IVIg versus placebo, Outcome 3 50% or greater reduction in seizure frequency for refractory epilepsy, best-case.	21
Analysis 1.4. Comparison 1 IVIg versus placebo, Outcome 4 50% or greater reduction in seizure frequency for refractory partial epilepsy, ITT analysis.	21
Analysis 1.5. Comparison 1 IVIg versus placebo, Outcome 5 50% or greater reduction in seizure frequency for refractory partial epilepsy, per-protocol.	22
Analysis 1.6. Comparison 1 IVIg versus placebo, Outcome 6 50% or greater reduction in seizure frequency for refractory partial epilepsy, best-case.	22
Analysis 1.7. Comparison 1 IVIg versus placebo, Outcome 7 Global assessment for refractory epilepsy, ITT analysis.	23
Analysis 1.8. Comparison 1 IVIg versus placebo, Outcome 8 Global assessment for refractory epilepsy, per-protocol.	23
Analysis 1.9. Comparison 1 IVIg versus placebo, Outcome 9 Global assessment for refractory epilepsy, best-case.	24
APPENDICES	24
WHAT'S NEW	26
HISTORY	26
CONTRIBUTIONS OF AUTHORS	27
DECLARATIONS OF INTEREST	27
SOURCES OF SUPPORT	27
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	28
INDEX TERMS	28

Intravenous immunoglobulins for epilepsy

JinSong Geng¹, JianCheng Dong¹, Youping Li², Hengjian Ni¹, Kui Jiang¹, Li Li Shi³, GuoHua Wang⁴

¹Evidence-based Medicine Center, Medical School of Nantong University, Nantong, China. ²Chinese Cochrane Centre, Chinese Evidence-Based Medicine Centre, West China Hospital, Sichuan University, Chengdu, China. ³Evidence-based Medicine Center, Medical School of Nantong University, Nantong, China. ⁴Institute of Nautical Medicine, Nantong University, Nantong, China

Contact address: JianCheng Dong, Evidence-based Medicine Center, Medical School of Nantong University, 19 Qixiu Road, Medical School of Nantong, Nantong, Jiangsu, 226001, China. dongjc@ntu.edu.cn.

Editorial group: Cochrane Epilepsy Group.

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 7, 2017.

Citation: Geng J, Dong J, Li Y, Ni H, Jiang K, Shi LL, Wang G. Intravenous immunoglobulins for epilepsy. *Cochrane Database of Systematic Reviews* 2017, Issue 7. Art. No.: CD008557. DOI: 10.1002/14651858.CD008557.pub3.

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Epilepsy is a common neurological condition, with an estimated incidence of 50 per 100,000 persons. People with epilepsy may present with various types of immunological abnormalities, such as low serum immunoglobulin A (IgA) levels, lack of the immunoglobulin G (IgG) subclass and identification of certain types of antibodies. Intravenous immunoglobulin (IVIg) treatment may represent a valuable approach and its efficacy has important implications for epilepsy management. This is an updated version of the original Cochrane review published in Issue 1, 2011.

Objectives

To examine the effects of IVIg on the frequency and duration of seizures, quality of life and adverse effects when used as monotherapy or as add-on treatment for people with epilepsy.

Search methods

For the latest update, we searched the Cochrane Epilepsy Group Specialized Register (2 February 2017), the Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (2 February 2017), MEDLINE (Ovid, 1946 to 2 February 2017), Web of Science (1898 to 2 February 2017), [ISRCTN registry](#) (2 February 2017), [WHO International Clinical Trials Registry Platform](#) (ICTRP, 2 February 2017), the US National Institutes of Health [ClinicalTrials.gov](#) (2 February 2017), and reference lists of articles.

Selection criteria

Randomized or quasi-randomized controlled trials of IVIg as monotherapy or add-on treatment in people with epilepsy.

Data collection and analysis

Two review authors independently assessed the trials for inclusion and extracted data. We contacted study authors for additional information. Outcomes included percentage of people rendered seizure-free, 50% or greater reduction in seizure frequency, adverse effects, treatment withdrawal and quality of life.

Main results

We included one study (61 participants). The included study was a randomized, double-blind, placebo-controlled, multi-centre trial which compared the treatment efficacy of IVIg as an add-on with a placebo add-on in patients with refractory epilepsy. There was no significant difference between IVIg and placebo in 50% or greater reduction in seizure frequency. The study reported a statistically significant effect for global assessment in favour of IVIg. No adverse effects were demonstrated. We found no randomized controlled trials that investigated the effects of IVIg monotherapy for epilepsy. Overall, the included study was rated as low/unclear risk of bias. Using GRADE methodology, the quality of the evidence was rated as low.

Authors' conclusions

We cannot draw any reliable conclusions regarding the efficacy of IVIg as a treatment for epilepsy. Further randomized controlled trials are needed.

PLAIN LANGUAGE SUMMARY

Intravenous immunoglobulins for epilepsy

Background

Epilepsy is a disorder where recurrent seizures are caused by abnormal electrical discharges in the brain. People with epilepsy may present with various types of immunological abnormalities. Most seizures can be controlled by antiepileptic drugs, but sometimes seizures develop which are resistant to these drugs. People may require other types of treatment, such as intravenous immunoglobulins (IVIg). IVIg is a sterile, purified blood product extracted from the plasma of blood donors. IVIg treatment may present a valuable approach and its efficacy has important implications for epilepsy management.

This review assessed the efficacy of IVg as a treatment for the control of epilepsy. Only one study (61 participants) which compared the treatment efficacy of IVIg as an add-on with a placebo add-on in patients with refractory epilepsy was included.

Results

Results of the review suggest that there is no convincing evidence to support the use of IVIg as a treatment for epilepsy and further randomized controlled trials are needed.

Quality of the evidence

The included study was rated as low/unclear risk of bias. Using GRADE methodology, the quality of the evidence was rated as low.

The evidence is current to 2 February 2017.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

IVIg compared to placebo for refractory epilepsy						
Patient or population: patients with refractory epilepsy Settings: three participating hospitals-Ottignies (Belgium), Zurich (Switzerland) and Kehl-Kork (Germany) Intervention: IVIg Comparison: placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	IVIg				
Seizure freedom	Not reported					
Satisfactory seizure control 50% or greater reduction in seizure frequency for refractory epilepsy	278 per 1000	525 per 1000 (236 to 1000)	RR 1.89 (0.85 to 4.21)	58 (1 study)	⊕⊕○○ low ^{1,2}	
Incidence of adverse or harmful effects	Not reported					
Global assessment	167 per 1000	548 per 1000 (188 to 1000)	RR 3.29 (1.13 to 9.57)	60 (1 study)	⊕⊕○○ low ^{1,2}	
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio						

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Unclear risk of selection bias: no information was obtained on generation of the random sequence or concealment of allocation of the randomisation.

² More trials and patients are needed to allow more precise estimation of the treatment effects of IVIg.

BACKGROUND

Description of the condition

Epilepsy is a common neurological condition, with an estimated incidence of 50 per 100,000 persons overall and a prevalence of five to 10 per 1000 persons in the developed world (Sander 1996). People with epilepsy present with various types of immunological abnormalities, for instance low serum immunoglobulin A (IgA) levels, lack of the immunoglobulin G (IgG) subclass (Duse 1986; Shiihara 1995) and identification of antibodies which are pathogenic or secondary to the primary disease, for example, to voltage-gated potassium (VGKC) and calcium channels (VGCC) (Majoie 2006), glutamic acid decarboxylase (GADA) (Errichiello 2009) and N-methyl-D-aspartate receptor (NMDAR) (Niehusmann 2009). Between 2% and 3% of the population will be diagnosed with epilepsy at some time in their lives, the majority of whom will go into remission. However, up to 30% of those with epilepsy continue to have seizures, despite monotherapy with standard antiepileptic drugs (AEDs) (Cockerell 1995; Hauser 1993) and may require newer modes of treatment.

Description of the intervention

Intravenous immunoglobulins (IVIg) are sterile, purified blood products extracted from the plasma of over 1000 human blood donors. The products typically contain more than 95% unmodified immunoglobulin G (IgG) and trace amounts of IgA or IgM. As early as 1977, children presenting with epileptic encephalopathy treated with repeated large doses of gamma globulin showed improvements in both clinical seizures and electroencephalography (EEG) (Péchadre 1977). Since then, many trials have evaluated the use of immunoglobulins in epilepsy. Encouraging results have been reported in West syndrome (WS) (Ariizumi 1987) and Lennox-Gastaut syndrome (LGS) (Gross-Tsur 1993; van Rijckevorsel-Harmant 1986). There are also studies which support the efficacy of IVIg in the treatment of children with recurrent seizures that are resistant to conventional anticonvulsant therapy (Billiau 2007; Sandstedt 1984; Spina 1989; Sterio 1992; Türkay 1996). IVIg therapy may induce notable changes in seizure frequency, behavior and power EEG spectra in some children with severe organic epilepsy (Bedini 1985). Single-course IVIg could be effective as an adjunctive therapy for juvenile spasms and such benefits may persist for many months (Bingel 2003).

How the intervention might work

A large body of clinical observation supports the involvement of immune mechanisms in the pathogenesis of certain types of epilepsy (Billiau 2005; Bostantjopoulou 1994; Najjar 2008; Nieto 2000; Vezzani 2005). The mechanism of action of IVIg in epilepsy

appears to be mainly immunological. The major component of the IVIg preparation (IgG) crosses the blood-cerebrospinal fluid (CSF) barrier, significantly increases the CSF IgG concentration, and is likely to reach the brain and act centrally (van Engelen 1994b). The therapeutic effects of IVIg may also have an impact on immune pathways, including modulating plasma levels of interferon- γ (IFN- γ), interleukin-6 (IL-6) and IL-8 (Billiau 2007; Ling 1993). In addition, the immediate treatment effect presents not only in one single type, but in various types of idiopathic and symptomatic epilepsies, indicating non-immunological mechanisms of action or an anticonvulsant effect through direct neuromodulation.

Why it is important to do this review

Immune system dysfunction plays an important role in epilepsy. Studies carried out to date support the efficacy of IVIg for different forms of epilepsy, especially intractable childhood epilepsy. IVIg treatment may represent a valuable approach and its efficacy has important implications for epilepsy management. However, at present there is no systematic review on IVIg for epilepsy. Without strict appraisal of the evidence, the benefits and risks of IVIg remain unclear. In this systematic review, we aimed to assess and summarize existing evidence regarding the efficacy and adverse effects of IVIg for people with epilepsy.

This review is an update of a previously published review in The Cochrane Database of Systematic Reviews (Issue 1, 2011) on 'Intravenous immunoglobulins for epilepsy'.

OBJECTIVES

To examine the effects of IVIg on the frequency and duration of seizures, quality of life and adverse effects when used as monotherapy or as add-on treatment for people with epilepsy.

We aimed to evaluate whether people with epilepsy receiving IVIg monotherapy or add-on therapy:

1. increased their chances of becoming seizure-free;
2. reduced the frequency and duration of seizures;
3. improved their quality of life, as measured by recognized and validated quality of life scales or tools;
4. experienced associated adverse effects.

METHODS

Criteria for considering studies for this review

Types of studies

We included trials meeting the following criteria:

1. randomized controlled trials (RCTs) or quasi-randomized controlled trials (e.g. sequence generated by date of birth or clinical record number);
2. double, single or unblinded trials;
3. parallel-group studies;
4. overall duration of treatment of at least one week;
5. a minimum period of follow up of one month after the last IVIg treatment.

Types of participants

All people with a diagnosis of epilepsy ([Engel 2001](#); [Engel 2006](#)) irrespective of their seizure type or epilepsy syndrome.

Types of interventions

1. IVIg monotherapy versus placebo or another antiepileptic drug (AED) treatment.
2. IVIg as add-on treatment to any AED versus add-on placebo or no add-on treatment.

Types of outcome measures

Primary outcomes

1. Seizure freedom: proportion of participants with complete cessation of seizures during the treatment period.
2. Satisfactory seizure control: proportion of participants with at least 50% or greater reduction in seizure frequency at the end of the study compared with the baseline.

Secondary outcomes

1. Incidence of adverse or harmful effects:
  - i) sedation;
  - ii) cognitive side effects;
  - iii) allergic reactions;
  - iv) other serious adverse events.
2. Dropout or withdrawal due to side effects, lack of efficacy, or other reasons.
3. Absolute or percentage reduction in seizure frequency and duration.
4. Improved quality of life as assessed by validated and reliable rating scales.
5. Economic analysis, if available.

In addition, we noted physiological outcomes such as resolution of immunological abnormalities, but did not take these into account in the data analysis.

Search methods for identification of studies

Electronic searches

Searches were run for the original review in June 2010, and subsequent searches were run in July 2012, January 2013, August 2014, April 2015, May 2016, and February 2017. For the latest update we searched the following databases. There were no language restrictions.

1. Cochrane Epilepsy Group Specialized Register (2 February 2017) using the search strategy set out in [Appendix 1](#).
2. Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (2 February 2017) using the search strategy set out in [Appendix 2](#).
3. MEDLINE (Ovid, 1946 to 2 February 2017), using the search strategy set out in [Appendix 3](#).
4. Web of Science (1898 to 2 February 2017) using the search strategy set out in [Appendix 4](#).
5. [ISRCTN registry](#), formerly Current Controlled Trials (2 February 2017) using the search strategy set out in [Appendix 5](#).
6. [WHO International Clinical Trials Registry Platform](#) (ICTRP, 2 February 2017) using the search terms set out in [Appendix 5](#).
7. The US National Institutes of Health [ClinicalTrials.gov](#) (2 February 2017) using the search terms set out in [Appendix 5](#).

Searching other resources

We searched the bibliographies of included studies for further references. We contacted the authors of identified trials for additional information and unpublished data.

Data collection and analysis

Selection of studies

Two review authors (Geng JS and Shi LL) independently screened all the titles and abstracts of publications identified by the searches to assess their eligibility. We excluded at this stage publications that did not meet the criteria. Following screening, we assessed the full texts of eligible citations for inclusion. We reached consensus on the selection of trials and the final list of studies. We discussed and resolved any disagreements where possible. We consulted a third member of our team (Dong JC) if consensus could not be reached.

Data extraction and management

Two review authors (Geng JS and Dong JC) independently extracted the information on the following characteristics of each included trial from the published reports, where possible. We contacted the chief investigators for additional data.

Participant factors

- Age
- Sex
- Epileptic seizure type and epilepsy syndrome
- Etiological factors of epilepsy
- Duration of epilepsy
- Number of seizures or seizure frequency prior to randomization
- Number and types of AEDs previously taken
- Comparability of groups at baseline (yes or no)
- Presence of neurological deficit or signs at baseline
- Electroencephalography (EEG) results at baseline
- Neuroimaging data at baseline

Trial design

- Criteria used to diagnose epilepsy
- Inclusion and exclusion criteria
- Method of randomization
- Method of allocation concealment
- Method of blinding
- Stratification factors
- Number of participants allocated to each group

Intervention and control

- Intervention given to controls
- Interval between IVIg infusion (weeks)
- Number of infusions (grams of IVIg per kilogram body weight and number of days per course)
- Duration of treatment period

Follow-up data

- Duration of follow-up
- Reasons for incomplete outcome data
- Dropout or loss to follow-up rates
- Methods of analysis (e.g. intention-to-treat (ITT), per protocol, the worst-case scenario or the best-case scenario analysis)

Assessment of risk of bias in included studies

Two review authors (Geng JS and Dong JC) assessed the risk of bias of each trial using the approach described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We assessed the risk of bias as: high, low or unclear.

We evaluated the following characteristics:

- adequate sequence generation;
- allocation concealment;
- blinding;
- whether incomplete outcome data were addressed;
- selective reporting;

- other sources of bias.

Measures of treatment effect

We used statistical methods in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) to measure treatment effects.

We used mean difference (MD) with 95% confidence interval (CI) for continuous data if data were provided as mean and standard deviation.

We used risk ratio (RR) with 95% CI for dichotomous data.

Unit of analysis issues

The duration of trials might vary considerably. If the range seemed too great to combine all trials into one meta-analysis, we divided the results into smaller time periods and conducted a separate meta-analysis for each time period.

If the outcome of interest was an event that occurred more than once, we adopted statistical methods for counting the data.

For trials comparing more than two intervention groups, we assessed the relevant intervention group.

Dealing with missing data

For missing data, such as because of dropout or loss to follow-up, we used an ITT analysis, whenever possible. We included trials with missing information on the outcomes of interest, or summary data such as sample sizes, numbers of events or standard errors. We contacted the chief investigators of included trials to request missing data, if possible. We addressed the potential implications of missing data (for example, loss to follow-up and no outcome obtained, receiving the wrong treatment, lack of compliance or ineligibility) in the [Discussion](#) section.

Assessment of heterogeneity

We tested the heterogeneity of intervention effects among trials using the standard χ^2 test (P value) or the I^2 statistic. We considered a P value of less than 0.10 as evidence of heterogeneity. The interpretation of the I^2 for heterogeneity was as follows:

- 0% to 40%, was not important;
- 30% to 60%, represented moderate heterogeneity;
- 50% to 90%, represented substantial heterogeneity;
- 75% to 100%, represented considerable heterogeneity.

Where there was no substantial or considerable heterogeneity, then we adopted a fixed-effect model in the data synthesis; otherwise, we used a random-effects model. We assessed possible sources of heterogeneity (for example clinical heterogeneity, methodological heterogeneity or statistical heterogeneity) by sensitivity analysis, as described below.

Assessment of reporting biases

We planned to use a funnel plot to detect reporting biases if sufficient numbers of studies were available. Possible sources of funnel plot asymmetry are publication bias, language bias, citation bias, poor methodological quality, and true heterogeneity. However, we identified only one relevant study so therefore funnel plot analysis was not undertaken.

Data synthesis

We planned to pool studies in forest plots only if there was no important clinical heterogeneity. However, only one relevant study was identified, and results were displayed in forest plots. We used fixed-effect or random-effects models, as appropriate. We used Review Manager 5.3 to analyze trial data ([RevMan 2014](#)).

Summary of Findings and Quality of the Evidence (GRADE)

The GRADE approach ([Guyatt 2011](#)) was used to interpret findings and the GRADE profiler ([GRADEPro 2004](#)) allowed us to import data from Review Manager 5.3 ([RevMan 2014](#)) to create 'Summary of findings' tables. These tables provided outcome-specific information about the quality of the body of evidence, the magnitude of effects of the interventions examined, and the summary of available data on the main outcomes.

We downgraded the evidence quality from 'high quality' by one level for serious (or by two for very serious) study limitations (risk of bias), inconsistency, indirectness of evidence, imprecision of effect estimates or potential publication bias.

The following outcomes were included in the 'Summary of findings' tables:

- seizure freedom;
- satisfactory seizure control;
- incidence of adverse or harmful effects
- global assessment

Subgroup analysis and investigation of heterogeneity

We planned to synthesize data according to epilepsy syndromes (for example, West syndrome, Lennox-Gastaut syndrome, juvenile myoclonic epilepsy) and types of interventions (for example, IVIg monotherapy or add-on therapy). However, as one study was included in the review no subgroup analysis was carried out.

Sensitivity analysis

We planned to evaluate the robustness of the results of the data analysis by comparing the fixed-effect model and random-effects model estimates, comparing the results of different types of trials, removing trials with low methodological quality, or excluding trials with a large effect size. Nevertheless, we did not do the sensitivity analysis as mentioned because only one study was included in the review. We did the ITT analysis, per protocol analysis and the best-case scenario instead to test the robustness of results. If the results remained unchanged, then we considered the evidence to be robust.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Results of the search

We found ten clinical trials investigating the use of IVIg as a treatment for epilepsy, of which only one met our inclusion criteria. See [Figure 1](#) and [Appendix 6](#).

Figure 1. Study flow diagram.

Included studies

The included study ([van Rijckevorsel-Harmant 1994](#)) was a randomized, add-on, double-blind, placebo-controlled, multi-centre trial. The aim of this trial was to evaluate the efficacy of three different dosages of IVIg (100, 250 and 400 mg/kg) compared with placebo in people with refractory epilepsy. Sixty-one people were enrolled in the study, 4 of whom with Lennox-Gastaut syndrome (LGS). Partial epilepsy was the commonest diagnosis among patients enrolled (n=49) and was equally distributed in each group. Patients were enrolled from three centres in Belgium, Switzerland and Germany. The age of the participants ranged from two to 51 years, with the mean age of each group ranging from 18.5 to 26.2 years. The ratio of females to males was about 0.45. Participants received IVIg four times during the first week and then once a week in the second, third and sixth weeks. The last infusion was performed optionally as a booster six months after the first infusion. All participants were also treated with classic AEDs. The primary efficacy endpoint was the proportion of participants with at least 50% or greater reduction in seizure frequency by the sixth month after the first infusion compared with the four weeks before inclusion in the trial. Global assessment took into account the reduction of frequency and severity of seizures, the evolution of EEGs, the interictal status and the perception of the participant, his or her family or the nurses and was performed at the end of the study.

Excluded studies

We excluded nine studies. One study ([Munn 1995](#)) was merely an abstract of an RCT aiming to compare the efficacy of IVIg with other therapy for intractable infantile spasms or myoclonic seizures. One study ([Arts 2009](#)) was a historical control trial, and the other study ([Geva-Day 2012](#)) was a retrospective, multi-centre study. For one RCT ([Bien 2013](#)), four people with rasmussen encephalitis (RE) were diagnosed with 'no epilepsy' at baseline. The remaining five studies ([Billiau 2007](#); [Gross-Tsur 1993](#); [Illum 1990](#); [Mikati 2010](#); [van Engelen 1994a](#)) were all self-controlled trials.

Risk of bias in included studies

Allocation

Randomization was mentioned in the trial design but detailed methods of random sequence generation were not defined. Whether the randomized sequence was adequately concealed remains unknown.

Blinding

Double-blind methods were used in this trial. Investigators were blinded regarding IVIg versus placebo, but not regarding the dosages. External outcome assessors (neurologists) were totally blinded regarding both dosages and IVIg versus placebo.

Incomplete outcome data

Three patients with partial epilepsy were excluded from the statistical evaluation of seizure frequency by authors of the included study. The reasons for exclusion were as follows: one had unaccountable seizures after baseline (100 mg/kg IVIg), one had continuous partial motor seizures at the beginning and rarely after the IVIg treatment (250 mg/kg IVIg), and one patient dropped out (100 mg/kg IVIg) for unknown reasons. The patient who dropped out (100 mg/kg IVIg) was also excluded from the global assessment. These excluded patients contributed to the best and worst-case scenario analyses.

Selective reporting

We judged the included study as being at low risk of reporting bias.

Other potential sources of bias

Baseline imbalance between the IVIg and placebo group existed.

Effects of interventions

See: [Summary of findings for the main comparison IVIg compared to placebo for refractory epilepsy](#)

IVIg versus placebo

We extracted the data for the following outcomes from the one included trial ([van Rijckevorsel-Harmant 1994](#)). All of the participants who dropped out from the trial were from the IVIg group. Therefore, the results of the ITT analysis were the same as the worst-case scenario.

Reduction in seizure frequency of 50% or greater

Intention-to-treat (ITT) analysis

There was no statistically significant result in favour of IVIg for refractory epilepsy (risk ratio (RR) 1.76, 95% confidence interval

(CI) 0.79 to 3.93) and refractory partial epilepsy (RR 3.08, 95% CI 0.84 to 11.34).

Per protocol analysis

The RR was 1.89 (95% CI 0.85 to 4.21) indicating no statistically significant difference of IVIg in the management of refractory epilepsy. There was no statistically significant difference between IVIg and placebo for refractory partial epilepsy (RR 3.35, 95% CI 0.91 to 12.30).

Best-case scenario

No statistically significant difference was demonstrated between IVIg and placebo for refractory epilepsy (RR 2.01, 95% CI 0.91 to 4.43) and for refractory partial epilepsy (RR 3.57, 95% CI 0.98 to 13.00).

Global assessment

Although 'global assessment' was not stated in the review protocol, it was reported as an important outcome in the included study. The global assessment was considered to integrate several clinical aspects including reduction in the number and severity of seizures, evolution of EEG, interictal status and perception of the patients and caregivers.

Intention-to-treat (ITT) analysis

There was a significant advantage in favour of IVIg for refractory epilepsy (RR 3.21, 95% CI 1.10 to 9.36).

Per protocol analysis

There was a statistically significant difference showing benefit of IVIg for refractory epilepsy (RR 3.29, 95% CI 1.13 to 9.57).

Best-case scenario

A statistically significant improvement in favour of IVIg for refractory epilepsy was found (RR 3.35, 95% CI 1.15 to 9.73).

Incidence or severity of adverse effects

No severe side effects were found in this trial.

Dropout or withdrawal due to side effects, lack of efficacy, or other reasons

One patient in 100mg/kg IVIg group had to stop infusions for possible related side effects (vomiting).

Other pre-defined outcomes of the review were not reported in the included study.

Main results on seizure frequency and global assessment are summarised in [Summary of findings for the main comparison](#).

DISCUSSION

Evidence for the use of intravenous immunoglobulin (IVIg) is mainly available from non-randomized, non-concurrent studies. One randomized controlled trial (RCT) ([van Rijkevorsel-Harmant 1994](#)) aimed to investigate the efficacy of IVIg in patients with refractory epilepsy and was included in this systematic review. A total of just 61 participants provided data for the analysis and the small sample size might have contributed to the lack of power to detect a difference, if one was present. Methods of randomization were unclear and whether allocation concealment was used remains unknown. Baseline imbalance between the randomized groups could be caused by unconcealed allocation of intervention or exclusion of participants from the IVIg group. A double-blind method was used in the trial to avoid performance and measurement bias. Three participants excluded from the statistical analysis of seizure frequency were all from the IVIg group. Detailed reasons for why one participant dropped out were unknown. Reasons for the exclusion of the other two participants were unrelated to the IVIg treatment.

There was no evidence of a significant difference between IVIg and placebo for 50% or greater reduction in seizure frequency currently. A statistically significant effect for global assessment in favour of IVIg was found. No severe adverse effects of IVIg were reported in the trial. The duration of treatment in this trial was six weeks, not long enough to demonstrate efficacy in the longer term. Trials with a longer duration of treatment and follow up are needed to address this issue. Patients were allocated to groups receiving three different doses of IVIg. However, the results from this trial suggested no correlation between better therapeutic effects and increased doses of IVIg. As a result, we were unable to examine the dose-dependent effects of IVIg. No information could be found on other outcome measures, such as quality of life and cost-effectiveness.

It is impossible to make any general statements about the effectiveness of IVIg as we found only one RCT evaluating the role of IVIg in refractory epilepsy. Participants with any type of refractory partial or generalized epilepsy were included in the trial. Whether IVIg may be an effective treatment for certain types of refractory epilepsy, such as Lennox-Gastaut syndrome, West syndrome, etc. remains unknown. No conclusion can be drawn about IVIg as monotherapy or as an add-on to other AEDs. This is an extremely important issue for clinicians who are faced with an ever-increasing number of AEDs to choose from and need to make an evidence-

based choice between IVIg and other types of AEDs. There is also currently no RCT assessing the effects of IVIg for the treatment of non-refractory epilepsy.

AUTHORS' CONCLUSIONS

Implications for practice

No reliable conclusions can be drawn at present regarding the effects of intravenous immunoglobulin (IVIg) as a treatment for epilepsy.

Implications for research

There are several implications for research.

1. Randomized controlled trials (RCTs) are needed to investigate the effects of IVIg in epileptic patients.
2. The efficacy of IVIg treatment among a homogenous subset of patients with refractory epilepsy is unclear and could be assessed by future research.
3. Reporting of RCTs should be according to the CONSORT Statement (Schulz 2010) to enable readers to judge the reliability and relevance of the findings.
4. Large sample sizes, with statistical power to detect a clinically significant difference, should be taken into consideration.
5. Studies should be performed to determine the optimal dose of IVIg.

6. Control treatments may include antiepileptic drugs.
7. Studies should be designed to allow for assessment of long-term effects and adverse events.
8. Future trials should include all clinically relevant outcomes (not only the seizure endpoints) to provide sufficient evidence.
9. Given the protective role of IVIg in the immune system, whether IVIg may have some effects on epilepsy caused by antibodies deserves further investigation.

ACKNOWLEDGEMENTS

We are grateful for technical assistance from the Cochrane Epilepsy Group. We sincerely thank Professor Sridharan Ramaratnam (editorial mentor) for important advice on how to write and revise the protocol. We acknowledge the contribution of Rachael Kelly (Managing Editor), Markus Reuber (subject expert), Ann Johnston (subject expert), Karla Hemming (statistician) and Keven Hearn (consumer). We thank Professor Marcel Delire for providing us with additional information about the included trial. We thank Professor Taixiang Wu and Professor GuanJian Liu at the Chinese Cochrane Center and Chinese Evidence-based Medicine Center for guidance on how to teach and carry out research in evidence-based medicine. We acknowledge the help of the teachers at the Chinese Cochrane Center and Chinese Evidence-based Medicine Center, West China Hospital and Department of Medical informatics, Medical School of Nantong University.

REFERENCES

References to studies included in this review

- van Rijckevorsel-Harmant 1994 *{published data only}*
* Van Rijckevorsel-Harmant K, Delire M, Schmitz-Moorman W, Wieser HG. Treatment of refractory epilepsy with intravenous immunoglobulins. Results of the first double-blind/dose finding clinical study. *International Journal of Clinical & Laboratory Research* 1994;**24**(3):162–6.
Van Rijckevorsel-Harmant K, Delire M, Schmitz-Moorman W, Wieser HG. Refractory epilepsy treated by IVIg in a dose finding, double blind study. *Canadian Journal of Neurological Sciences* 1993;**20**(Suppl 4):S181, Abstract no: 6-11-15.

References to studies excluded from this review

- Arts 2009 *{published data only}*
Arts WF, Aarsen FK, Scheltens-de Boer M, Catsman-Berrevoets CE. Landau-Kleffner syndrome and CSWS

syndrome: treatment with intravenous immunoglobulins. *Epilepsia* 2009;**50** Suppl 7:55–8.

- Bien 2013 *{published data only}*
Bien CG, Tiemeier H, Sassen R, Kuczaty S, Urbach H, Von Lehe M, et al. Rasmussen encephalitis: incidence and course under randomized therapy with tacrolimus or intravenous immunoglobulins. *Epilepsia* 2013;**54**(3):543–50.

- Billiau 2007 *{published data only}*
Billiau AD, Witters P, Ceulemans B, Kasran A, Wouters C, Lagae L. Intravenous immunoglobulins in refractory childhood-onset epilepsy: effects on seizure frequency, EEG activity, and cerebrospinal fluid cytokine profile. *Epilepsia* 2007;**48**(9):1739–49.

- Geva-Dayana 2012 *{published data only}*
Geva-Dayana K, Shorer Z, Menascu S, Linder I, Goldberg-Stern H, Heyman E, et al. Immunoglobulin treatment for

- severe childhood epilepsy. *Pediatric Neurology* 2012;**46**(6): 375–81.
- Gross-Tsur 1993** {published data only}
Gross-Tsur V, Shalev RS, Kazir E, Engelhard D, Amir N. Intravenous high-dose gammaglobulins for intractable childhood epilepsy. *Acta Neurologica Scandinavica* 1993;**88**(3):204–9.
- Illum 1990** {published data only}
Illum N, Taudorf K, Heilmann C, Smith T, Wulff K, Mansa B, et al. Intravenous immunoglobulin: a single-blind trial in children with Lennox-Gastaut syndrome. *Neuropediatrics* 1990;**21**(2):87–90.
- Mikati 2010** {published data only}
Mikati MA, Kurdi R, El-Khoury Z, Rahi A, Raad W. Intravenous immunoglobulin therapy in intractable childhood epilepsy: open-label study and review of the literature. *Epilepsy & Behavior* 2010;**17**(1):90–4.
- Munn 1995** {published data only}
Munn R, Doucette J, Connolly M, Peng S, Matheson D, Puterman M, et al. Controlled study of intravenous immunoglobulin in children with intractable generalized epilepsy. *Epilepsia* 1995;**36** Suppl 4:106.
- van Engelen 1994a** {published data only}
Van Engelen BG, Renier WO, Weemaes CM, Strengers PF, Bernsen PJ, Notermans SL. High-dose intravenous immunoglobulin treatment in cryptogenic West and Lennox-Gastaut syndrome; an add-on study. *European Journal of Pediatrics* 1994;**153**(10):762–9.
- References to ongoing studies**
- NCT02697292** {unpublished data only}
NCT02697292. IVIG in patients with VGKC Ab associated autoimmune epilepsy [A randomized double blind placebo controlled study of intravenous immunoglobulin (IVIG) patients with voltage gated potassium channel complex (VGKC) antibody associated autoimmune epilepsy]. <https://clinicaltrials.gov/ct2/show/record/NCT02697292> (first received 19 February 2016).
- Additional references**
- Ariizumi 1987**
Ariizumi M, Baba K, Hibio S, Shiihara H, Michihiro N, Ogawa K, et al. Immunoglobulin therapy in the West syndrome. *Brain and Development* 1987;**9**(4):422–5.
- Bedini 1985**
Bedini R, De Feo MR, Orano A, Rocchi L. Effects of gamma-globulin therapy in severely epileptic children. *Epilepsia* 1985;**26**(1):98–102.
- Billiau 2005**
Billiau AD, Wouters CH, Lagae LG. Epilepsy and the immune system: is there a link?. *European Journal of Paediatric Neurology* 2005;**9**(1):29–42.
- Bingel 2003**
Bingel U, Pinter JD, Sotero de Menezes M, Rho JM. Intravenous immunoglobulin as adjunctive therapy for juvenile spasms. *Journal of Child Neurology* 2003;**18**(6): 379–82.
- Bostantjopoulou 1994**
Bostantjopoulou S, Hatzizisi O, Argyropoulou O, Andreadis S, Deligiannis K, Kantaropoulou M, et al. Immunological parameters in patients with epilepsy. *Functional Neurology* 1994;**9**(1):11–15.
- Cockerell 1995**
Cockerell OC, Johnson AL, Sander JW, Hart YM, Shorvon SD. Remission of epilepsy: results from the National General Practice Study of Epilepsy. *Lancet* 1995;**346**(8968): 140–4.
- Duse 1986**
Duse M, Tiberti S, Plebani A, Avanzini MA, Gardenghi M, Menegati E, et al. IgG2 deficiency and intractable epilepsy of childhood. *Monographs in Allergy* 1986;**20**:128–34.
- Engel 2001**
Engel J Jr, International League Against Epilepsy (ILAE). A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE Task Force on Classification and Terminology. *Epilepsia* 2001;**42**(6): 796–803.
- Engel 2006**
Engel J Jr. Report of the ILAE classification core group. *Epilepsia* 2006;**47**(9):1558–68.
- Errichiello 2009**
Errichiello L, Perruolo G, Pascarella A, Formisano P, Minetti C, Striano S, et al. Autoantibodies to glutamic acid decarboxylase (GAD) in focal and generalized epilepsy: a study on 233 patients. *Journal of Neuroimmunology* 2009;**211**(1-2):120–3.
- GRADEPro 2004** [Computer program]
Brozek J, Oxman A, Schunemann H. GRADEPro GDT. Version 3.6 for Windows. Hamilton (ON): GRADE Working Group, McMaster University, 2004.
- Guyatt 2011**
Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. *Journal of Clinical Epidemiology* 2011;**64**(4):380–2.
- Hauser 1993**
Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935–1984. *Epilepsia* 1993;**34**(3):453–68.
- Higgins 2011**
Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org.
- Lefebvre 2011**
Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from <http://handbook.cochrane.org/>.

Ling 1993

Ling ZD, Yeoh E, Webb BT, Farrell K, Doucette J, Matheson DS. Intravenous immunoglobulin induces interferon-gamma and interleukin-6 in vivo. *Journal of Clinical Immunology* 1993;**13**(5):302–9.

Majoie 2006

Majoie HJ, de Baets M, Renier W, Lang B, Vincent A. Antibodies to voltage-gated potassium and calcium channels in epilepsy. *Epilepsy Research* 2006;**71**(2-3):135–41.

Najjar 2008

Najjar S, Bernbaum M, Lai G, Devinsky O. Immunology and epilepsy. *Reviews in Neurological Diseases* 2008;**5**(3):109–16.

Niehusmann 2009

Niehusmann P, Dalmau J, Rudlowski C, Vincent A, Elger CE, Rossi JE, et al. Diagnostic value of N-methyl-D-aspartate receptor antibodies in women with new-onset epilepsy. *Archives of Neurology* 2009;**66**(4):458–64.

Nieto 2000

Nieto M, Roldán S, Sánchez B, Candau R, Rodríguez R. Immunological study in patients with severe myoclonic epilepsy in childhood. *Revista de Neurologia* 2000;**30**(5):412–4.

Pé Chadre 1977

Pé Chadre JC, Sauvezie B, Osier C, Gibert J. The treatment of epileptic encephalopathies with gamma globulin in children. *Revue Electroencephalographie et de Neurophysiologie Clinique* 1977;**7**(4):443–7.

RevMan 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Sander 1996

Sander JW, Shorvon SD. Epidemiology of the epilepsies. *Journal of Neurology, Neurosurgery, and Psychiatry* 1996;**61**(5):433–43.

Sandstedt 1984

Sandstedt P, Kostulas V, Larsson LE. Intravenous gamma globulin for post-encephalitic epilepsy. *Lancet* 1984;**2**(8412):1154–5.

Schulz 2010

Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMC Medicine* 2010;**8**:18.

Shiihara 1995

Shiihara H, Michihiro N, Sakuta R, Saga T, Ojima K, Ariizumi M. Changes in the lymphocyte subsets during high dose immunoglobulin therapy for intractable childhood epilepsy. *Psychiatry and Clinical Neurosciences* 1995;**49**(3):S251–3.

Spina 1989

Spina A, Losito R, Marzocco P, Damato R. Treatment of “intractable childhood epilepsy” with high doses of intravenous gamma-globulins. *Acta Neurologica (Napoli)* 1989;**11**(6):415–22.

Sterio 1992

Sterio M, Gebauer E, Felle D, Vucicević G, Zalisevskij G. Malignant epilepsy in children: therapy with high doses of intravenous immunoglobulin. *Medicinski Pregled* 1992;**45**(5-6):220–4.

Türkay 1996

Türkay S, Baskin E, Dener S, Gultekin A, Tanzer F, Sekreter E. Immune globulin treatment in intractable epilepsy of childhood. *Turkish Journal of Pediatrics* 1996;**38**(3):301–5.

van Engelen 1994b

Van Engelen BG, Renier WO, Weemaes CM. Immunoglobulin treatment in human and experimental epilepsy. *Journal of Neurology, Neurosurgery, and Psychiatry* 1994;**57** Suppl:72–5.

van Rijckevorsel-Harmant 1986

Van Rijckevorsel-Harmant K, Delire M, Rucquoy-Ponsar M. Treatment of idiopathic West and Lennox-Gastaut syndromes by intravenous administration of human polyvalent immunoglobulins. *European Archives of Psychiatry and Neurological Sciences* 1986;**236**(2):119–22.

Vezzani 2005

Vezzani A, Granata T. Brain inflammation in epilepsy: experimental and clinical evidence. *Epilepsia* 2005;**46**(11):1724–43.

References to other published versions of this review**Geng 2010**

Geng J, Dong J, Li Y, Ni H, Jiang K, Shi LL, et al. Intravenous immunoglobulins for epilepsy. *Cochrane Database of Systematic Reviews* 2010, Issue 6. [DOI: 10.1002/14651858.CD008557]

Geng 2011

Geng J, Dong J, Li Y, Ni H, Jiang K, Shi LL, et al. Intravenous immunoglobulins for epilepsy. *Cochrane Database of Systematic Reviews* 2011, Issue 1. [DOI: 10.1002/14651858.CD008557.pub2]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

van Rijckevorsel-Harmant 1994

Methods	Randomized, add-on, double-blind, placebo-controlled, multi-centre trial	
Participants	Setting: multi-centre (Centre Neurologique William Lennox, Ottignies, Belgium; Department of Neurology, University Hospital Zurich, Zurich, Switzerland; Epilepsy Center, Kehl-Kork, Germany) Number of participants enrolled: 61 (43 in IVIg group, 18 in placebo group) Sex: 42 male (31 in IVIg group, 11 in placebo group), 19 female (12 in IVIg group, 7 in placebo group) Mean age (years): IVIg group (24.4 to 26.2), placebo group (18.5) Mean duration of epilepsy (years): IVIg group (15.33 to 19.44), placebo group (12.54) (data from 58 participants who were included in the seizure frequency analysis) Race: Caucasian Types of participants: refractory epilepsy Inclusion criteria: patients suffering from West syndrome, Lennox-Gastaut syndrome or an early myoclonic encephalopathy were enrolled as soon as the diagnosis had been made. Patients with any kind of intractable epilepsy were allowed to enter the trial, provided the diagnosis had been made at least 1 year previously and that the seizure frequency was at least 1 per week during the previous 6 months before admission Exclusion criteria: patients presenting with any kind of neoplasia, any progressive and/or expansive cerebral disorders (except for Rasmussen syndrome), symptoms of severe renal insufficiency (serum creatinine > 3 mg/100 ml), a known intolerance to blood products, a seropositivity to HIV1 and 2 or a known chromosomal abnormality. Involvement in another clinical trial during the course of the study or the previous 6 months was also excluded	
Interventions	Comparison: IVIg as add-on treatment to classic AEDs versus add-on placebo 1. IVIg (BI61011, Behringwerke, Germany): 100 mg/kg, 250 mg/kg, 400 mg/kg 2. Placebo consisted of 2% human albumin solution Duration of treatment period: 6 weeks	
Outcomes	1. 50% or greater reduction in seizure frequency 2. Incidence or severity of adverse effects 3. Global assessment	
Notes	Participants with any type of refractory partial or generalized epilepsy were included in the trial IVIg and placebo groups were not comparable at baseline, including age and median number of daily seizures All the withdrawals were from IVIg-treated groups	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk	A multi-centre, randomized trial
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinding. Investigators were blinded regarding IVIg versus placebo. External outcome assessors (neurologists) were totally blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 patients were excluded from the evaluation of seizure frequency: 1 with unaccountable seizures after baseline (100 mg/kg), 1 with continuous partial motor seizures at the beginning and rarely after the IVIg treatment (250 mg/kg) and 1 patient who dropped out (100 mg/kg) The 1 patient who dropped out (100 mg/kg) was also excluded from the global assessment Conclusions remained unchanged for the sensitivity analysis of missing data
Selective reporting (reporting bias)	Low risk	The main outcome measure for this trial was the reduction of seizure frequencies, and secondary outcome measure was the type and severity of seizures, the interictal status and neurophysiological parameters. 'Global assessment' was used to evaluate several clinical outcomes listed above
Other bias	Unclear risk	IVIg and placebo groups were not comparable in terms of some baseline data including the mean duration of epilepsy and median number of daily seizures. For patients in the IVIg group, mean duration of epilepsy seemed to be longer than comparison, while median number of daily seizures were less

AED: antiepileptic drugs

IVIg: intravenous immunoglobulin

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Arts 2009	A historical controlled trial; results of the trial were compared with those reported in the literature and with data from a retrospective survey of their earlier patients
Bien 2013	16 patients with Rasmussen encephalitis (RE) were randomized to tacrolimus or IVIg. However, 4 patients were diagnosed with “no epilepsy” at baseline
Billiau 2007	A self-controlled trial; each patient served as his or her own control before or after treatment
Geva-Dayana 2012	A retrospective, multi-centre study comprised of patients treated with immunoglobulins for either epileptic encephalopathy or refractory epilepsy
Gross-Tsur 1993	A self-controlled trial; each patient served as his or her own control before or after treatment
Illum 1990	A self-controlled trial; each patient served as his or her own control before or after treatment
Mikati 2010	A self-controlled trial; each patient served as his or her own control before or after treatment
Munn 1995	Patients were randomized to receive IVIG or 'best available therapy' for a period of 12 weeks. Patients who did not respond to BAT crossed over to receive IVIG. However, data from the totally randomized phase were not available
van Engelen 1994a	A self-controlled trial; each patient served as his or her own control before or after treatment

Characteristics of ongoing studies *[ordered by study ID]*

[NCT02697292](#)

Trial name or title	IVIG in Patients With VGKC Ab Associated Autoimmune Epilepsy
Methods	Randomized, crossover, double blind (subject, caregiver, investigator, outcomes assessor) study
Participants	Cases of autoimmune epilepsy with ≥ 2 seizures per week (mean of total over 1 week) and duration of epilepsy < 3 years
Interventions	IVIG (0.5g/kg not exceeding 80 gr) for 1 day, then IVIG (1g/kg not exceeding 80 gr) for 1 day, then once every 2 weeks for 4 weeks (0.6g/kg IVIG) with placebo crossover
Outcomes	Decrease in seizure frequency
Starting date	February 2016
Contact information	Jessica Sagen, Mayo Clinic, United States, sagen.jessica@mayo.edu

[NCT02697292](#) (Continued)

Notes	This study is currently recruiting participants (verified February 2016)

DATA AND ANALYSES

Comparison 1. IVIg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 50% or greater reduction in seizure frequency for refractory epilepsy, ITT analysis	1	61	Risk Ratio (M-H, Fixed, 95% CI)	1.76 [0.79, 3.93]
2 50% or greater reduction in seizure frequency for refractory epilepsy, per-protocol	1	58	Risk Ratio (M-H, Fixed, 95% CI)	1.89 [0.85, 4.21]
3 50% or greater reduction in seizure frequency for refractory epilepsy, best-case	1	61	Risk Ratio (M-H, Fixed, 95% CI)	2.01 [0.91, 4.43]
4 50% or greater reduction in seizure frequency for refractory partial epilepsy, ITT analysis	1	49	Risk Ratio (M-H, Fixed, 95% CI)	3.08 [0.84, 11.34]
5 50% or greater reduction in seizure frequency for refractory partial epilepsy, per-protocol	1	46	Risk Ratio (M-H, Fixed, 95% CI)	3.35 [0.91, 12.30]
6 50% or greater reduction in seizure frequency for refractory partial epilepsy, best-case	1	49	Risk Ratio (M-H, Fixed, 95% CI)	3.57 [0.98, 13.00]
7 Global assessment for refractory epilepsy, ITT analysis	1	61	Risk Ratio (M-H, Fixed, 95% CI)	3.21 [1.10, 9.36]
8 Global assessment for refractory epilepsy, per-protocol	1	60	Risk Ratio (M-H, Fixed, 95% CI)	3.29 [1.13, 9.57]
9 Global assessment for refractory epilepsy, best-case	1	61	Risk Ratio (M-H, Fixed, 95% CI)	3.35 [1.15, 9.73]

Analysis 1.1. Comparison 1 IVIg versus placebo, Outcome 1 50% or greater reduction in seizure frequency for refractory epilepsy, ITT analysis.

Review: Intravenous immunoglobulins for epilepsy

Comparison: 1 IVIg versus placebo

Outcome: 1 50% or greater reduction in seizure frequency for refractory epilepsy, ITT analysis

Analysis 1.2. Comparison 1 IVIg versus placebo, Outcome 2 50% or greater reduction in seizure frequency for refractory epilepsy, per-protocol.

Review: Intravenous immunoglobulins for epilepsy

Comparison: 1 IVIg versus placebo

Outcome: 2 50% or greater reduction in seizure frequency for refractory epilepsy, per-protocol

Analysis 1.3. Comparison 1 IVIg versus placebo, Outcome 3 50% or greater reduction in seizure frequency for refractory epilepsy, best-case.

Review: Intravenous immunoglobulins for epilepsy

Comparison: 1 IVIg versus placebo

Outcome: 3 50% or greater reduction in seizure frequency for refractory epilepsy, best-case

Analysis 1.4. Comparison 1 IVIg versus placebo, Outcome 4 50% or greater reduction in seizure frequency for refractory partial epilepsy, ITT analysis.

Review: Intravenous immunoglobulins for epilepsy

Comparison: 1 IVIg versus placebo

Outcome: 4 50% or greater reduction in seizure frequency for refractory partial epilepsy, ITT analysis

Analysis 1.5. Comparison 1 IVIg versus placebo, Outcome 5 50% or greater reduction in seizure frequency for refractory partial epilepsy, per-protocol.

Review: Intravenous immunoglobulins for epilepsy

Comparison: 1 IVIg versus placebo

Outcome: 5 50% or greater reduction in seizure frequency for refractory partial epilepsy, per-protocol

Analysis 1.6. Comparison 1 IVIg versus placebo, Outcome 6 50% or greater reduction in seizure frequency for refractory partial epilepsy, best-case.

Review: Intravenous immunoglobulins for epilepsy

Comparison: 1 IVIg versus placebo

Outcome: 6 50% or greater reduction in seizure frequency for refractory partial epilepsy, best-case

Analysis 1.7. Comparison 1 IVIg versus placebo, Outcome 7 Global assessment for refractory epilepsy, ITT analysis.

Review: Intravenous immunoglobulins for epilepsy

Comparison: 1 IVIg versus placebo

Outcome: 7 Global assessment for refractory epilepsy, ITT analysis

Analysis 1.8. Comparison 1 IVIg versus placebo, Outcome 8 Global assessment for refractory epilepsy, per-protocol.

Review: Intravenous immunoglobulins for epilepsy

Comparison: 1 IVIg versus placebo

Outcome: 8 Global assessment for refractory epilepsy, per-protocol

Analysis 1.9. Comparison 1 IVIg versus placebo, Outcome 9 Global assessment for refractory epilepsy, best-case.

Review: Intravenous immunoglobulins for epilepsy

Comparison: 1 IVIg versus placebo

Outcome: 9 Global assessment for refractory epilepsy, best-case

APPENDICES

Appendix 1. Cochrane Epilepsy Group Specialized Register search strategy

#1 MeSH DESCRIPTOR Immunoglobulins, Intravenous Explode All
#2 intravenous immun* OR IV immunoglobulin* OR IVIG OR intravenous IG
#3 intraglobi* OR intravenous antibod* OR IV antibod*
#4 #1 OR #2 OR #3
#5 INREGISTER AND >18/05/2016:CRSCREATED
#6 #4 AND #5

Appendix 2. CENTRAL via CRSO search strategy

#1 MESH DESCRIPTOR Immunoglobulins, Intravenous EXPLODE ALL TREES
#2 (intravenous immun* OR IV immunoglobulin* OR IVIG OR intravenous IG):TI,AB,KY
#3 (intraglobi* OR intravenous antibod* OR IV antibod*):TI,AB,KY
#4 #1 OR #2 OR #3
#5 (epilep* OR seizure* OR convuls*):TI,AB,KY
#6 MESH DESCRIPTOR Epilepsy EXPLODE ALL TREES
#7 MESH DESCRIPTOR Seizures EXPLODE ALL TREES
#8 #5 OR #6 OR #7
#9 * NOT INMEDLINE AND 31/05/2016 TO 28/02/2017:DL
#10 #4 AND #8 AND #9

Appendix 3. MEDLINE (Ovid) search strategy

This strategy is based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials published in [Lefebvre 2011](#).

1. exp Immunoglobulins, Intravenous/
2. (intravenous immu* or IV immunoglobulin* or IVIG or intravenous IG).tw.
3. (intraglobi* or intravenous antibod* or IV antibod*).tw.
4. 1 or 2 or 3
5. exp Epilepsy/
6. exp Seizures/
7. (epilep\$ or seizure\$ or convuls\$).tw.
8. 5 or 6 or 7
9. exp *Pre-Eclampsia/ or exp *Eclampsia/
10. 8 not 9
11. (randomized controlled trial or controlled clinical trial or pragmatic clinical trial).pt. or (randomi?ed or placebo or randomly).ab.
12. clinical trials as topic.sh.
13. trial.ti.
14. 11 or 12 or 13
15. exp animals/ not humans.sh.
16. 14 not 15
17. 4 and 10 and 16
18. remove duplicates from 17
19. limit 18 to ed= 20160518-20170202

Appendix 4. Web of Science search strategy

Timespan=2016-2017

#5	#3 AND #2 AND #1 Refined by: [excluding]:Databases: (MEDLINE)
#4	#3 AND #2 AND #1
#3	TOPIC: (intravenous immunoglobulin* OR IV immunoglobulin* OR IVIG OR intravenous IG OR intravenous antibod*)
#2	TOPIC: (epilepsy OR seizures)
#1	TOPIC: (random* or placebo* or trial or study)

Appendix 5. Search strategies for other databases

WHO ICTRP

Advanced Search

Condition: epilepsy

Intervention: immunoglobulin OR IVIG

Date of registration between 18/05/2016 and 02/02/2017

ISRCTN registry (formerly Current Controlled Trials)

Condition: epilepsy AND Interventions: immunoglobulin or IVIG

ClinicalTrials.gov

Condition: epilepsy

Intervention: immunoglobulin or IVIG

received from 05/18/2016 to 02/02/2017

Appendix 6. Sources searched and number of hits retrieved

Source	Date range searched	Hits retrieved
CENTRAL (CRSO)	Up to 2 February 2017	44
MEDLINE (Ovid)	Up to 2 February 2017	160
Web of Science (All databases)	Up to 2 February 2017	158
WHO ICTRP	Up to 2 February 2017	2
ISRCTN registry	Up to 2 February 2017	7
ClinicalTrials.gov	Up to 2 February 2017	6

WHAT'S NEW

Last assessed as up-to-date: 2 February 2017.

Date	Event	Description
2 February 2017	New search has been performed	Searches updated 2 February 2017; no new studies identified. The methodology has been updated and GRADE has been used in this review update
2 February 2017	New citation required but conclusions have not changed	Conclusions are unchanged.

HISTORY

Protocol first published: Issue 6, 2010

Review first published: Issue 1, 2011

Date	Event	Description
26 June 2013	New search has been performed	Searches updated 24 January 2013.
24 January 2013	New search has been performed	No new studies identified for inclusion. Conclusions remain the same

CONTRIBUTIONS OF AUTHORS

Geng JS - all correspondence; drafting protocol and review versions; searching for trials; selection of trials for inclusion and exclusion; extraction of data; interpretation of data analyses; updating review.

Dong JC - arbiter of selection of trials for inclusion and exclusion; drafting review versions; extracting data; updating review.

Li YP - methodology expert.

Ni HJ - obtaining copies of trial reports.

Jiang K - search for trials; updating review.

Shi LL - selection of trials for inclusion and exclusion.

Wang GH - conduct of analyses; data entry.

DECLARATIONS OF INTEREST

JG: none known

JD: none known

YL: none known

HN: none known

LS: none known

GW: none known

SOURCES OF SUPPORT

Internal sources

- Project of Humanities and Social Sciences (Project No. 14YJCZH035), Ministry of Education in China, China.
- National Natural Science Foundation of China (Project No. 71603138), China.

External sources

- National Institute for Health Research (NIHR), UK.

This review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Epilepsy Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Although 'global assessment' was not stated in the review protocol, it was reported as an important outcome in the included study. The global assessment was considered to integrate several clinical aspects including reduction in the number and severity of seizures, evolution of EEG, interictal status, and perception of the participants and caregivers.

INDEX TERMS

Medical Subject Headings (MeSH)

Epilepsy [*drug therapy]; Immunoglobulins, Intravenous [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans