What are the effects of intravenous immunoglobulins on seizures and quality of life of people with epilepsy? A Cochrane Review summary with commentary

AISHAH AHMAD FAUZI | JULIA PATRICK ENGKASAN

Department of Rehabilitation Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia.

The aim of this commentary is to discuss from a rehabilitation perspective the published Cochrane Review 'Intravenous immunoglobulins for epilepsy' by Geng et al.,[1] under the direct supervision of the Cochrane Epilepsy Group. This Cochrane Corner is produced in agreement with *Developmental Medicine & Child Neurology* by Cochrane Rehabilitation.

BACKGROUND

Epilepsy is a common neurological condition, with an estimated incidence of 50 per 100 000 overall and a prevalence of 5 to 10 per 1000 in the developed world.[2] Epilepsy has been associated with immune system dysfunction, including low serum IgA levels, lack of the IgG subclass,[3,4] and presence of antibodies, often related to the primary disease.[5–7] This brought the notion that immunoglobulin-based therapy could be a treatment option for epilepsy.

Intravenous immunoglobulins (IVIg) are extracted from the plasma of over 1000 human blood donors and typically contain more than 95% unmodified IgG and trace amounts of IgA or IgM. IgG have the ability to cross the blood–cerebrospinal fluid (CSF) barrier and are likely to reach the brain and become central-acting agents.[8] IVIg may also regulate plasma levels of interferon-R, IL-6, and IL-8.[9,10] The evidence above suggest IVIg infusion might represent a valuable alternative to treat epilepsy. Thus, there is a need for a systematic review to critically assess the benefit and risk of IVIg treatment for epilepsy.

This summary is based on a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2019, Issue 12, Art. No.: CD008557, DOI: 10.1002/14651858.CD008557.pub4. (see www.cochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review. The views expressed in the summary with commentary are those of the Cochrane Corner authors and do not represent the Cochrane Library or Wiley.

INTRAVENOUS IMMUNOGLOBULINS FOR EPILEPSY[1]

What is the aim of this Cochrane Review?

The aim of this Cochrane Review[1] was 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.

What was studied in the Cochrane Review?

The population addressed in this review included all people with a diagnosis of epilepsy, irrespective of their seizure type or epilepsy syndrome. The interventions studied were: IVIg monotherapy compared to placebo or another antiseizure medication (ASM) treatment; and IVIg as add-on treatment to any ASM compared to add-on placebo or no add-on treatment.

The primary outcomes studied were: seizure freedom (i.e. the proportion of participants with complete cessation of seizures during the treatment period) and satisfactory seizure control (defined as the proportion of participants with at least 50% reduction in seizure frequency at the end of the study compared with the baseline). Secondary outcomes included: incidence of adverse or harmful effects (sedation, cognitive side effects, allergic reactions, and other serious adverse events), dropout or withdrawal due to adverse effects, lack of efficacy, or other reasons, absolute or percentage reduction in seizure frequency and duration, improved quality of life as assessed by validated and reliable rating scales, as well as economic analysis, if available.

Up-to-dateness of the Cochrane Review

The authors searched for studies that had been published up to December 2018 from multiple databases including the Cochrane Register of Studies, MEDLINE, Web of Science, ISRCTN registry, WHO International Clinical Trials Registry Platform, the US National Institutes of Health ClinicalTrials.gov, and reference lists of articles.

What are the main results of the Cochrane Review?

The review included only one clinical trial amongst the 10 full text articles that were retrieved. The included study

was a randomized, add-on, double-blind, placebo-controlled, multicentre trial with 61 participants, comparing three different dosages of IVIg (100mg/kg, 250mg/kg, and 400mg/kg) versus placebo in people with drug-resistant epilepsy.[11] The age of the participants ranged from 2 to 51 years, with the mean age of each group ranging from 18 years 6 months to 26 years 2 months. The ratio of females to males was 0.45.

The included study showed that:

There was no evidence of a significant difference between IVIg and placebo for 50% or greater reduction in seizure frequency.

- Based on the intention-to-treat analysis, on average, participants with drug-resistant epilepsy who received IVIg compared to placebo were two times (risk ratio [RR] 1.76) more likely to have 50% or greater reduction in seizure frequency. However, they could also have worse outcome compared to placebo (95% confidence interval [CI] 0.79–3.93).
- Similarly, on average, participants with drug-resistant focal epilepsy who received IVIg were three times more likely to have reduction in seizure frequency but could also have worse outcome compared to participants who received placebo (RR 3.08, 95% CI 0.84–11.34).

There was statistically significant difference between IVIg and placebo for global assessment which included reduction in the number and severity of seizures, evolution of electroencephalography, interictal status, and perception of the participants and caregiver.

- Based on intention-to-treat analysis, participants with drug-resistant epilepsy who received IVIg were three times more likely to have better global assessment outcomes compared to participants who received placebo (RR 3.21, 95% CI 1.10–9.36).

The certainty of evidence for all the outcomes described above was low.

How did the authors conclude on the evidence?

The authors concluded that there was no convincing evidence to support the use of IVIg as a treatment for epilepsy and further randomized controlled trials are needed. The small sample size might have contributed to the lack of power to detect a difference. The duration of treatment in this trial was 6 weeks, which is not long enough to demonstrate long-term efficacy.

What are the implications of the Cochrane evidence for practice in rehabilitation?

Poorly controlled seizures may affect brain cognition in developing children as young as 2 years, and could potentially limit their functional potentials.[12] IVIg was seen as a promising therapy to counteract this issue, but unfortunately no reliable conclusions can be drawn from this Cochrane Review.[1] Clinicians who need to make an evidence-based treatment decision on prescribing IVIg should be aware of the poor and low-quality evidence of its efficacy. Considering the high cost of IVIg therapy coupled with the inconclusive evidence, this option should be carefully discussed with patients who may request such therapy.

This review highlights the need to produce better quality evidence to assess the efficacy of IVIg for treating epilepsy. Researchers should consider conducting randomized control studies with different IVIg doses, including all clinically relevant outcomes, with long-term follow-up. Since IVIg demonstrated a protective role on the immune system, further studies could focus on its efficacy for the treatment of autoimmune epilepsy.

ACKNOWLEDGEMENTS

The authors thank Cochrane Rehabilitation and the Cochrane Epilepsy Group for reviewing the contents of the Cochrane Corner. The authors have stated that they had no interests that could be perceived as posing a conflict or bias.

REFERENCES

1. Geng J, Dong J, Li Y, et al. Intravenous immunoglobulins for epilepsy. *Cochrane Database Syst Rev* 2019; **12**: CD008557.
2. Sander JW, Shorvon SD. Epidemiology of the epilepsies. *J Neurol Neurosurg Psychiatry* 1996; **61**: 433–43.
3. Duse M, Tiberti S, Plebani A, et al. IgG2 deficiency and intractable epilepsy of childhood. *Monogr Allergy* 1986; **20**: 128–34.
4. 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 Clin Neurosci* 1995; **49**: S251–3.
5. Majoie HJ, De Baets M, Renier W, Lang B, Vincent A. Antibodies to voltage-gated potassium and calcium channels in epilepsy. *Epilepsy Res* 2006; **71**: 135–41.
6. Errichiello L, Perruolo G, Pascarella A, et al. Autoantibodies to glutamic acid decarboxylase (GAD) in focal and generalized epilepsy: a study on 233 patients. *J Neuroimmunol* 2009; **211**: 120–3.
7. Niehusmann P, Dalmau J, Rudlowski C, et al. Diagnostic value of N-methyl-D-aspartate receptor antibodies in women with new-onset epilepsy. *Arch Neurol* 2009; **66**: 458–64.
8. Van Engelen BG, Renier WO, Weemaes CM. Immunoglobulin treatment in human and experimental epilepsy. *J Neurol Neurosurg Psychiatry* 1994; **57**(Suppl): 72–5.
9. Billiau AD, Wouters CH, Lagae LG. Epilepsy and the immune system: is there a link? *Eur J Paediatr Neurol* 2005; **9**: 29–42.
10. Ling ZD, Yeoh E, Webb BT, Farrell K, Doucette J, Matheson DS. Intravenous immunoglobulin induces interferon-gamma and interleukin-6 in vivo. *J Clin Immunol* 1993; **13**: 302–9.
11. 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. *Eur J Pediatr* 1994; **153**: 762–9.
12. Holmes G. Effect of seizures on the developing brain and cognition. *Semin Pediatr Neurol* 2016; **23**: 120–6.