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Review

The Effectiveness of Plasmapheresis Compared to Intravenous Immunoglobulin in Guillain-Barre Syndrome Patients

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ABSTRACT

Introduction: Guillain-Barré syndrome (GBS) is the second most common cause of acute and subacute general paralysis. The management is symptom-adjusting, but plasmapheresis (plasma exchange/PE) and intravenous immunoglobulin immunotherapy (IVIG) can be administered to accelerate the return of neurological function. This study aim to determine PE's effectiveness compared to IVIG in GBS patients and the side effects or complications that may arise.

Method: The literature study is carried out on four databases. Selection is carried out using inclusion and exclusion criteria. The articles were screened and extracted independently by two investigators.

Results: The literature study obtained three systematic review studies. In the first study, shows the outcomes in the form of improved Hughes Score (OR 1.9; 95% CI 1.11-3.28) and mortality (OR 0.8; 95% CI 0.31-2.29) against IVIG. The second study, outcomes shown in the form of improved disability scores (WMD -0.02, p: 0.83), and secondary outcomes such as mortality or relapse (p >0.05, respectively). The third study showed that IVIG had higher efficacy (OR 1.6, p: 0.067, 95% CI 0.972-2.587), shorter duration of hospitalization, 38 days, compared to 49-day PE therapy (SMD -3.389, 95% CI -11.601-4.824; p: 0.419), however, had higher side effect (OR 0.8, p: 0.430, 95% CI 0.389-1.495).

Conclusion: PE efficacy is generally lower than IVIG, as indicated by disability scores/motor ability scores in various studies, as well as the duration of hospitalization. The safety of therapy is assessed by the side effects that appear and appear more often in IVIG therapy rather than PE.

Keywords: guillain barre syndrome; intravenous immunoglobulin; paralysis; plasmapheresis; plasma exchange

INTRODUCTION

Guillain-Barré syndrome (GBS) is an acute polyneuropathy caused by an autoimmune reaction to peripheral nerves, characterized by symptoms and signs of acute lower motor muscle parse (LMN) accompanied by dissociation of cytoalbumin in cerebrospinal fluid. GBS is the most common cause of acute and subacute generalized paralysis after polio. GBS is also known as Landry-Guillain-Barré-Strohl syndrome and Acute Inflammatory Demyelinating Polyneuropathy (AIDP).[1,2,3] The incidence of GBS in the world reaches 0.6-2.4 cases/100,000 population per year. GBS is less common in children than adults, and the incidence of GBS increases with age. Men are 1.5 times more often affected than women.[2] The

Indonesian data, shown by research at RSCM, shows that the number of new cases of GBS in RSCM is around 7.6 cases per year. GBS patients at RSCM are primarily young adults with an average age of 40 years and a male: female ratio of about 1.2:1.[3]

The diagnosis of GBS is confirmed through 8 clinical findings that can support the diagnosis of GBS, namely worsening of muscle weakness that occurs no later than day 28, symmetrical distribution of deficits, minimal sensory disturbances (not exceeding motor symptoms), cranial nerve disorders, especially nerve VII, autonomic dysfunction, pain, cerebrospinal fluid findings consistent with GBS (increased protein), as well as typical EMG electrodiagnostic findings from SGB.[3,4,5]

GBS is a disease that will heal by itself. The most basic treatment is supportive and symptomatic, but plasmapheresis (*plasma exchange*/PE) and intravenous immunoglobulin immunotherapy (IVIG) can be given to speed the return of neurological function and reduce the length of ventilator use. To determine treatment, use the Guillain-Barré Syndrome Disability Score or Hughes Score. Immunotherapy and plasmapheresis will provide the best results for GBS patients with a Hughes Score of 3 and above. For those with a score below 3, immunotherapy and plasmapheresis did not provide a significant difference in output. Plasmapheresis is performed five times in 2 weeks with a maximum amount of plasma exchange of 5 times the estimated plasma volume (200-250 mL/kgBB). IGIV dose 2g/kgBB, given within five days.[3,4,5]

However, to date, no guideline or study clearly states the difference in the selection of the two therapy options. This study aims to determine the advantages and disadvantages of both therapies.

METHODS

A comprehensive literature search was conducted using clinical questions from Pubmed, Embase, and Scopus databases. The literature search updated on October 13, 2023. Keywords used include *plasmapheresis/plasma exchanges* and *intravenous immunoglobulin* using the MeSH terms. The inclusion criteria were *systematic review* study design, meta-analysis, and *randomized control trial*. Exclusion criteria include complete journal manuscripts not being available, full manuscripts not being in English or Indonesian, age less than 18 years, and studies not being conducted on humans.

After the article is obtained, a critical review will be carried out based on the Center of Evidence-based Medicine University Oxford 2011 guidelines. Two reviewers checked titles and abstracts identified from these sources and obtained the full text of all potentially relevant studies for independent assessment. Two reviewers decided which trials fitted the inclusion criteria and extracted data independently into specially designed forms. Disagreements were resolved by reference to the original reports and discussion.

RESULTS

The literature search found 180 articles. Furthermore, 48 duplicate articles were eliminated, so the screening of 132 articles continued. Of the 132 articles, 90 were excluded because the title and abstract were irrelevant to the clinical questions. Of the 42 articles obtained, deletion was carried out so that three articles were included in the inclusion criteria, did not fall into the exclusion criteria, and could be continued for critical review.

Table 1. Keywords and Databases

Database	Keyword	Search result
Pubmed	(((((review, systematic[MeSH Terms]) OR (meta analysis[MeSH Terms])) OR (clinical trials, randomized[MeSH Terms])) OR (controlled clinical trials, randomized[MeSH Terms])) OR ((((((((systematic review[Title/Abstract]) OR (meta analysis[Title/Abstract])) OR (clinical trial[Title/Abstract])) OR (systematic reviews[Title/Abstract])) OR (randomized controlled clinical trials[Title/Abstract])) OR (randomized controlled clinical trial[Title/Abstract])) OR (randomized clinical trials[Title/Abstract])) OR (randomized clinical trial[Title/Abstract]))) AND (((((guillain barre syndrome[MeSH Terms]) OR (guillaine barre syndrome[MeSH Terms])) OR ((guillain barre syndrome[Title/Abstract]) OR (guillaine barre syndrome[Title/Abstract]))) AND (((plasmaphereses[MeSH Terms]) OR (plasmapheresis[MeSH Terms])) OR ((plasmaphereses[Title/Abstract]) OR (plasmapheresis[Title/Abstract])))) AND (((intravenous immune globulin[MeSH Terms])OR (intravenous immunoglobulins[MeSH Terms])) OR (((intravenous immune globulin[Title/Abstract]) OR (intravenous immunoglobulins[Title/Abstract])) OR (intravenous immunoglobulins[Title/Abstract]))))	41

Embase	('guillain barre syndrome'/exp OR 'fisher syndrome' OR 'guillain barre' OR 'guillain barredisease' OR 'guillain barre polyradiculitis' OR 'guillain barre polyradiculoneuritis' OR 'guillainbarre syndrome' OR 'guillain-barre syndrome' OR 'landry guillain barre strohl syndrome' OR 'landry guillain barre syndrome' OR 'landry paralysis' OR 'landry syndrome' OR 'miller fisher syndrome' OR 'acute febrile polyneuritis' OR 'acute postinfective polyradiculoneuropathy'OR 'infectious neuronitis' OR 'inflammatory acute polyradiculoneuropathy' OR 'polyradiculoneuritis guillain-barre' OR 'polyradiculoneuropathy, acute postinfective' OR 'polyradiculoneuropathy, inflammatory acute') AND ('plasmapheresis'/exp OR 'plasma apheresis' OR 'plasma pheresis' OR 'plasmapheresis' OR 'plasmaphoresis') AND 'immunoglobulin'/exp AND ('randomized controlled trial'/exp OR 'controlled trial, randomized' OR 'randomised controlled study' OR 'randomised controlled trial' OR 'randomized controlled study' OR 'randomized controlled trial' OR 'trial, randomized controlled' OR 'systematic review'/exp OR 'review, systematic' OR 'systematic review' OR 'meta analysis'/exp OR 'analysis, meta' OR 'metaanalysis' OR 'meta-analysis' OR 'metaanalysis') AND ([article]/lim OR [article in press]/lim) AND [embase]/lim	51
Scopus	(((TITLE-ABS-KEY (systematic AND review)) OR (TITLE-ABS-KEY (meta ANDanalysis)) OR (TITLE-ABS-KEY (meta-analysis)) OR (TITLE-ABS-KEY (randomized AND controlled AND clinical AND trials)) OR (TITLE-ABS-KEY (randomized AND clinical AND trials))) AND((TITLE-ABS-KEY (guillain AND barre AND syndrome)) AND (TITLE-ABS-KEY (plasmapheresis)) AND ((TITLE-ABS-KEY (intravenous AND immunoglobulins)) OR (TITLE-ABS-KEY (intravenous AND immune AND globulin))))) AND NOT (TITLE-ABS-KEY (letter)) AND NOT (TITLE-ABS-KEY (short AND survey)) ANDNOT (TITLE-ABS-KEY (editorial)) AND NOT (TITLE-ABS-KEY (note)) AND NOT (TITLE-ABS-KEY (conference AND paper))	88

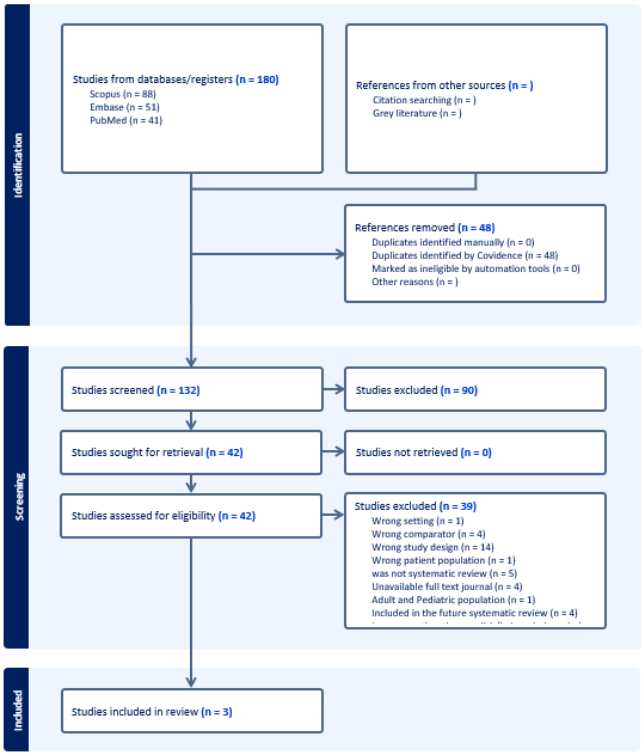

Figure 1. The diagram of identification, screening, and selection of articles

The three articles selected were systematic review that conducted by Fergusson et al. on 2005, Hughes et al. on 2007, and Ortiz-Salas et al. on 2016. Data from the included studies are summarized in Table 2. From the articles selected, the risk of bias was assessed, rated as high, low or unclear (Table 3).

Table 2 Summary of papers identified

Author	Study design, level of evidence	Title of article	Population	Determinant	Outcome
Fergusson et al. (2005)	Systematic review, 1	Use of intravenous immunoglobulin for treatment of neurologic conditions: a systematic review	Any neurologic conditions that have IVIG and plasmapheresis as therapy options	IVIG, plasmapheresis, placebo, other active control	Disability, mortality, and time to recovery
Hughes et al. (2007)	Systematic review, 1	Immunotherapy for Guillain-Barre syndrome: a systematic review	Guillain-Barre syndrome, Acute polyradiculoneuritis and plasma exchange	Plasma exchange, intravenous immunoglobulin, corticosteroid, adrenocorticotrophic hormone	Improvement in disability grade, duration of ventilation, time needed to recover independent walking, death
Ortiz-salas et al. (2016)	Systematic review, 1	Human Immunoglobulin Versus Plasmapheresis in Guillain–Barre Syndrome and Myasthenia Gravis: A Meta-Analysis	Autoimmune neurologic diseases.	Polyradiculoneuropathy, chronic inflammatory demyelinating, guillain-barré syndrome, myasthenia gravis	improvement in Hughes scale for guillain–Barré syndrome

Table 3. Risk of bias assessment

	Fergusson et al. (2005)	Hughes et al. (2007)	Ortiz-salas et al. (2016)
Same experimental conditions	-	-	+
Blinding during study	-	-	+
Incomplete data	+	?	+
Exposure characterization	-	?	?
Outcome assessment	+	+	+
Reporting	+	+	+
Other	+	+	+

DISCUSSION

Mr. BS, age 64, walked into the emergency room complaining of tingling in all four extremities for nine days, tingling from both feet to ankles. Eight days before the admission, tingling also appeared in the hands, accompanied by thick sensations in the hands and feet. Complaints of numbness get worse, extending to the ankles and hands, and weakness appears in the fingers and toes. He goes to a neurologist and undergoes a series of examinations. One day before admission, the patient underwent a KHS-EMG examination at an external hospital and was declared to have GBS. On examination, the motoric strength of both wrist, fingers, ankle and toes were 4/5 while both upper arm, elbow, hips, knee were 5/5. He has numbness in a glove and stocking distribution affecting hands and feet. Negative cranial nerve palsies, babinski sign, and autonomic abnormalities.

Fergusson et al. [6] in 2005 conducted a *systematic review* of various studies from 1996 to June 2003 using two *databases*, namely Medline and Cochrane. The study looked for various neurological diseases that have IVIG as one of the therapeutic options. This study only used the *keywords* IVIG and RCT and did not limit it to specific ages or languages. In the article search method, no determination was made regarding establishing the diagnosis of GBS or population uniqueness, such as clinical degree or severity, dose determination, or frequency of PE or IVIG. In addition, explanations related to when a therapy is given, for example, when certain acute conditions occur, are not listed. The study initially received 3,160 studies, ending with 37 studies to review. In determining each study's quality level, a scoring system is used for aspects of randomization, *double-blinding*, and the presence or absence of *withdrawal*. This study also presents a third *reviewer* if two *reviewers* have different opinions. It is unclear whether this study used PRISMA's guidelines. Although the search was carried out for various neurological diseases, the discussion of studies was carried out on each disease, including the GBS. A table shows the characteristics of each RCT

study by showing the RCT design, IVIG dose used, number of participants between groups, inclusion criteria, average age, and *baseline characteristics*. This study showed differences between therapies using *odds ratio* (OR) *confidence interval* (CI) with *random forest plots* but did not show heterogeneity test results. The outcomes shown include improved disability scores using *the Hughes score* and mortality. On improving disability scores, the IVIG therapy group showed higher improvement, followed by statistical significance (OR 1.9; 95% CI 1.11-3.28). Mortality outcomes were also higher on IVIG therapy but not statistically significant (OR 0.8; 95% CI 0.31-2.29).

Another *systematic review* study was also conducted by Hughes et al. [7] in 2007. The study was conducted by searching all *randomized trials*, with searches conducted until July 13, 2006. Unlike Fergusson et al.[6,] who searched extensively for various neurological diseases, Hughes et al. conducted searches only on the SGB population. The study wrote a headline looking at GBS and IVIG therapy, but the search technique Hughes et al. used included other keywords such as PE, corticosteroids, and adrenocortisone hormone. The article search uses three *databases*: Medline, Embase, and Cochrane Trials. If there is a conflict of opinion at the article selection stage, the solution is to discuss it again without presenting a third party. It also does not include whether there are language restrictions in the exclusion criteria. In addition, there are no rules related to the requirements for establishing the diagnosis of GBS, explanations related to the presence of populations with special conditions such as mild or severe clinical degrees or severity, explanations related to the dose/frequency of PE or IVIG administration, and the point of time of administration of therapy such as whether from the beginning of diagnosis or when specific clinical manifestations appear. No scoring was done to determine each RCT study's quality level. Still, the authors wrote which studies used specific randomization or randomized studies but did not perform *concealment* techniques. It

did not specify whether this study was conducted based on PRISMA principles. This study discusses IVIG therapy in quite depth, but the same is shown in other therapies such as corticosteroids and hormone use. Ten studies related to IVIG therapy were obtained. The table shows several aspects such as study design, IVIG dosage, number of participants between groups, and results obtained. This study uses forest plots to display output as fixed weighted mean difference (fixed WMD) and CI. The I2 test and the funnel plot method show the heterogeneity strategy. The heterogeneity test results showed negligible heterogeneity (p: 0.15, I^2: 41.3%). The only outcome demonstrated in this study was an improvement in disability scores with WMD -0.02 (p: 0.83), which showed almost no difference between the two therapies and was not statistically significant. The study also showed secondary outcomes, including mortality, mortality or disability within one year, or relapses, all of which showed no statistical significance.

In 2016, Ortiz-Salas et al.[8] systematically reviewed autoimmune neurological diseases, namely GBS and myasthenia gravis. In the study, both diseases and the choice of PE and IVIG therapy were used as keywords. The study searched five *databases*: Medline, Embase, HINARI, Ovid, and Cochrane Library. Language restrictions are only on English, Spanish, French, and Portuguese. No age restriction is carried out. If there is a difference of opinion between two *reviewers*, the proposed solution is a re-discussion or presentation by a third *reviewer*. This study did not include the rules for SGB diagnosis criteria in its article search; there is an exclusion if specific population characteristics such as mild or severe clinical degrees or various severity of the condition are obtained. There is also no information about the dose/ frequency of PE or IVIG therapy or the moment of time of therapy. The authors followed PRISMA's rules in making this study. Although searching for two diseases, this study did discuss both in detail and in each disease. Studies related to GBS obtained 14 articles. The table

shown contains the study design in the form of *evidence level* and the number of total and intergroup participants. The study also attached heterogeneity test results. The heterogeneity test found that this study was very heterogeneous (I^2: 99%). The first outcome was efficacy, which showed that IVIG was superior to PE but not statistically significant (OR 1.6, p: 0.067, 95% CI 0.972-2.587). The second outcome is in the form of various side effects, respiratory disorders, cardiovascular, genitourinary disorders, CNS, and others, which show the most frequent side effects of IVIG therapy. However, they do not have statistical significance (OR 0.8, p: 0.430, 95% CI 0.389-1.495). The third outcome was the duration of hospital stay, where the PE therapy group had a longer duration of 49 days (95% CI 11.6-85) than the IVIG therapy group, which was only 38 days (95% CI 7.3-58.9). Comparison between the two therapies did not show statistically different duration (SMD -3.389, 95% CI: -11.601-4.824; p: 0.419). The fourth outcome demonstrated in this study was the duration of ventilator use, where the PE therapy group also had a longer duration of 29 days (95% CI 11-50) compared to the IVIG therapy group, which was only 26 days (95% CI 13-43.3). The comparison of the two therapies does not show statistical significance.

CONCLUSION

PE efficacy is generally lower than IVIG, as indicated by disability scores/motor ability scores in various studies and the duration of hospitalization. The safety of therapy is indicated by the side effects that appear. Side effects seem more often in IVIG therapy than in PE. Side effects shown in one of the studies included respiratory disorders (*dyspnea*, pneumonia), cardiovascular (hypertension, arrhythmias, vasospasm, venous thrombosis, *syncope*, vasovagal reactions), genitourinary (hematuria, acute renal failure), CNS disorders (meningism, cephalgia, vertigo), and others (increased body temperature, nausea, vomiting, chills, sepsis, *phlebitis*,

hypocalcemia, hemolytic anemia, hematomas, allergic reactions, diarrhea).The choice of therapy is adjusted to the characteristics of each patient, such as the presence or absence of comorbidities, age, and comfort preferences, considering that IVIG therapy is generally carried out more often than PE, as well as financing aspects in the form of limitations in covering costs by the JKN system, as well as the ability of patients to make payments independently. Data obtained from patients in the form of age and comorbidities in the form of hypertension are not known for how long it has been. The 64-year-old patient is one consideration for providing a less aggressive therapy, PE. The presence of comorbid comorbidities can be a consideration for choosing PE.

The limitations of this EBCR study are that search exploration is not carried out on databases containing *ongoing trial studies*, and there are language restrictions in conducting searches.

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