

Efficacy and safety of double-filtration plasmapheresis treatment of myasthenia gravis

A systematic review and meta-analysis

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Abstract

Objectives: To evaluate the efficacy of double-filtration plasmapheresis (DFPP) treatment of myasthenia gravis (MG) through a systematic review and meta-analysis.

Methods: PubMed, Cochrane Library, Embase, China National Knowledge Infrastructure (CNKI), Chinese Scientific Journals Database (VIP), and Wanfang databases were searched for randomized controlled trials (RCTs) and clinical controlled trials (CCTs) on DFPP for MG from database establishment to June 2019. Two researchers independently screened the articles, extracted the data, and cross checked the results. RevMan 5.3 was used for statistical analyses.

Results: Seven RCTs and 2 CCTs were found comprising 329 patients. The results showed that clinical MG remission rate after DFPP treatment was significantly higher (OR=4.33; 95% confidence interval [CI], 1.97–9.53; $P < .001$) and the serum levels of antititin antibody was significantly decreased (standardized mean difference [SMD]=9.30; 95% CI, 7.51–11.08; $P < .001$). In addition, the quantitative MG (QMG) score, hospital stay and time to remission of MG symptoms, and acetylcholine receptor antibody (AchRAb) decreased in the DFPP treatment group; however, these outcomes had high heterogeneity among the studies. Only one study has reported on the adverse effects, including hypotension and hematoma.

Conclusion: This meta-analysis suggests that DFPP can be recommended for the short-term mitigation of MG. Because our review was limited by the quantity and quality of the included studies, the above conclusions should be verified by additional high-quality studies.

Abbreviations: AchRAb = acetylcholine receptor antibody, CCT = clinical controlled trial, DFPP = double-filtration plasmapheresis, MG = myasthenia gravis, OR = odds ratio, QMG = quantitative MG, RCT = randomized controlled trial, SMD = standardized mean difference.

Keywords: double-filtration plasmapheresis, myasthenia gravis, plasma exchange

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1. Introduction

Myasthenia gravis (MG) is an autoimmune disease in which antibodies bind to acetylcholine receptor (AChR) or to functionally related molecules in the postsynaptic membrane at the neuromuscular junction.^[1] The disease is characterized by fluctuating muscle weakness and abnormal fatigability.^[2] Current therapeutic options for MG are acetylcholinesterase inhibitors; glucocorticoids (GC); intravenous immunoglobulin (IVIg); plasma exchange (PE); thymectomy; monoclonal antibodies; and immunosuppressive agents.^[3]

PE is appropriately used as a short-term treatment for MG patients who have life-threatening signs, such as respiratory insufficiency or dysphagia.^[4] The PE procedure consists of filtering venous blood and removing plasma constituents, including normal and pathogenic immunoglobulins, after which the removed plasma is usually replaced with fresh-frozen plasma or albumin.^[5] PE has been shown to induce a rapid recovery, corresponding to the decline in acetylcholine receptor antibody (AchRAb)^[6]; however, this treatment comes with many complications,^[7–9] such as allergic reactions, sepsis, and affecting the blood's ability to coagulate. In recent years, newly developed techniques for plasmapheresis, including double-filtration plasmapheresis (DFPP)^[10] and immunoadsorption (IA),^[11] have provided more selective removal of pathogenic substances without the need for plasma supplementation. DFPP consists

of a first filter to separate plasma from blood (a plasma separator) and a second filter to separate albumin from larger molecules, such as immunoglobulins, immune complexes, and lipoproteins, in the plasma (a plasma fractionator).^[12]

The systematic review and meta-analysis of DFPP treatment for MG is lacking; therefore, the purpose of this study was to systematically and objectively evaluate the efficacy and safety of DFPP in the treatment of MG using evidence-based medicine to provide a reference for clinical decision making.

2. Methods

2.1. Search strategy

A computer search of PubMed, Cochrane Library, Embase, CNKI, Vip, and Wanfang databases was conducted to locate all clinical research articles on DFPP treatment of MG from the time of database establishment to June 2019. In the database search, the following subject words and free words were combined for full text retrieval: (myasthenia gravis) or (myasthenia gravis, ocular) or (ocular myasthenia gravis) or (myasthenia gravis, generalized) or (generalized myasthenia gravis) and (double filtration plasmapheresis) or DFPP.

2.2. Selection criteria

2.2.1. Types of studies. We searched for randomized controlled trials (RCTs) and quasi-randomized trials (clinical controlled trial [CCTs]) on DFPP treatment of MG, which involved clinical studies on groups of patients divided according to the type of intervention in any form in Chinese or English.

2.2.2. Participants. Patients with MG that was confirmed by clinical manifestations, a neostigmine test, neuroelectrophysiological examination, and detection of AChRAb were included in the studies.

2.2.3. Interventions. Patients who had been treated with DFPP.

2.2.4. Comparator. The control groups were healthy volunteers treated with DFPP or MG patients treated with IVIG, PE, or IA, as shown in Table 1.

2.2.5. Outcomes. The primary outcome was clinical efficacy rate during the treatment period.

The secondary outcomes were reduced quantitative MG (QMG) score, rate of adverse reactions and number of respiratory supports, duration of hospital stay, time to MG remission, serum antibody levels.

2.3. Exclusion criteria

The exclusion criteria were as follows: animal experiments or in vitro studies, the original data could be extracted, and the effective data could not be obtained by contacting the author, case reports, reviews, or meta-analyses; or repeated publication of the articles.

2.4. Data extraction and quality assessment

Two researchers (PL and MM) independently screened the articles, extracted the data, and cross checked the information. When there was disagreement, a third researcher was used to help resolve the issue. Any lack of data was supplemented as much as possible by contacting the author. Standardized data

Table 1
Demographic and clinical characteristics of the myasthenia gravis patients included in the study.

Study and year	Patients (T/C)	Male (T/C)	Mean age (T/C)	Mean duration of symptoms, month (T/C)	Osseman class (T/C)				Interventions		Outcome measures
					IIA	IIIB	IIIC	IIID	Treatment group	Control group	
Chien, 2011	20/16	5/9	45.2/38.0	60.6/NA	10/NA	7/NA	3/NA	3/NA	DFPP	Healthy controls	The course of treatment consisted of 3 consecutive DFPP sessions every other day. (2) (5)
Zhang, 2014	15/20	9/10	54.1/50.2	NA	6/NA	5/NA	4/NA	4/NA	DFPP	NA	DFPP was performed 3 times within 1 week using an apheresis monitor. (1) (2) (6) (7)
Yeh, 2009	19/6	7/2	46	174.6/NA	4/NA	8/NA	7/NA	7/NA	MG patients with DFPP	Healthy volunteers with DFPP	Each course of treatment consisted of a mean of 4.7 consecutive DFPP sessions every other day. (2) (5)
Yeh, 1999	8/8	4/4	38.5/49	NA	NA	4/3	0/1	0/1	DFPP	IA	Each course of treatment consisted of 5 sessions of apheresis every other day with 1 plasma volume processed for each patient. (2)
Liu, 2010A	15/10	9/6	55.2/57.2	NA	5/2	3/5	7/3	7/3	DFPP	IA	Each patient received 3 treatments every 24–48 h. (1) (2) (3) (6) (7)
Liu, 2010B	15/15	9/8	55.2/53.2	NA	5/6	3/4	7/5	7/5	DFPP	IVIG	Each patient received 3 treatments every 24–48 h. (1) (2) (3) (5) (7)
Okada, 1997	4/8	NA	42/41.5	NA	NA	NA	NA	NA	DFPP	PE	DFPP treatment was administered with ~1 plasma volume at each session for 3 d. (2) (5)
Gong, 2005	26/23	11/9	42.3/38.2	12.5/10	0	19/17	7/6	7/6	DFPP	NA	The course of treatment consisted of 3 consecutive DFPP sessions every other day. (2) (4)
Han, 2015	26/20	16/13	45.6/43.9	NA	NA	NA	NA	NA	DFPP	NA	Each patient received 3 treatments every 48 h. (1) (2) (4) (6) (7)
Zang, 2015	35/35	16/17	37.8/38.6	13.9/14.3	NA	NA	NA	NA	DFPP	IA	Every 3 d for a course of treatment. (2) (4)

C = control group, DFPP = double-filtration plasmapheresis, IA = immunoadsorption, IVIG = intravenous immunoglobulin, MG = myasthenia gravis, NA = not available, PE = plasma exchange, QMG = the quantitative MG, T = trial group. (1) QMG score (2) acetylcholine receptor (AChR) removal rate (3) clinical absolute and relative scores (5) MG score (6) duration of hospital stay (7) time to MG remission.

extraction tables were adopted to extract information from eligible articles. The extracted data included the following information: basic: the first author and the year of publication; basic subject characteristics: sample size, age, course of disease, MG severity (Osserman classification); intervention content: intervention measures and DFPP implementation time; and outcome measurement.

The evaluation of the methodological quality of the studies included random sequence generation, allocation concealment, patient blinding, observer blinding, incomplete outcome data, selective reporting, and other bias.^[13]

2.5. Statistical analyses

Review Manager (RevMan 5.3) provided by Cochrane Collaboration Network (<https://us.cochrane.org/>) was used for statistical analyses. Measurement data were evaluated using the weighted mean difference (WMD) or SMD. The heterogeneity among the studies was tested using the Q value and I^2 value.

If $P \geq .1$ and $I^2 \leq 50\%$, there was no heterogeneity among the studies and the fixed effects model was used for analyses; if $P < .1$ or $I^2 > 50\%$, there was heterogeneity among the studies and the random effects model was used for analyses. If the data from each study could not be analyzed by meta-analysis, descriptive analyses were used. The data for continuous variables were summarized by the mean \pm standard deviation, and dichotomous outcomes were calculated using the risk ratio (RR). The results were expressed as the 95% confidence interval (95% CI). Subgroup analyses were used to find the source of heterogeneity, and sensitivity analyses were used to evaluate whether the results of the meta-analysis were stable and reliable, if appropriate. $P < .05$ was considered a significant difference.

2.6. Ethical approval

This study did not involve ethical approval or informed consent of patients because we did not recruit patients. We integrated and analyzed the data from research papers.

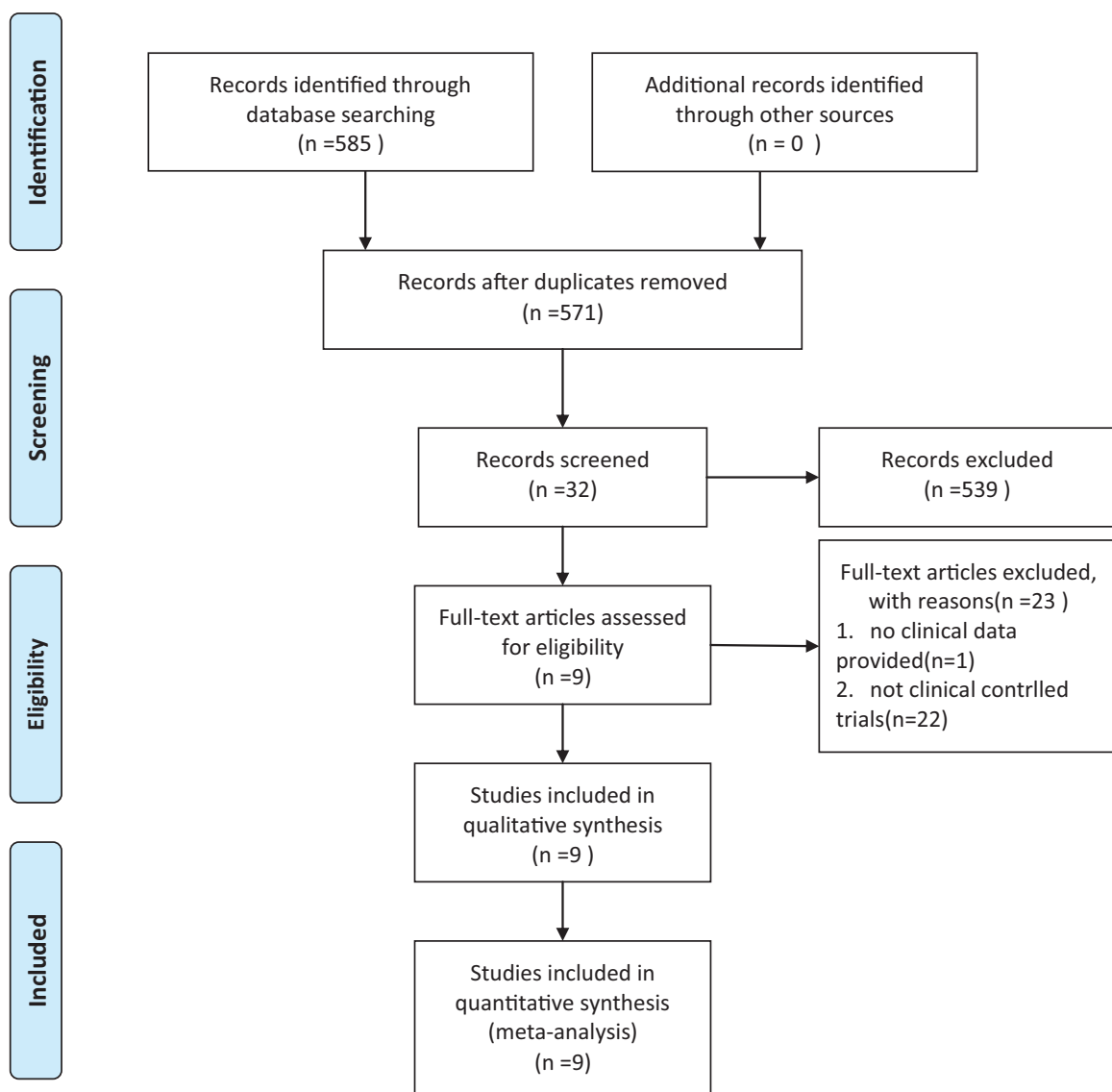


Figure 1. Screening process for this meta-analysis.

3. Results

3.1. Study selection and characteristics

Using the above retrieval strategies, 585 papers were found, with 571 remaining after removing duplicates. Of these, 539 were excluded after reading the title and abstract. Of the remaining 32 papers, 9 (7 RCTs and 2 CCTs)^[12,14–20,22] were included after reading the full text. The screening process for this meta-analysis is provided in Fig. 1. The 9 studies comprised 329 patients. The basic features of the included papers are provided in Table 1.

3.2. Risk of bias and study quality

The quality of the studies was assessed using the Cochrane recommended tool for assessing the risk of bias (Fig. 2).

3.3. Primary outcome measures

3.3.1. Clinical efficacy rate. The relative score, calculated as follows:

$$\left(\frac{[\text{post} - \text{QMG score}] - [\text{pre} - \text{QMG score}]}{[\text{pre} - \text{QMG score}]} \right) \times 100\%$$

was used to evaluate the therapeutic efficacy. A relative score of $\geq 95\%$ was considered to be full recovery, 80% to 95% partial recovery, 50% to 80% partially effective, 25% to 50% improved, and $\leq 25\%$ ineffective. Clinically effective was defined as relative scores above 25%. Clinically effective was defined as relative scores above 25%.^[21] Five studies^[22,15–18] comprising 192 patients reported the clinical efficacy rate of DFPP treatment for MG. The clinical MG remission rate after DFPP treatment was not heterogeneous among the study groups ($P = .59$, $I^2 = 0\%$). Analyses using the fixed effects model showed that the clinical MG remission rate after DFPP treatment was significantly higher than that in the control group (OR = 4.33; 95% CI, 1.97–9.53; $P = .0003$), as shown in Fig. 3.

3.4. Secondary outcome measures

3.4.1. QMG score descent range. Three studies^[14,16,22] comprising 136 patients reported the QMG score descent range in MG. The QMG score descent range after DFPP treatment was heterogeneous among each study group ($P < .01$, $I^2 = 99\%$). Analyses using the random-effects model showed that this score was significantly higher than that of the control group (MD = 37.64; 95% CI, 36.33, 38.95; $P < .01$), as shown in Fig. 4.

3.4.2. Serum antibody removal rate. Serum antibody removal rate was calculated as follows:

$$\left(\frac{[\text{post} - \text{AChR}] - [\text{pre} - \text{AChR}]}{[\text{pre} - \text{AChR}]} \right) \times 100\%$$

The AChRab removal rate was evaluated in 7 studies^[12,14–18,22] comprising 275 patients. After the heterogeneity test, the random effects model was used to analyze the results ($P < .01$, $I^2 = 100\%$). The combined MD was 18.86 (95% CI, 1.17–36.55; $P = .04$), as shown in Fig. 5.

Two studies^[16,22] comprising 65 patients evaluated the serum levels of the removal rate of antititin antibody. After the heterogeneity test, the random effects model was used to analyze

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chien,2011	–	–	+	+	+	+	?
Gong, 2005	?	?	+	+	+	+	?
Han,2015	+	+	+	+	+	+	?
Liu,2010	?	–	?	?	+	+	?
Okada,1997	–	–	?	+	+	+	?
Yeh,1999	?	–	+	+	+	+	?
Yeh,2009	–	–	+	+	+	+	?
Zang,2015	+	+	+	+	+	+	?
Zhang,2014	?	?	+	+	+	+	?

Figure 2. Risk of bias summary based on the review authors' judgement for each included study.

the results ($P = .20$, $I^2 = 39\%$). The combined SMD was 9.30 (95% CI, 7.51–11.08; $P < .01$). The results showed that the serum levels of anti-AChR-ab and anti-titin antibody significantly decreased after DFPP treatment ($P < .05$), as shown in Fig. 6.

3.4.3. Duration of hospital stay (day). Three studies^[16,17,22] comprising 136 patients were evaluated for the duration of hospital stay. Random effects model analyses ($P < .01$, $I^2 = 99\%$) showed that the duration of hospital stay for MG patients after DFPP treatment was significantly decreased (MD = –5.71; 95% CI, –8.30 to –3.12; $P < .01$), as shown in Fig. 7.

3.4.4. Time to MG remission (day). Three studies^[16,17,22] comprising 136 patients evaluated the time to MG remission.

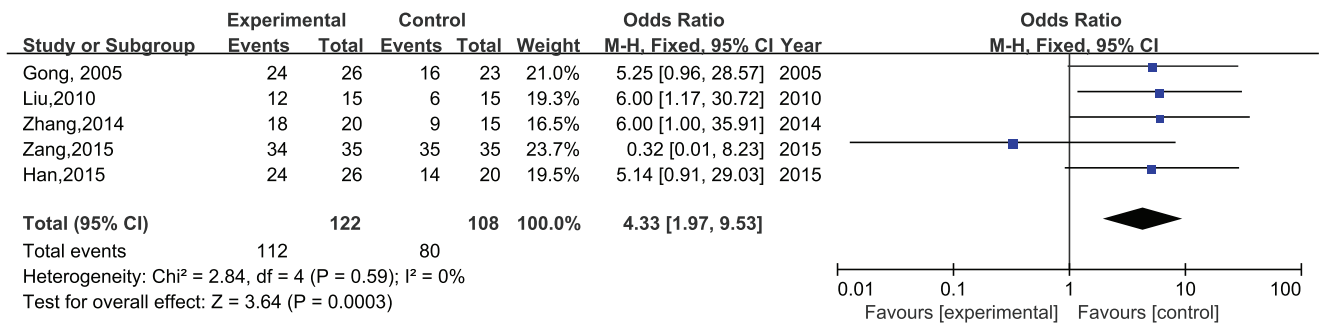


Figure 3. Clinical efficacy rate after double-filtration plasmapheresis treatment.

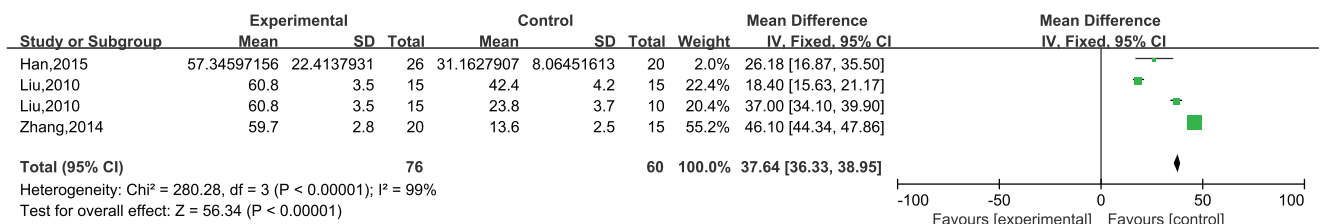


Figure 4. Descent range of the quantitative myasthenia gravis score after double-filtration plasmapheresis treatment.

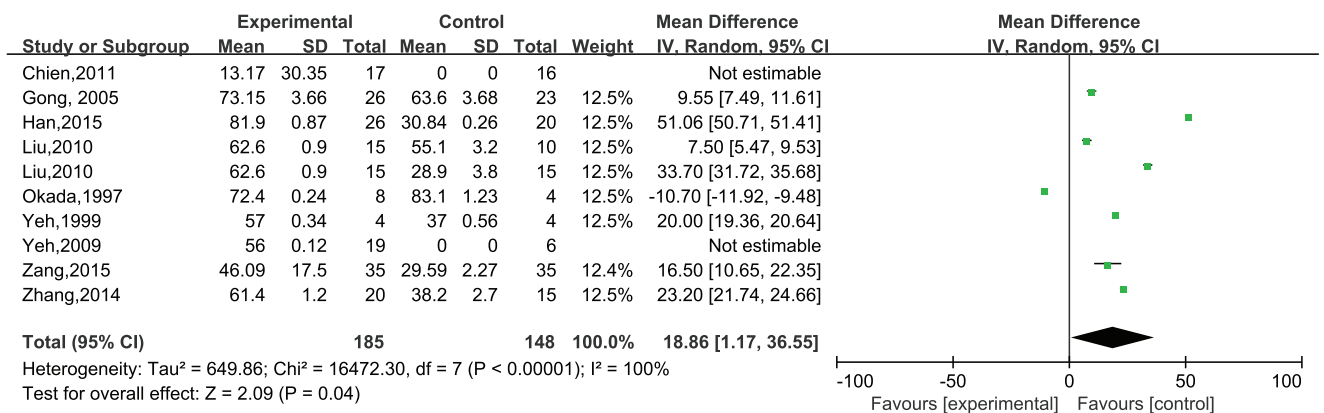


Figure 5. Acetylcholine receptor antibody levels after double-filtration plasmapheresis treatment.

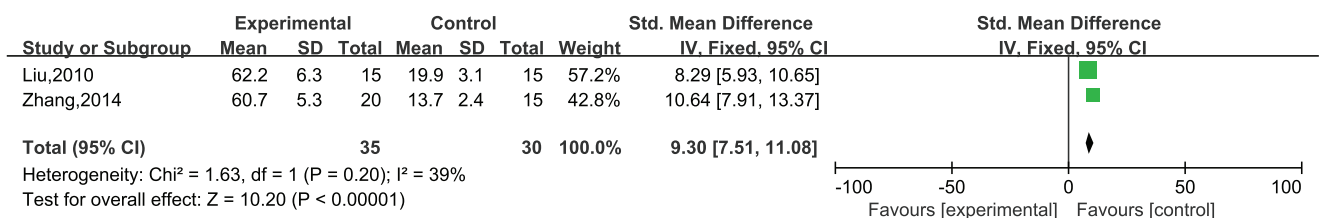


Figure 6. Serum levels of anti-titin antibody after double-filtration plasmapheresis treatment.

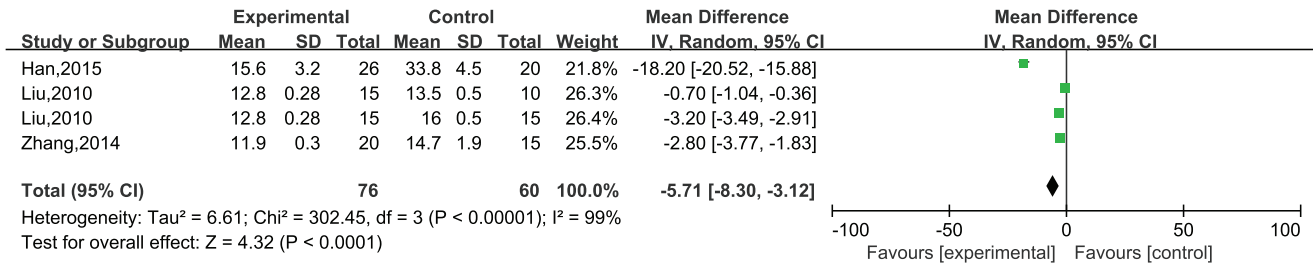


Figure 7. Duration of hospital stay for myasthenia gravis patients after double-filtration plasmapheresis treatment.

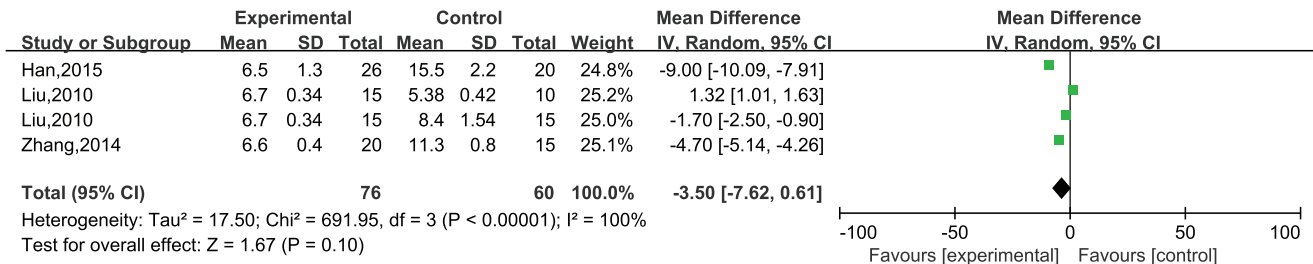


Figure 8. Time to myasthenia gravis remission after double-filtration plasmapheresis treatment.

Random effects model analyses ($P < .001$, $I^2 = 100\%$) showed that the time to MG remission after DFPP treatment was significantly decreased (MD = -3.50; 95% CI, -7.62–0.61; $P < .01$), as shown in Fig. 8.

3.5. Safety evaluation

Only one study^[22] has reported any adverse effects. In 15 patients with MG, 3 had adverse reactions during DFPP treatment that comprised hypotension (2), and hematoma (1).

4. Discussion

4.1. Summary of main results

In this study, the efficacy and safety of DFPP treatment for MG from 7 RCTs and 2 CCTs comprising 329 patients were evaluated by meta-analysis. The results showed that the clinical MG remission rate after DFPP treatment was significantly higher and the serum levels of antititin antibody significantly lower. In addition, the results showed that compared with the control group, the QMG score in the DFPP treatment group significantly decreased, hospitalization time and time to remission of MG symptoms decreased, anti-AChR antibody levels decreased; however, these outcomes had high heterogeneity among the studies. Only one study reported adverse events, which were fewer than those in the control group and the symptoms were mild. A possible mechanism underlying the effect of DFPP on MG is the alleviation of symptoms by reducing the pathogenic antibodies to MG; therefore, current research results support the recommendation of DFPP as a routine treatment option for short-term mitigation of MG.

4.2. Interpretation of the results

Treatment paradigms for MG include therapies such as intravenous immunoglobulin and therapeutic plasma

exchange.^[23,24] The administration of IVIg is convenient and safe, with few complications, but the price is very high.^[25]

PE is an accepted, effective therapy for some patients with MG^[14]; however, the major drawbacks of plasma exchange are the need for plasma supplements and the possible risk of allergic reactions and transfusion-related infection.^[26]

New techniques for PE include IA and DFPP. IA uses an affinity adsorbent of tryptophan-linked polyvinyl alcohol gel that selectively adsorbs most large proteins, including most AchRab, through hydrophobic interactions.

DFPP is a relatively selective plasma-separation method that transfers the blood through 2 filtration membranes of different pore sizes, and separates and discards pathogenic high molecular-weight substances, plasma albumin, and other physiological substances to selectively remove or reduce pathogenic substances in the patient's blood. In recent years, several of the complications of DFPP have been overcome, and this method has been widely used in clinics to treat autoimmune diseases. Because of the need for indwelling central venous catheters during DFPP treatment and anticoagulant therapy, it is also possible to increase the associated risk, such as infection, thrombus, and bleeding.^[27]

In this study, the efficacy and safety of DFPP treatment of MG were evaluated by meta-analysis. The results showed that DFPP treatment of MG is 91% effective, which confirms the rationale of DFPP treatment for this disease. As for the mechanism by which DFPP treatment affects MG, the current research results focus mostly on its clearance of the pathogenic autoantibodies in circulating blood to correct immune disorders, alleviate MG symptoms. In view of the advantages of the short-term clinical efficacy of DFPP treatment, this choice of treatment is important for patients, especially for severe or critical MG, for which the clinical symptoms must be alleviated. The results showed that compared with the control group, the QMG score of the DFPP treatment group significantly decreased, and that hospitalization time and the time for remission of MG symptoms also decreased.

The QMG scores^[28] are used mainly to assess the extent of MG and muscle weakness. Several studies^[14,16,22] have shown that DFPP treatment could significantly improve the endpoints, including the QMG scores. Yeh et al^[29,30] have reported that a better response in patients with an age at onset <40 years was associated with a higher QMG score and that the QMG score decreased in all courses in ≤3 months after DFPP. Chien et al^[31] have reported that after 1 course of DFPP treatment, the reduced clinical QMG score was correlated with a decrease in the percentage of T-cells. In this study, the QMG score descent range after DFPP treatment of MG significantly increased over that in the control group. MG symptoms were significantly relieved, and MG remission time and hospital stay were significantly reduced.

Anti-AChRab is a classic autoantibody for MG. The binding of antibodies to the postsynaptic membrane at the neuromuscular junction accelerates antigen regulation by internalization, destroys postsynaptic membrane by activating complements, or blocks the binding to ACHR. This affects the normal conduction of neuromuscular signals, resulting in trigger symptoms such as skeletal muscle weakness and muscle paralysis. In addition, autoimmune antibodies against presynaptic membrane (PrsmR) and titin reportedly compromise neuromuscular transmission, which leads to skeletal muscle weakness.^[32,33]

Titin is a major antigenic determinant for cross-striational antibodies. Titin antibodies are found in the sera of 85.7% of MG patients with thymoma (all age groups) and in 58% of nonthymomatous MG with late-onset and detectable AChR-ab.^[34] Recent studies have shown that AChR-ab titers are not associated with the clinical manifestations of late-onset MG, but that anti-titin antibodies is associated with the severity of the disease.^[35] Romi et al^[36] have shown that titin antibodies occurred only in the IgG 1 and IgG 4 subclasses and mean total IgG and IgG 1 titin antibody titers decreased during long-time patient observation together with improvement in the MG symptoms. The results showed that AChR-ab and titin-ab in MG patients significantly decreased after DFPP treatment. The results are highly heterogeneous, which might be the result of the small sample sizes of the including studies, the different proportions of autoantibody-positive samples in the baseline data, or the nonuniform methods of antibody detection. Limited by the quantity and quality of the included studies, the above conclusions need to be verified by more high-quality studies.

5. Conclusions

The meta-analysis and systematic review supply evidence that DFPP treatment can effectively eliminate autoantibodies and has a definite clinical effect on MG patients. It may also significantly reduce AChRab levels, QMGs, duration of hospital stay, and time to MG remission. DFPP treatment may be a beneficial option for treating MG.

5.1. Implications for practice

The use of DFPP to treat MG has increased over the past few decades; however, the choice of DFPP use is empirical and lacks consensus among doctors. This study found that DFPP can effectively improve MG symptoms within a short period of time.

5.2. Implications for research

In future randomized or nonrandomized prospective studies, a stratified design study will be conducted for the different positive

conditions of autoantibodies. There is no international consensus and no implementation criteria; therefore, the treatment methods implemented by each institute were slightly different. We recommend that large-scale, in-depth RCTs be conducted on the different plasma volume, treatment times, treatment intervals, and the safety of different sites of intravascular catheterization by central venous puncture for DFPP in critically ill patients.

5.3. Study limitations

There were several limitations to our study as follows:

- (1) Most of the included studies did not describe specific stochastic methods, allocation hiding, and blinding methods; therefore, there could be bias in implementation and measurements.
- (2) Only Chinese and English studies were included, and no other languages and gray studies were included; therefore, there could be publication bias.
- (3) Outcome indicators were scattered, and each outcome indicator involved few studies, which could have affected the accuracy of the results.
- (4) In the DFPP treatment of MG, the effects of different courses of treatment and blood filtration volume need to be more fully analyzed.
- (5) None of the 9 studies included in this study mentioned whether patients were tested for Musk antibodies. In the future, randomized controlled trials will be needed to prove the efficacy of DFPP treatment in Musk-positive patients need.
- (6) Only one study reported the side effects of DFPP and there was insufficient evidence for a meta-analysis.

Author contributions

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Project administration: Guoyan Qi.

Validation: Guoyan Qi.

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Writing – review & editing: Chaoying Liu.

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