Plasmapheresis or Intravenous Immunoglobulin for Myasthenia Gravis Crisis in King Chulalongkorn Memorial Hospital†

Rapat Pittayanon MD*,
Sombat Treeprasertsuk MD*, Kammant Phanthumchinda MD*

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** Department of Medicine, Faculty of Medicine, King Chulalongkorn Memorial Hospital, Chulalongkorn University, Bangkok, Thailand*

Background: *Myasthenia gravis (MG) crisis is a life-threatening and unpredictable complication of MG. Prognosis of MG crisis has dramatically improved due to modern immunomodulation. However, the choice of plasmapheresis or intravenous immunoglobulin (IVIG) is still a controversial issue.*
Objective: *Evaluate the efficacy and outcomes of MG crisis treatment with plasmapheresis or IVIG in King Chulalongkorn Memorial Hospital (KCMH) during the past 5 years.*
Material and Method: *Episodes of MG crisis with respiratory failure were recruited retrospectively from database of KCMH between 2001 and 2006.*
Results: *Thirty-three episodes of MG crisis with respiratory failure from 26 patients (9 males and 17 females) were documented. Plasmapheresis and IVIG were prescribed in 21 and 9 episodes of MG crisis, respectively. There was no statistical significant difference in baseline characteristics between both groups. The mean duration of intubation in plasmapheresis group was 12 $\pm$ 11.1 days and in IVIG group was 10.3 $\pm$ 4.6 days. The mean length of hospital stay (LOS) in plasmapheresis and IVIG were 30.7 $\pm$ 29.6 days and 25.4 $\pm$ 16.2 days, respectively. Hospital acquired pneumonia (HAP) occurred in four episodes (18.2%) in plasmapheresis and 1episode (11.1%) in IVIG. There was no statistical difference in the outcome of both treatment groups. All patients in both groups were well upon discharge.*
Conclusion: *MG crisis with respiratory failure was safely managed with either plasmapheresis or IVIG in KCMH. The present study cannot demonstrate any differences in the efficacy of plasmapheresis or IVIG. This may be due to inadequate sample size thus more patients should be recruited for further study.*

Keywords: *MG crisis, Plasmapheresis, IVIG, Outcome*

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Myasthenia gravis (MG) crisis is a well documented life-threatening and unpredictable complication of MG[1]. However, prognosis of MG crisis has dramatically improved due to the modern immunomodulative therapies. Its mortality rate was decreased from 75% in the past to a current rate of less than 5%[2,3]. Plasmapheresis and intravenous immunoglobulin (IVIG) treatment are immunomodulative techniques that can promptly control disease activity and reverse the crisis[4]. Plasmapheresis is an expensive and sophisticated technique and is available only in some tertiary care centers[4,5]. The complications of plasmapheresis include complications of intravenous access, hypotension, and coagulation disorders[4,5]. IVIG is also expensive but, a more simple technique[4,5]. Choice for plasmapheresis or IVIG in MG crisis is still controversial. In some case series, plasmapheresis showed more effective and reversed the course of crisis faster than IVIG[4,6]. IVIG has been shown to be

Correspondence to: Pittayanon R, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Phraram IV Rd, Patumwan, Bangkok 10330, Thailand. Phone: 0-2256-4246, 0-2256-4563, 081-313-2112, 083-716-3330, Fax: 0-2256-7858, E-mail: Rapat125@gmail.com, Rapat125@hotmail.com

Table 1. Associated and co-morbid diseases in Myasthenia gravis crisis patients

Number of patients	Associated diseases	Co-morbid diseases				
	Thyrotoxicosis	Hypertension	Ischemic heart disease	Diabetes mellitus	Atrial fibrillation	Others*
13 (50%)	1	10	5	3	2	4

* Others: breast cancer, thyroid nodule, endometriosis and vestibular neuritis

effective in long-term treatment in some selective cases of MG (but not in MG crisis)[7]. In a direct comparison of both therapies, they were equally effective in the overall disease stabilization[1]. According to Stricker et al[8], the patients who failed to respond to initial treatment with IVIG subsequently, responded to plasmapheresis. There is no conclusion for the best choice of treatment in MG crisis. The authors aimed at determining the outcomes of MG crisis treated with plasmapheresis or IVIG at King Chulalongkorn Memorial Hospital (KCMH) in the past 5 years.

Material and Method

Episodes of MG crisis between June 1, 2001 and June 30, 2006 in KCMH were recruited retrospectively from database of KCMH. Diagnosis indexes using MG crisis and respiratory failure were searched for cases. MG was diagnosis by clinical features, electrodiagnostic test (EMG/NCV) and therapeutic response to pyridostigmine. Crisis was defined by "weakness of respiration that required respiratory assistance"[9]. The baseline data including age, gender, and duration of MG before the crisis, associated disease, co-morbid disease, precipitating factors, clinical features during the crisis, history of thymectomy and thymus gland pathology were collected. Treatment with plasmapheresis, IVIG or combination, was based on the decision of the attending physicians, accessibility to plasmapheresis service and affordability of the patients. In the plasmapheresis group, 3-5 cycles of volume exchange were performed on alternate days. IVIG regimen consisted of 400mg/kg/day administer for 5 days. Outcomes of treatment including duration of intubation, length of hospital stay (LOS), complications during hospitalization and discharge status were reviewed. SPSS version 13 was used for data analysis. The statistical analysis methods were Unpaired t-test, Fisher's Exact Test, Pearson Chi-Square (Exact) test and Mann-Whitney U-test where appropriate. A p-value of less than 0.05 was considered statistically significant.

Results

Thirty-three episodes of MG crisis with respiratory failure from 26 patients were reviewed. The age of the patients ranged from 20-75 years (mean $\pm$ SD, 44.4 $\pm$ 15.0 years). Nine were males and seventeen were females. The mean duration of MG before the crisis was 2.9 $\pm$ 5.9 years and the first MG crisis presented within 2 years in 69.7% after the diagnosis of MG. Thirteen patients (50%) had associated diseases and co- morbid diseases.

The most common precipitating factor for MG crisis was respiratory tract infection (45.5%), ten episodes (30.3%) were associated with the treatments.

The first presenting symptoms of MG crisis were difficult to breathe (66.7%) or bulbar symptoms (33.3%). Thymectomy was performed in 16 cases, 11 of which were done before the crisis (post-thymectomy crisis). About half of the pathology of thymus gland showed involuted thymus. There were not any significant differences in baseline data including age, gender, duration of MG before the crisis, associated disease, co-morbid disease, precipitating factors, clinical

Table 2. Precipitating factors for Myasthenia gravis crisis patients

Precipitating causes	Episodes (%) total = 33
Respiratory tract infection	15 (45.5)
Upper respiratory tract infection	7 (21.2)
Pneumonia	6 (18.2)
Bronchitis	1 (3.0)
Hospital acquired pneumonia	1 (3.0)
Associated with the treatments	10 (30.3)
Increase dose of steroid	5 (15.2)
Thymectomy	2 (6.1)
Discontinuation of medication	2 (6.1)
Inadequate treatment	1 (3.0)
Progression of disease	1 (3.0)
Acute myocardium infraction	1 (3.0)
Stress	1 (3.0)
Unknown	4 (12.1)

features during the crisis, history of thymectomy and thymus gland pathology. Twenty-one episodes (63.6%) and nine episodes (27.3%) were treated by plasmapheresis and IVIG, respectively. Three episodes (9.1%) needed both treatments. Two patients did not recover after plasmapheresis, and were treated with IVIG successfully. One patient did not respond to IVIG but was successfully treated by plasmapheresis.

The duration of intubation in plasmapheresis group (21 episodes) varied between 5 and 45 days (mean ± SD, 12 ± 11.1 days). The duration of intubation in IVIG treatment (9 episodes) was 5-18 days (mean ± SD, 10.3 ± 4.6 days). The mean duration of LOS in IVIG treatment (mean ± SD, 25.4 ± 16.7 days) was less than in plasmapheresis treatment (mean ± SD, 30.7 ± 29.2 days). However, no statistical significant differences were found in terms of duration of intubation and LOS. The most common complication during hospitalization was respiratory tract infection (8 from 35 episodes, 24.2%). Hospital acquired pneumonia occurred in four episodes (18.2%) in plasmapheresis and one episode (11.1%) in IVIG. There were fewer complications in IVIG treatment but no statistical difference was detected among these outcomes (p, 0.073). All patients in both groups were discharged from the hospital uneventfully.

Table 3. Pathology of thymus gland in Myasthenia gravis crisis patients

Thymus gland pathology	Number of patients (%) total =16
Involuted thymus	9 (56.2)
Lymphoid hyperplasia	4 (25.0)
Thymoma	2 (12.5)
No data	1 (6.25)

Discussion

MG is an acquired autoimmune disorder of neuromuscular junction and characterized by fluctuating and variable weakness of the striated muscle[9]. Severe muscular weakness may cause an

Table 4. Characters of plasmapheresis and intravenous immunoglobulin in Myasthenia gravis crisis patients

	1. PP (21 episodes)	2. IVIG (9 episodes)	3. Combine (3 episodes)	Total	p-value (1, 2)
Sex					0.687
Male	7 (33.3%)	4 (44.4%)	1 (33.3%)	12	
Female	14 (66.7%)	5 (56.6%)	2 (66.7%)	21	
Age (years old)	42.8 ± 13.4	45.1 ± 16.7	60.7 ± 2.1	44.4 ± 15.0	0.692
Under 50	14 (66.7%)	4 (44.4%)	0	18	
50 or more	7 (33.3%)	5 (55.6%)	3 (100%)	15	
Associated disease	1 (100%)	0	0	1	1.000
Duration of MG (year)	1.9 ± 2.3	5.3 ± 10.6	2.3 ± 3.2		0.609
2 year or less	15 (65.2%)	6 (21.7%)	2 (8.7%)	23 (69.7%)	
Presenting symptoms					0.681
Difficult to breath	14 (66.7%)	7 (77.8%)	1 (33.3%)	22 (66.7%)	
Bulbar	7 (33.3%)	2 (22.2%)	2 (66.7%)	11 (33.3%)	
Precipitating causes					1.000
Infectious disease	10 (47.6%)	4 (44.4%)	2 (66.7%)	16 (55.2%)	
None infectious	11 (52.4%)	5 (55.6%)	1 (33.3%)	17 (44.8%)	
Complications					0.073
VAP/HAP	4 (18.2%)	1 (11.1%)	1 (25.0%)	6 (17.1%)	
Others*	9 (40.9%)	1 (11.1%)**	3 (75.0%)	13 (37.2%)	
None	9 (40.9%)	7 (77.8%)	0 (0%)	16 (45.7%)	
Duration of intubation (day)	12.0 ± 11.1	10.3 ± 4.6	55.0 ± 31.9	-	0.682
Length of hospital stay (day)	30.7 ± 29.6	25.4 ± 16.7	70.0 ± 36.9	-	0.786

PP = plasmapheresis, IVIG = intravenous immunoglobulin, VAP/HAP = ventilator associated pneumonia/ hospital acquired pneumonia

** Aspiration pneumonia, catheter related infection, urinary tract infection, hemothorax, pneumothorax, chylothorax, acute renal failure and sepsis

** Sepsis

acute respiratory failure and failure of the bulbar function known as MG crisis. Crisis usually occurs within 2 years after the diagnosis of MG[10], and our data followed this observation. Common factors that precipitate MG crisis are infection, surgery, pregnancy, emotional upset and certain drugs that compromised the neuromuscular transmission[10]. Infections are the most common precipitating factors and are detected in about one-third of cases with MG crisis[11]. Murthy JM et al demonstrated that the precipitant of crisis which related to infection (65%) were bronchopneumonia, viral fever and urinary tract infection[1]. In the present series, infection was also the most common precipitating factor for MG crisis and half of them were upper respiratory tract infection.

The prevention and critical care of the crisis required intubation and appropriate immunomodulation as well as other symptomatic and supportive treatment. Most patients needed mechanical ventilation less than 2 weeks after immunomodulative treatment[12] and hospital-associated pneumonia (HAP) is the most common complications of MG crisis[13], which is not different from the data in the present study.

Plasmapheresis is one of the immunomodulation treatments for MG crisis and was supported by NIH consensus statement in 1986[14]. The complications include local infection, catheter related infection of intravenous access, hypotension, and coagulation disorder[5,6]. In the present study, catheter related infection occurred in 9.1%, which was higher than previous study[16]. The side effects of IVIG are allergic reactions, renal failure, thrombotic events and serum sickness[15]. However, in the present study, only two patients in IVIG treatment group had complications; hospital acquired pneumonia and sepsis.

Comparing with the results in other countries, the authors found only one article that had the same research design. Murthy et al[1] revealed no significant difference in efficacy of both plasmapheresis and IVIG treatments in MG crisis. However, IVIG treatment showed a trend of fewer complications than plasmapheresis but there was no statistical significant difference. This result was not against the present study.

There are few examples of combination of IVIG and plasmapheresis in MG crisis. Stricker et al[8] reported four patients who developed MG crisis characterized by progressive bulbar weakness and respiratory compromise (without intubation) and finally responded to a combination treatment with IVIG and plasmapheresis. They started with IVIG for 48 hours then plasmapheresis was added. In the present study, one patient responded to subsequent plasmapheresis starting 2 weeks after failure to IVIG.

Conclusion

In summary, plasmapheresis and / or IVIG were demonstrated to be effective and safely used to rescue MG crisis in King Chulalongkorn Memorial Hospital. Due to the rather small sample size in each treatment group, no statistical significant difference in effectiveness of both treatment groups was demonstrated and IVIG seemed to have fewer complications than plasmapheresis treatment

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การศึกษาเปรียบเทียบวิธีการรักษาโดยวิธีเปลี่ยนถ่ายพลาสมาและอิมมูโนโกลบูลินสำหรับผู้ป่วยไมแอสติเนียเกรวิสในภาวะวิกฤตในโรงพยาบาลจุฬาลงกรณ์

รภัส พิทยานนท์, สมบัติ ตรีประเสริฐสุข, กัมมันต์ พันธุมจินดา

ภูมิหลัง: *ไมแอสติเนียเกรวิสในภาวะวิกฤต เป็นภาวะที่คุกคามต่อชีวิตและเป็นภาวะแทรกซ้อนของไมแอสติเนียเกรวิสที่ไม่สามารถคาดเดาได้ การทำนายโรคของภาวะนี้ดีขึ้นมากหลังจากมีการรักษาใหม่ อย่างไรก็ตาม การเลือกวิธีการรักษาสมัยใหม่ระหว่างการเปลี่ยนถ่ายพลาสมา หรือ อิมมูโนโกลบูลินยังหาข้อสรุปไม่ได้ วัตถุประสงค์ของการศึกษานี้ คือ เพื่อประเมินประสิทธิภาพ และผลของการรักษาภาวะไมแอสติเนียเกรวิส ในภาวะวิกฤตโดยวิธีเปลี่ยนถ่ายพลาสมาหรืออิมมูโนโกลบูลินในโรงพยาบาลจุฬาลงกรณ์ ในช่วงเวลา 5 ปีที่ผ่านมา*

วัสดุและวิธีการ: *จำนวนการเกิดไมแอสติเนียเกรวิสในภาวะวิกฤตที่มีการหายใจล้มเหลว ซึ่งเกิดขึ้นระหว่าง พ.ศ. 2544-2549 ได้ถูกรวบรวมจากหน่วยเวชระเบียนของโรงพยาบาลจุฬาลงกรณ์*

ผลการศึกษา: *ไมแอสติเนียเกรวิสที่อยู่ในภาวะวิกฤต เกิดขึ้นทั้งหมด 33 ครั้ง มีผู้ป่วยทั้งหมด 26 คน (เป็นชาย 9 คน หญิง 17 คน) มีการรักษาด้วยการเปลี่ยนถ่ายพลาสมา 21 ครั้ง อิมมูโนโกลบูลิน 9 ครั้ง โดยไม่พบความแตกต่างกันในข้อมูลพื้นฐานของผู้ป่วยทั้งสองกลุ่ม ระยะเวลาการใส่ท่อช่วยหายใจในการรักษาด้วยการเปลี่ยนถ่ายพลาสมาคือ 12 $\pm$ 11.1 วัน และในการรักษาด้วยอิมมูโนโกลบูลินคือ 10.3 $\pm$ 4.6 วัน ระยะเวลาการนอนโรงพยาบาลในผู้ป่วยที่ได้รับรักษาด้วยการเปลี่ยนถ่ายพลาสมา และ อิมมูโนโกลบูลิน คือ 30.7 $\pm$ 29.6 วัน และ 25.4 $\pm$ 16.2 วัน ตามลำดับ ภาวะปอดติดเชื้อในโรงพยาบาล เกิดขึ้น 4 ครั้ง (18.2%) ในการรักษาด้วยการเปลี่ยนถ่ายพลาสมา และ 1 ครั้ง (11.1%) ในการรักษาด้วยอิมมูโนโกลบูลิน ไม่พบความแตกต่างกันทางสถิติในการรักษาทั้งสองวิธี และไม่มีผู้ป่วยเสียชีวิต*

สรุป: *ไมแอสติเนียเกรวิสในภาวะวิกฤตที่มีการหายใจล้มเหลว สามารถรักษาได้อย่างปลอดภัย ในโรงพยาบาลจุฬาลงกรณ์ ไม่ว่าจะโดยวิธีเปลี่ยนถ่ายพลาสมา หรือ อิมมูโนโกลบูลิน อย่างไรก็ตาม การศึกษานี้ ไม่สามารถแสดงความแตกต่างในประสิทธิภาพของการรักษาทั้งสองวิธีนี้ได้ เนื่องจากจำนวนประชาการที่ใช้ศึกษาไม่เพียงพอ และควรมีการศึกษาในอนาคตที่มีจำนวนประชากรมากกว่านี้*