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REVIEW ARTICLE

Acetylcholinesterase Inhibitors in Myasthenic Crisis: A Systematic Review of Observational Studies

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Abstract

Current myasthenia gravis guidelines recommend intravenous immunoglobulin or plasmapheresis and discontinuation of pyridostigmine during myasthenic crisis. However, intravenous immunoglobulin or plasmapheresis is expensive and frequently not available in developing countries. This study aims to summarize the evidence of giving an acetylcholinesterase inhibitor in myasthenic crisis. Medline, Embase, and Cochrane databases and references were searched for observational studies that determined the use of acetylcholinesterase inhibitor in myasthenic crisis. The eligibility criteria were as follows: population, patients with myasthenic crisis, intervention (acetylcholinesterase inhibitor administration), and outcome (clinical improvement and complications). In total, 106 studies were identified, 92 through database searching (after removing duplicates) and 14 through other sources. Only eight were analyzed in the present systematic review. In five, acetylcholinesterase inhibitor was given at the start of the crisis, whereas in the other three, acetylcholinesterase inhibitor was discontinued initially and then restarted prior to extubation. Two observational analytic studies and three case reports showed improvement in different outcome measures. In the other three, improvement of outcome measures was also observed. Overall, a small proportion of patients developed cardiac arrhythmia and pneumonia after administration of acetylcholinesterase inhibitor alone, although this was not statistically different compared with those subjected to plasmapheresis. In summary, continuous intravenous infusion of pyridostigmine or neostigmine can be a substitute for intravenous immunoglobulin or plasmapheresis if these are not available during crisis; however, caution should be observed because of the aforementioned possible complications.

Keywords: Myasthenic crisis, Acetylcholinesterase inhibitor, Pyridostigmine, Myasthenia gravis

Introduction

Myasthenia gravis (MG) is a rare autoimmune condition of the neuromuscular junction characterized by fluctuating muscle weakness [1]. Frequently, it affects the eye and bulbar muscles and rarely the limbs [2]. Because of advancement in the diagnosis and treatment, the mortality rate has declined from 40 to 5% even in worst conditions [3]. Most of the time, MG symptoms are precipitated by infection, initiation of steroids, intake of medications that affect the neuromuscular junction and surgery [4].

Severe affection of the bulbar and accessory muscles and diaphragm that necessitates invasive or noninvasive ventilation is termed myasthenic crisis (MC) [3]. MC should be differentiated from cholinergic crisis, a condition with similar presentation, brought about by excessive intake of acetylcholinesterase inhibitor (AChEI). Although theoretically the management of MC and cholinergic crisis (CC) differs, CC has rarely been diagnosed in any studies [3, 5, 6].

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Once the respiration of a patient with MC has been stabilized, intravenous immunoglobulin (IVIG) or plasmapheresis (PLEx) with an addition of corticosteroids is administered [7]. Because of possible worsening from increased bronchial secretions, many review articles and guidelines suggest discontinuation of AChEI during the acute period of MC [8]. However, these recommendations were based on few observational studies with a limited number of subjects. Conversely, earlier studies suggest that administration of AChEI may actually complement IVIG, PLEx, and corticosteroids in improving the condition [6, 9].

PLEx and IVIG are the first-line treatments for MC [10]. However, aside from the their cost and side effects, technical skills for their administration and dependence to machines for PLEx limit their use in developing countries [1]. This study determines the evidence of AChEI in patients with MC in improving the outcome of this condition in the setting where PLEx and IVIG are not available.

Objectives

This study aims to determine the utility of AChEI in patients with MC by collecting all the possible available evidence for its use. Specifically, it aims to answer the following questions:

1. Can we use AChEI in MC?
2. If yes, what type(s) of AChEI can be given?
3. What is the preferred route of administration and dosage?
4. When is the best time to give AChEI in patients with MC?
5. What is the effect of adding AChEI to existing recommended first-line medications or management for MC?
6. What are the side effects/complications associated with AChEI?
7. Is AChEI safe when given alone during MC?

Methodology

Protocol Registration

Upon searching Cochrane and Prospero Registered Systematic Reviews, no existing reviews of the same objectives were found.

Eligibility Criteria

Only studies fulfilling the following eligibility criteria were included.

Study Population

Studies in which the inclusion criteria contained patients with MC or Myasthenia Gravis Foundation of America (MGFA) 5 treated with AChEI alone or in combination with other treatment options during the crisis period were selected.

Type of Exposure or Intervention Used

Studies wherein AChEI was given during intubation or restarted prior to extubation were included in the analysis. The routes of administration included intravenous (IV), intramuscular (IM), and oral forms of AChEI, combined with the standard of care treatment for patients in MC (i.e., IVIG, Total Plasma Exchange, and high-dose corticosteroids, or combination thereof). Any studies in which AChEI in MC has been analyzed as a secondary objective were also considered.

Type of Studies

Because studies about the utility of AChEI in MC were sparse, case reports, case series, case–control studies, and retrospective and prospective cohort and nonrandomized trials were included. Further, including nonrandomized trials made the search more comprehensive and generalizable. Published peer-reviewed journals were given priority, although other related unpublished literatures were also considered to decrease publication bias. All studies from 1963 to 2020 were scanned and considered to increase the sensitivity of the search. English written journals and English-translated journals were considered.

Information Sources

The following databases and registries were searched:

- Pubmed/Medline (1963 to 2020)
- Cochrane Central/Review (2002 to 2020)
- Embase
- Trial registers and clinical study reports (Clincaltrials.gov and World Health Organization International Clinical trials Registry Platform; no result)

Peer-reviewed journals were searched for studies fulfilling the eligibility criteria. Authors of studies were emailed to gather more information if needed. The primary authors (MBP and KJA) conducted search of these databases. Ongoing and unpublished data sources were also searched whenever possible by using RIAT.

Search Process

Two review authors (MBP and KJA), both neurologists, conducted the search and selected the journals. Whenever there was disagreement, a third-party consultant (KP) was involved in the decision-making process. The present systematic review, guided by the Meta-Analyses of Observational Studies in Epidemiology guidelines [11],

was based on our reading of the standard medical texts and search of Cochrane, PubMed Medline, and Embase for articles from 1963 to 2020 using the terms ((((myasthenic crisis) OR (MGFA V))) AND ((((Acetylcholinesterase inhibitor) OR (pyridostigmine)) OR (pyridostigmine bromide)))). The search strategy terms were approved by authors and was done in September 2020. No additional filters were included in the search.

Data Extraction and Management

Both review authors independently extracted data from eligible studies using a pretested data collection form. Data collected include name of the author; year published; country; study design; duration of data collection; the baseline characteristics of the population, including the mean age, sex, duration of the symptoms, mean time to crisis, and precipitating factors; the participants, outcome measures, results, and conclusions. The collated data are summarized in Table 1. Excluded articles and reasons of exclusion are summarized in Table 2.

Because of the heterogeneity and lack of consensus for the application of risk assessment tools for observational studies, assessment of bias was not done. Nevertheless, observational studies were considered as biased and subject to the effect of confounders.

Results

Result of the Search

In total, 111 studies were identified, 97 through database searching (Medline: 93, Cochrane: 4) and 14 through other sources (see Fig. 1). After duplicated records were removed, only 106 were screened based on titles and abstracts. Whenever full articles were not available, and the titles and abstracts were deemed irrelevant to the present systematic review, they were excluded. In total, 79 records were excluded. The full articles of the 27 journals were retrieved and assessed for eligibility. Although all articles came from different countries, such as India, USA, England, and other European countries, all were written in English. Some authors were emailed to request for the full article, but without reply. Only eight journals satisfied the eligibility criteria and were included in the present review. The search had 100% sensitivity and 29.6% precision.

Excluded Articles

Of the 27 articles initially deemed eligible, 19 were excluded. Ten were review articles, four did not fulfil the eligibility criteria, three had no abstract and full articles, and two were letters to the editor (see Table 2).

Studies Included

Summaries of the characteristics of all the included studies were tabulated (see Table 1). The eight studies spanned from 1983 to 2013 and were conducted in the USA (3), India (3), Greece (1), and Germany (1). There were three case reports and three retrospective and two prospective case reviews.

Participants

Patient enrollment spanned from 1970 to 2010 and amassed 445 patients with MG, 183 of whom had 189 episodes of MC. The median age of patients who had MC was 41.5 years (range 10 to 65 years), and the median interval from onset of symptoms to first crisis was 8 months. The most common triggers were infections, cholinesterase withdrawal, thymectomy, and steroid initiation. All eight studies included patients with MC. Among retrospective and prospective case studies, one limited the subjects to older patients only. Among the case reports, two patients had postthymectomy crisis.

Types of Intervention

AChEI was given during MC in all studies. In five studies, AChEI was given at the start of the MC, whereas the other three studies discontinued AChEI initially and restarted it prior to extubation or near discharge. The five studies that gave AChEI during the onset of MC, used either pyridostigmine (3) or neostigmine (2) via continuous IV infusion (3), IM (1), or oral (1) routes. The dose for continuous IV infusion of pyridostigmine was 2–4 mg/hr titrated by 0.5 mg/hr to 1.0 mg/hr increments, whereas for continuous IV infusion of neostigmine, a dose was 0.002 to 0.012 mg/kg/hr titrated using 0.002-mg/kg/hr increments. The dose for the IM route was 1 mg every 6 h [12]. In the case report that used oral pyridostigmine, dose as high as 120 mg every 4 h, combined with intermittent noninvasive ventilation, was given [13]. In studies that discontinued AChEI initially, low-dose oral pyridostigmine was started.

In all studies, there was cointervention of methylprednisolone pulse therapy (MPPT), IVIG, PLEx, azathioprine, or a combination of these with AChEI, except for one study in which the effect of IV pyridostigmine was compared with that of pyridostigmine plus prednisone and PLEx cohorts to given.

Types of Outcomes

Six studies assessed for incidence of complications, and five studies assessed duration of MC with invasive or noninvasive ventilation. Five studies also used clinical

Table 1 Summary of included studies

Author	Year of study/country	Enrollment	Type of study	Baseline characteristics	Population	Intervention	Outcome	Results	Conclusion
Berrouschout (1997) [6]	1997/Germany	1970–1995	Single-center population-based prospective case review	44/235 patients with MG developed 63 episodes of MC (Annual incidence of 2.5%) M:F: 1:1.44 Mean time to crisis: 37 (range:1–216 years) Prethymectomy MC: 14 (22%) After thymectomy MC: 29 (46%) No thymectomy MC: 20 (32%) Most common trigger of MC: Myasthenic weakness: 32 Respiratory infection: 27 Post thymectomy: 17	Patients with MC	Continuous IV infusion of pyridostigmine alone at 1 to 2 mg/hr ($n=24$) vs. pyridostigmine plus prednisolone ($n=18$) vs. Plasma exchange alone ($n=21$)	(1) Duration of mechanical ventilation (2) Complications (3) Outcome on release from ICU (4) Outcome after 3 months (5) Incidence of complications	No significant differences between the three treatment groups with respect to clinical characteristics, duration of mechanical ventilation, complications and outcome on release from ICU and after 3 months Complications: 11 (17%) patients had severe cardiac arrhythmia, which ended fatally for six patients	None of the therapeutic regimens applied demonstrated any advantage over others

Table 1 (continued)

Author	Year of study/ country	Enrollment	Type of study	Baseline characteristics	Population	Intervention	Outcome	Results	Conclusion
Saltis (1993) [16]	1993/USA	n/a	Case series	Patient 1: 62-year-old man, on oral pyridostigmine 240 mg/day, not responsive to PLEx and increased dosages of steroids Patient 2: 21-year-old woman with MG, maintained on pyridostigmine, prednisone, and azathiophrine developed acute noncardiogenic pulmonary edema during an outpatient PLEx procedure	Patients with MC	Patient 1: Continuous infusion of pyridostigmine (25 mg in 100 ml of 5% dextrose in water) at a rate of 2–4 mg/hr, titrated by 0.5 to 1.0 mg/hr increments Cointervention: corticosteroid therapy and six PLEx treatments Patient 2: IM Pyridostigmine at 1 mg every 6 h in hospital day 2, later on changed to continuous IV infusion at 2–3 mg/hr	Patient 1: (1) Improvement of symptoms monitored by patient interview and serial pulmonary function tests (2) Cholinergic side effects Patient 2: (1) Improvement of symptoms (2) Improvement of respiratory strength	Patient 1: Initial 7 h of infusion: (1) NIF: increased from − 35 to − 53 cm H_2O (2) FVC: increased from 0.75 to 2.4 l Cholinergic side effects were markedly decreased when the pyridostigmine was switched to infusion Patient 2: (1) Resolution of ptosis (2) Tolerate weaning from mechanical ventilation 36 h after the start of the infusion	Continuous administration of pyridostigmine is a potentially useful alternative in the management of myasthenic exacerbations and may be particularly valuable in critical care situations Pyridostigmine may be safely administered IV as a continuous infusion

Table 1 (continued)

Author	Year of study/country	Enrollment	Type of study	Baseline characteristics	Population	Intervention	Outcome	Results	Conclusion
Thomas (1997) [12]	1997/USA	1983–1994	Single-center retrospective case review	53 patients developed 73 episodes of MC Median Age of MC onset: 55 (range: 20–82) M:F: 1:2 Median interval from onset of symptoms to first crisis: 8 months	Patients with MC	Discontinuation of pyridostigmine and restarted 1–2 days prior to extubation Cointervention: steroids, plasmapheresis or IVIG, or combination of the three	Pulmonary functions immediately prior to extubation Complications	Mean VC 3 days post intubation: 21 ml/kg Mean VC immediately prior to extubation: 27 ml/kg Mean PEF immediately prior to extubation: 50 cm H_2O Mean PIF immediately prior to extubation: −43 cm H_2O Overall hospital mortality: 10% (7/73), all caused by comorbidities No mention of complications specific to pyridostigmine	The median duration of intubation for MC has changed remarkably little since the 1960s

Table 1 (continued)

Author	Year of study/ country	Enrollment	Type of study	Baseline characteristics	Population	Intervention	Outcome	Results	Conclusion
Panda (2004) [13]	2004/India	1999–2001	Single-center retrospective case review	11/114 (9.64%) patients developed 12 episodes of MC Mean age: 39.83 + 13.8 (range 22–66) M:F: 3:1 Median interval from onset of symptoms to first crisis: 8 months (range 7 days to 5 years) 7/11 patients underwent thymectomy prior to MC 75% of patients with MC were on pyridostigmine 33% of patients with MC were on neostigmine 60% of patients with MC were on steroids 42% of patients with MC were on azathiophrine Precipitant: Cholinesterase inhibitor and steroid withdrawal (3, 25%) Respiratory tract Infection (3, 25%) Thymectomy (2,16.6%) Gastrointestinal tract infection (1, 8.3%)	Patients with MC	Discontinuation of AChEI throughout the period of ventilation in all the patients and continuation at the time of discharge Cointervention: azathiophrine, steroids, or plasmapharesis	Duration of ventilatory support Improvement of symptoms Complications	40% could walk unsupported and 70% could feed orally No mention of complications specific to pyridostigmine	It is prudent to exercise great care while withdrawing cholinesterase inhibitors and steroids

Table 1 (continued)

Author	Year of study/ country	Enrollment	Type of study	Baseline characteristics	Population	Intervention	Outcome	Results	Conclusion
Mishra (2010) [17]	2009/ India	n/a	Case report	27-year-old woman with two episodes of crisis: 1st crisis: The patient developed post-thymectomy crisis, maintained on PLEx, pyridostigmine, azathiophrine and prednisolone, but had further worsening of symptoms and respiratory arrest after the pyridostigmine dosage was decreased 2nd crisis: Worsening of symptoms due to noncompliance to medications	Patient with post-thymectomy MC	1st crisis: Pyridostigmine 120 mg every 6 h over 2 days Cointervention: PLEx, azathiophrine, prednisolone 2nd crisis: 120 mg every 4 h over 3 days	1st crisis: withdrawal of ventilatory support 2nd crisis: Spirometric findings at the time of discharge	1st crisis: Ventilatory support withdrawn and patient returned to the ward 2nd crisis: FEV1: 1.84 l (84% of predicted value) FVC: 1.92 l (72%) PEF: 4.32 l/sec (66%) FEV1/FVC: 95.8 (114%)	A gradual increase in the dosage of AChEI drugs and provision of intermittent NIV during the dosing interval is a safe and easy method of managing respiratory difficulties in patients with MC during the postoperative period

Table 1 (continued)

Author	Year of study/ country	Enrollment	Type of study	Baseline characteristics	Population	Intervention	Outcome	Results	Conclusion
Sellman (1985) [14]	1983/USA	1983	Retrospective Case series	17/32 patients developed 20 episodes of MC 11/17 received neostigmine Mean age: 65 years (range: 52–85 years) Mean duration of illness: 5.6 years (range: 1–16 years) Mean crisis duration: 6–84 days	Older patients with MC	Neostigmine 1 mg IM every 6 h after prior 1 mg of edrophonium elicited no side effects Cointervention: Corticosteroids: 18 MC episodes PLEx: 7 MC episodes	Mean crisis duration Complication rate	All patients: Mean crisis duration: 33 days Range: 6–84 days Complication 50% MV plus drugs: 13 (65%) Mean crisis duration: 34 days Range 6–78 days Complication 54% ACh drugs only: only two patients (10%) Mean: 53 days Range: 22–84 days Complication: 50% Pred + other drugs: 18 patients (90%) Mean: 31 days Range: 6–78 days Complication: 50% Pred only: 6 patients (30%) Mean: 43 days Range: 17–42 days Complication: 67% Pred plus Ach: 9 (45%) Mean duration: 28 Range: 6–78 Complication: 56% PLEx + Pred: 7(35%) Mean duration: 18 Range 10–29 Complication: 29%	PLEx with prednisone combination is the most effective and safest

Table 1 (continued)

Author	Year of study/ country	Enrollment	Type of study	Baseline characteristics	Population	Intervention	Outcome	Results	Conclusion
Briassoulis (2000) [18]	1995/Greece	n/a	Case report	10-year-old boy with post thymectomy MC, on oral pyridostigmine 30 mg 4 × per day and prednisone 20 mg once per day	Juvenile patient with post-thymectomy MC	Continuous IV neostigmine 0.002 to 0.012 mg/kg/hr titrated using 0.002 mg/kg/hr increments over the next 2 days, converted to oral pyridostigmine 2 days prior to extubation Cointervention: Prednisolone and IVIG	Clinical improvement Side effects	Clinical improvement reported by the patient within the first day of continuous neostigmine infusion Resolution of ptosis and marked improvement in respiratory strength Weaning from mechanical ventilation started 36 h after reaching the maximum dosage of infusion Osserman scale grading from IIb to IIa On first day of infusion: NIF: increased from − 5 cm H_2O to − 35 cm H_2O Complication: Cholinergic side effects did not recur during the course of infusion	Continuous administration of neostigmine is a safe and potentially useful alternative in the management of postthymectomy myasthenic crisis

Table 1 (continued)

Author	Year of study/ country	Enrollment	Type of study	Baseline characteristics	Population	Intervention	Outcome	Results	Conclusion
Lal (2013) [15]	2013/India	2009–2010	Single center prospective study	10 patients developed MC Mean age: 42.5 (range 14–71 years) <50 years old: 8 patients M:F: 1:2.3 Mean disease duration: 4.52 years Trigger event: Infection (5, 50%) Inadequate treatment (3, 30%) Steroid initiation and hypokalemia (2, 20%)	Patients with MC	Discontinuation of pyridostigmine and restarted prior to weaning Cointervention: MPPT alone (3, 30%) MPPT + PLEx (4) MPPT + IVIG (1)	Duration of MC Hospital stay Mortality	Both patients who were not given any cointervention died due to arrhythmia and severe sepsis. It is unknown if they received AChEI	Mortality rate in developing countries may still be high

ACh Acethycholine, *AChEI* acetylcholinesterase inhibitor, *FEV1* forced expiratory volume 1, *FVC* forced vital capacity, *ICU* intensive care unit, *IM* intramuscular, *IV* intravenous, *IVIG* intravenous immunoglobulin, *MC* myasthenic crisis, *M:F* male:female, *MG* myasthenic gravis, *MPPT* methylprednisolone pulse therapy, *MV* mechanical ventilator, *n/a* not applicable, *NIF* negative inspiratory flow, *NIV* non-invasive ventilation, *PEF* peak expiratory flow, *PIF* peak inspiratory flow, *PLEx* plasma exchange, *Pred* prednisone, *VC* vital capacity

Table 2 Table of excluded studies

Title	Author	Year	Reason for exclusion
"Therapy for Myasthenic Crisis"	Mayer	1998	No abstract and full article
"Continuous Infusion of Pyridostigmine for Myasthenic Crisis"	Nicholson	1994	No abstract and full article
"Management of myasthenic crisis"	Kumar	2005	Letters
"Myasthenic Crisis—Your Assessment Counts"	Hickey	1991	No abstract and full article
"Prescription Profile of Pyridostigmine in a Population of Patients with Myasthenia Gravis"	Machado Alba	2015	Eligibility criteria for population not satisfied
"Administering Neostigmine as Subcutaneous Infusion: A Case Report of a Patient Dying with Myasthenia Gravis"	Hindmarsh	2019	Eligibility criteria for population not satisfied Pop: MG with anal carcinoma
"Coronary Vasospasm Secondary to Hypercholinergic Crisis: An Iatrogenic Cause of Acute Myocardial Infarction In Myasthenia Gravis"	Comerci	2005	Eligibility criteria for population not fulfilled Pop: patient with MG and MI
"Myasthenia Gravis: Management of Myasthenic Crisis and Perioperative Period"	Juel	2004	Review article
"An Update on Myasthenic Crisis"	Ahmed	2005	Review article
"Myasthenic Crisis"	Lacomis		Review article
"Approach to the Acute Management of Myasthenia Gravis and Guillain Barre Syndrome"	Lizzariaga	2016	Review article
"Myasthenic Crisis"	Kirmany	2004	Review article
"Myasthenic Crisis: Guidelines for Prevention and Treatment"	Jani-Acsadi	2007	Review article
"Myasthenic Crisis"	Wendell	2011	Review article
"The Patient in Myasthenic Crisis: An Update of the Management in Neurointensive Care Unit"	Godoy	2013	Review article
"Myasthenia Gravis Crisis"	Bershad	2008	Review article
"Myasthenic Crisis"	Chaudhuri	2008	Review article
"Comparative Effects Of Plasma Exchange And Pyridostigmine on Respiratory Muscle Strength and Breathing Pattern in Patients With Myasthenia Gravis"	Goti	1995	Eligibility criteria for population not fulfilled
"Management of Myasthenic Crisis: Continuous Anticholinesterase Infusions"	Borel	1993	Letter to the editor

MG myasthenic gravis, *MI* myocardial infarction, *Pop* population

improvement using serial pulmonary tests as outcome measures.

Risk of Bias in Included Studies

No bias assessment tool was employed in this systematic review. However, unlike in experimental studies, an exposure variable cannot be assigned to treatment groups in observational studies; hence, selection bias and confounding may be prevalent. In two studies, patients with infection and unstable hemodynamic status (cardiac problems) were given AChEI because these were contraindications to PLEx [6, 14]. Consequently, the duration of the MC period as well as the complication rate will be longer and higher, respectively, in the AChEI only group. One of these studies employed elderly patients only; hence, this effect was magnified [14].

Cointervention with other medications confounds the effect of AChEI to MC outcome measures and side effects.

Descriptive Analysis of the Studies

1. Berrouschot et al. (1997) [6] conducted a single-center population-based prospective case review that included 44 patients with MG who developed 63 episodes of MC. This study compared three possible treatment options (AChEI only, AChEI + steroids, and PLEx) for MC at that time. Patients with MC exacerbated by respiratory infections and steroids were only given AChEI (continuous IV pyridostigmine, $n = 24$), whereas those with no medical comorbidities and assumed to be primarily worsened by a pure myasthenic state were treated with a combination of AChEI + steroids ($n = 18$) or PLEx ($n = 21$). Of the three, patients given AChEI only were liberated from mechanical ventilation (MV) earlier (6 days) compared with those in the AChEI + steroids (7 days) and PLEx ($n = 14$ days) groups, although the difference was not statistically significant. In terms of complication, two had asystole and four had pneumonia (20.8% complication rate) in the AChEI only group; two had asystole and four had pneumonia (33.3% complication rate) in the AChEI + steroids group; and five had asystole and five had pneumonia in the PLEx group (47.6% complication rate). There were eight mortalities recorded, six due to cardiac arrhythmia and two from infection. Four out of the five who died of cardiac arrest received cholinergic drugs; however, signs of cholinergic excess, such

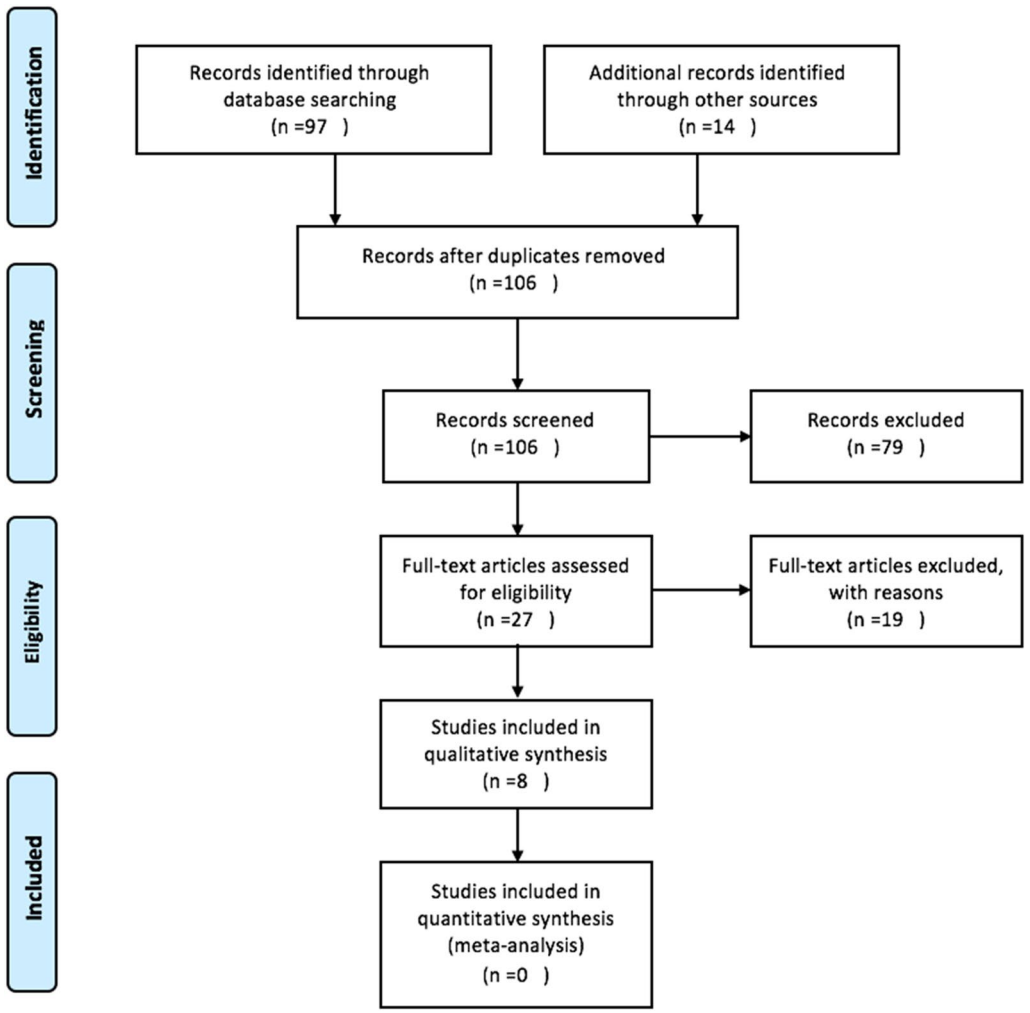

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-analysis PRISMA flow diagram

as diarrhea, salivation, bradycardia, and abdominal cramping, were not observed prior to their demise. Although the authors concluded that these deaths may not be related to AChEI, caution when using AChEI during MC should always be observed. Selection bias was observed in this study, as patients with respiratory infection were placed in the "AChEI only group" because infection was a contraindication to PLEx at that time.

2. Thomas et al. (1997) [15] performed a single-center retrospective case review in 53 patients with MC who developed 73 episodes of MC. They discontinued pyridostigmine for all the patients and restarted the drug 1–2 days prior to extubation. All were given azathioprine, steroids, or plasmapheresis during MC. They assessed the pulmonary functions immediately prior to extubation and complications. The mean vital capacity increased from 21 ml/kg 3 days post intubation to 27 ml/kg immediately prior to extubation. The mean peak expiratory flow and peak inspiratory flow immediately prior to extubation were 50 and − 43 cm H_2O, respectively. Overall hospital mortality was 10%, but there was no mention if the deaths were related to pyridostigmine.
3. Panda et al. (2004) [16] analyzed 11 patients who developed 12 episodes of MC out of 114 patients with MG. They discontinued the AChEI throughout the period of ventilation in all patients and continued the drug prior to discharge. All patients were given azathioprine steroids or PLEx. In these patients, 40% could walk unsupported and 70% could feed orally. There was no mention of complications specific to pyridostigmine. One of the most common precipitating factors for MC besides infection was withdrawal or noncompliance to AChEI.

4. Sellman and Mayer (1985) [14] conducted a case series involving 17 patients who developed 20 episodes of MC, 11 of whom received neostigmine. The neostigmine dose was 1 mg IM every 6 h administered after a trial of 1 mg of edrophonium elicited no cholinergic side effects. Combining the AChEI alone and AChEI + prednisone groups ($n = 11$) yielded an average MC duration of 32.5 days and complication rate of 55%. Compared with the PLEx + prednisone group ($n = 7$), the former group had worse MC duration and complication rates. However, unstable blood pressure, particularly hypotension, was one of the contraindications for PLEx. Although not mentioned, there was a high probability that the seven elderly patients with cardiac dysfunction, including fibrillation and arrhythmias, would not undergo PLEx, and most patients in this group were those with no, mild, or noncardiac complications only. It was established in the same study that those with medical problems had longer MC duration than those without (50 days vs. 18 days); hence, a selection bias may be prevalent. Nevertheless, the same study also recommended avoiding giving AChEI alone and concluded that PLEx in combination with prednisone was the most effective and safest among the groups. Because of the limited number of samples, this study lacked the power to determine any significant differences between groups.
5. Sharma et al. (2013) [17] conducted a prospective study of ten patients with MC from 2009 to 2010. They discontinued pyridostigmine and restarted prior to weaning. Despite being weaned off the ventilator, two of their patients died. One died of sudden cardiac arrhythmia, whereas the other one had thyrotoxicosis and cardiac arrest. Temporally, administration of pyridostigmine as a possible cause of these events cannot be excluded; nevertheless, the authors attributed these more to susceptibility of the heart muscle as another autoimmune target of MG.
6. Saltis et al. (1993) [18] described a 62-year-old man and a 21-year-old woman who were unresponsive to PLEx and in whom the dosage of steroids was increased during the MC period. In both cases, continuous IV infusion of pyridostigmine showed improvement of symptoms. In the first patient, the negative inspiratory flow increased from −35 to −53 cm H_2O and forced vital capacity (FVC) increased from 0.75 to 2.4 l in the first 7 h of infusion. In the second case, there was resolution of ptosis, and the patient was weaned from mechanical ventilation 36 h after the start of the infusion. Cholinergic side effects were also markedly decreased when pyridostigmine was switched from the IM route to infusion. They concluded that continuous administration of pyridostigmine is a potential alternative in the management of myasthenic exacerbations and may be particularly valuable in critical care situations.
7. Mishra et al. (2010) [13] reported a 27-year-old woman who had two episodes of MC post thymectomy, both triggered by sudden or inadequate intake of AChEI. In the first crisis, the patient was intubated after the primary physician decreased the existing AChEI dose. Oral pyridostigmine at a dose of 120 mg every 6 h was given over 2 days with significant improvement. One week after discharge, the patient had another MC episode due to noncompliance to medication. Oral pyridostigmine at a similar dose was restarted and she was placed on intermittent noninvasive ventilation for respiratory support. No PLEx or IVIG was given. In this episode, the forced expiratory volume 1 (1.84 l), forced vital capacity FVC (1.92 l), PEF (4.32 l/s), and FEV1/FVC (95.8%) improved. The authors concluded that a gradual increase in the dose of AChEI drugs and provision of intermittent non-invasive ventilation during the dosing interval was a safe and easy method of managing respiratory difficulties in patients with MC during the postoperative period. No cholinergic side effects were observed.
8. Briassoulis et al. (2000) [19] described a 10-year-old with postthymectomy MC who was administered continuous IV neostigmine after not responding to oral AChEI, prednisolone, and IVIG. On the first day of infusion, the negative inspiratory flow increased from −5 to −35 cm H_2O, and there was resolution of ptosis and marked improvement in respiratory strength. Weaning from mechanical ventilation started 36 h after reaching the maximum dose of infusion.

Utility of AChEI in MC

Two retrospective case studies and three case reports that utilized AChEI in the acute period of MC and three other observational studies that restarted the medication prior to weaning or extubation showed improvement in different outcome measures. Among those that utilized AChEI at the acute phase, one study showed that the outcome measures for continuous IV infusion of pyridostigmine alone had no significant difference when compared with combination of pyridostigmine and prednisone or PLEx alone [6]. Either pyridostigmine or neostigmine were given. Although several routes of administration were used, the continuous IV infusion of pyridostigmine at 1 to 2 mg/hour was utilized in the study with the largest sample size [6].

The duration of MC was shortened whether the patients were on AChEI alone or AChEI in combination with recommended first-line treatments.

Complications or Side Effects

In two case reports, cholinergic side effects were prominent when the patients were started on oral and IM pyridostigmine [20, 21]. However, when these were changed to continuous IV form, the cholinergic side effects disappeared. There was no documentation of occurrence of CC in all eight studies. Four out of five patients who died of cardiac arrhythmia received AChEI in one study [6]. However, these patients did not show any signs of cholinergic excess hence the authors concluded that these events were probably not AChEI related [6] Another study mentioned a complication rate as high as 55%, mostly consisting of respiratory infections and cardiac dysrhythmia when patients were given AChEI with or without steroids [14]. Nevertheless, most patients given with AChEI in this study had prior comorbidities because infection and hemodynamic instability were contraindications for PLEx [14]. In another study in which two of the patients died of cardiac arrest, the authors attributed the incidents to susceptibility of the heart muscle as another autoimmune target of MG [17].

Discussion

Most recent guidelines recommend the use of PLEx or IVIG in combination with corticosteroids and discontinuation of AChEI in the management of MC [22]. Possible co-occurrence of CC and increase in bronchial secretions were cited for this recommendation [22]. However, although cholinergic side effects were observed in few studies, overt CC was not documented in any studies included in this systematic review. In addition, the high proportion of pneumonia in the cohort in which AChEI was given was probably secondary to noninclusion of patients whose trigger was infection in the PLEx group. Moreover, five studies concluded that continuous IV infusion of either neostigmine or pyridostigmine was probably safe and beneficial to patients with MC.

An AChEI holiday may increase the sensitivity of the postsynaptic membrane and may be of benefit when the drug is restarted prior to extubation according to MC guidelines [23]. However, in the present review, a benefit was observed whether the drug was given during or prior to weaning or extubation of patients with MC. In addition, one common cause of impending respiratory failure in developing countries was noncompliance; hence, holding the drug may push the patient to an MC state [17]. In one of the case reports, increasing the oral dose of pyridostigmine, in combination with intermittent noninvasive ventilation, shortened the MC duration to 36 h after the correction even in the absence of IVIG or PLEx [13].

The benefits of PLEx and IVIG have been proven in several studies [24]. In contrast, because of ethical concerns, there are no randomized controlled trials that determine the safety and efficacy of using AChEI in the management of MC. However, PLEx and IVIG are costly and need technical skills and machines for their administration, whereas AChEI is a cheap, readily available, and easy to administer drug, whether in IV, IM, or oral forms [1]. In developing countries and in countries with poor health care system, an alternative to IVIG or PLEx may be needed. This systematic review showed that adding AChEI may shorten the MC duration among patients with MG [6, 10, 13, 14, 19]. Nevertheless, most of the studies included have PLEx, IVIG, or immunomodulator as cointerventions that may act as confounders [10, 13, 14, 16, 19]. Nonetheless, in one study, the clinical outcome and complication for giving AChEI alone was not statistically different from giving PLEx. [6].

Cardiac dysrhythmia is one of the fatal complications possibly associated with AChEI during the MC period [1, 25]. One case report even attributed hypercholinergic crisis to be a possible cause of vasospasm-induced myocardial infarction [26]. Nevertheless, the presence of several risk factors that predispose to cardiac complications, absence of parasympathetic symptoms suggestive of cholinergic overactivity, and no mention of AChEI dosage make the association less likely. Four out of five patients who received AChEI died of fatal arrhythmia in one of the studies included [6]; however, the absence of cholinergic symptoms prior to their demise led the authors to conclude that these events were probably not due to AChEI alone [6]. Takotsubo cardiomyopathy, giant cell myocarditis, and cardiac dysrhythmia were possible complications of thymomatous MG. Accordingly, high antistriational antibody titers may induce autoimmune attack to myocardium [27].

The limitation of this study is the high risk of bias inherent in observational studies. Because the assignment of exposure variable cannot be controlled as that of experimental studies, selection bias is unavoidable. Most patients with hemodynamic instability and sepsis were more likely to have AChEI alone because these were contraindications for PLEx. Unfortunately, these patients tended to have longer MC duration and higher complication and mortality rates whichever treatment group they were assigned.

Although the goal of this systematic review is to determine the efficacy and safety of AChEI alone to the management of MC, cointerventions with high-dose steroids, IVIG, PLEx, and/or other immunomodulatory drugs

in most studies confound its true effects. Hence, it was impossible to determine whether the benefit or the complication was from other treatment options or from AChEI alone. Nonetheless, because of the rarity of the condition, decision-making can only be based on systematic reviews supported by these types of studies at best.

Future Recommendations

A randomized controlled trial comparing continuous IV infusion of AChEI alone or in combination with steroids to IVIG or PLEx in patients with MC may give the best evidence on its use in this condition; however, current recommendations and guidelines prevent the use of AChEI in MC, and research proposals for such studies may have difficulty passing ethics standards. A systematic review of RCTs with meta-analysis can provide the best evidence for the use of AChEI in MC.

Conclusions

In places where IVIG or PLEx is not available, continuous IV infusion of pyridostigmine or neostigmine may be used with or without other cointerventions, provided that the patient is admitted in the intensive care unit and the airway has been secured adequately. Caution should be observed in using AChEI because of possible cardiac complications.

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Author contributions
MP designed the study. MP and KA collected the studies. MP and KA analyzed the data and wrote the manuscript. We also confirm that authorship requirements have been met, and the final manuscript has been approved by all authors.

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