Ephedrine treatment for autoimmune myasthenia gravis

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Highlights

- Anecdotal evidence suggests a symptomatic effect of ephedrine in myasthenia gravis.
- This series of randomized controlled n-of-1 trials compared ephedrine to placebo.
- Ephedrine significantly reduced QMG score by 1.0 point.
- Adverse events were mild, including palpitations, tremor and restlessness.
- Ephedrine add-on treatment resulted in a small but consistent reduction of symptoms.

Abstract

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Statistical analysis for the trial was performed by Erik W. van Zwet, Department of Medical Statistics and Bioinformatics, Leiden University Medical Center, Leiden, The Netherlands.

Author contributions

All authors were involved in drafting/revising the manuscript, study design and analysis or interpretation of the data. Statistical analysis for the trial was performed by Erik W. van Zwet. Alexander F. Lipka and Jan J.G.M. Verschuuren were responsible for data acquisition. Jan J.G.M. Verschuuren and Stephanie S.
Weinreich were responsible for obtaining funding and study supervision / coordination.

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ABSTRACT

We studied the effect and safety of ephedrine as add-on treatment for patients with myasthenia gravis with acetylcholine receptor antibodies (AChR MG), who do not sufficiently respond to standard treatment. Four patients with AChR MG were included in a placebo-controlled, double-blind, randomised, multiple crossover series of n-of-1 trials. Each n-of-1 trial consisted of 3 cycles, in which two 5-day intervention periods were followed by 2 days washout. In each cycle, ephedrine 50mg daily in 2 doses was compared with placebo in the alternate treatment period. Primary outcome was a change in QMG score. Add-on treatment with ephedrine compared with placebo improved QMG score by 1.0 point (95% confidence interval 0.21-1.79), which was significant for the group of trial patients as well as for the population treatment effect. Ephedrine also showed a significant trial average treatment effect for all secondary outcomes, improving MG-Composite by 2.7, MG-ADL by 1.0 and VAS score for muscle strength by 1.1. Adverse events were mild and included palpitations, tremor and restlessness. Although all ECGs were normal, ephedrine prolonged the corrected QT interval. Ephedrine as add-on treatment for myasthenia gravis resulted in a small but consistent reduction of symptoms and weakness, in patients with moderate disease severity.
1. INTRODUCTION

Myasthenia gravis (MG) is a rare autoimmune disease, characterised by fluctuating muscle weakness. Many patients initially respond favourably to symptomatic treatment with acetylcholinesterase inhibitors (AChIs) that act directly on the neuromuscular junction. The next step in treatment often consists of high doses of immunomodulating or immunosuppressive drugs, which may have serious side effects.[1]

Anecdotal evidence suggests that some MG patients may benefit from ephedrine as add-on treatment to pyridostigmine.[2, 3] Ephedrine might be an alternative which, together with AChIs or low-dose prednisone, may reduce disease severity, while avoiding the often severe side-effects related to the use of aggressive immunomodulating or immunosuppressive therapies. Ephedrine is a sympathomimetic agent which mainly affects the adrenergic receptors.[4, 5] Its mechanism of action in MG has been investigated, but is not well understood.[6-11] An increase in quantal content of the endplate potential and the probability of quantal release, as well as an antagonistic effect on acetylcholine receptor (AChR) conductance have been described, although these effects occurred at a much higher dose than is reached in patients.[7, 9, 12] Moreover, ephedrine could have a direct effect on fatigue, which is found in more than 40% of the MG patients and correlates poorly with muscle weakness.[13]

In contrast to congenital myasthenic syndromes, in which a maximal treatment effect of ephedrine is observed after weeks to months, the limited number of patients with autoimmune MG treated with ephedrine report an onset within hours to days.[2, 10,
Autoimmune MG is a rare disease with a low prevalence and moreover even consists of heterogeneous subgroups, due to differences related to age of onset, sex or associated thymic abnormalities. Therefore, a standard randomised controlled trial (RCT) is difficult to perform, as also highlighted by the limited success of therapeutic development in MG. The likely short-acting nature and rapid onset of response to symptomatic treatment in MG in general, permit a crossover design to test the effect of ephedrine. A series of n-of-1 trials has the advantage of using each patient as their own control in repeated crossover cycles, limiting the required sample size. We studied the effect and safety of ephedrine as add-on treatment in a series of n-of-1 trials in patients with AChR MG who do not sufficiently respond to standard treatment.

2. METHODS

For full details, we refer to the trial protocol, which has been previously published.

2.1 Patient population

Eligible subjects were adult patients with a diagnosis of generalised MG, based on clinical signs or symptoms and confirmed by presence of AChR antibodies. All screened subjects were being treated at the Leiden University Medical Center and enrolled between October and December 2014. Inclusion criteria were: treatment with pyridostigmine and/or low dose prednisone (max. 15mg daily) and/or other steroid-sparing immunosuppressive drugs, all of which at a stable dose for at least 6 weeks. All patients had remaining symptoms of MG that were too mild to justify starting or increasing immunosuppressive drugs, but that were not adequately
controlled by their current symptomatic treatment. Exclusion criteria were: regular or recent (<3 months) intravenous immunoglobulin or plasma exchange, recent (<3 months) myasthenic crisis, recent (<6 months) or planned thymectomy, any contra-indication for ephedrine (myocardial ischemia, any cardiac arrhythmia, prolonged QT interval, angle-closure glaucoma, current hypertension, poorly regulated diabetes mellitus, prostatic hypertrophy or thyrotoxicosis), relevant drug interactions, or inability to give informed consent or fill out the study questionnaires.

2.2 Intervention
During the n-of-1 trials, add-on treatment with ephedrine 50mg daily in 2 doses was compared with placebo, which was similar in shape, colour and flavour to the ephedrine tablets. During the entire trial, pyridostigmine, low dose prednisone and steroid-sparing drugs such as azathioprine were continued as before, at the same dose and time schedule.

2.3 Design
Each patient was treated for three single weeks with ephedrine and three single weeks with placebo add-on treatment in a randomised, double-blind n-of-1 trial. Treatment was administered in three treatment cycles, each consisting of 2 periods during which either ephedrine 50mg daily in 2 doses or placebo was administered for 5 days, followed by a 2-day washout period. This was followed by 5 days of the alternate treatment, again with a 2-day washout period. Treatment order within each cycle was block-randomised for each patient individually (example shown in Figure 1). Randomisation was performed by the hospital pharmacy. Patients and investigators were blinded to the treatment sequence until completion of each n-of-1 trial, after which the individual results were discussed and patients were invited to participate in a 6-month open label extension phase.
2.4 Endpoints

The primary endpoint was the effect of add-on therapy with ephedrine compared with placebo on the Quantitative Myasthenia Gravis (QMG) score.[19, 20] The QMG score is a severity score for muscle strength and fatigability consisting of 13 items, each scored from 0 (normal) to 3 (severe weakness). This endpoint was assessed for all patients enrolled, to determine the trial average treatment effect. Only in case of significant improvement, the population treatment effect was also assessed to determine generalisability to other MG patients. Secondary outcome parameters were the MG-Composite, MG-ADL scores and a VAS score for subjective assessment of muscle strength in a muscle group predefined by the patient.[21, 22] Individual treatment effects were also assessed for all outcome measures. All tests were performed on day 5 of treatment periods, at a predefined time and interval after all medication.

Adverse events were monitored during each treatment period using questionnaires, which included a list of known side effects of ephedrine, as well as vital signs, screening blood tests and ECGs at the end of treatment periods. On the first day of both periods in the first treatment cycle, patients were admitted to the hospital to monitor vital signs and adverse events, as well as ECGs at the time of estimated maximum serum concentration (Tmax).

Treatment preference was recorded for each treatment cycle. Blinding was assessed by recording presumed randomisation sequence by patient and investigator after each treatment period.
2.5 Statistics

Based on our observations during clinical care, we estimated that the standard deviation of repeated measurements of QMG within a single person is 2.95. For our sample size calculation, we assumed a mean treatment effect of 3.5 with a standard deviation of 1. Power calculation by means of Monte Carlo simulation showed a sample size of 4 patients would yield 77.2% power to detect a significant difference in the trial population.

For both primary and secondary outcomes measures, a linear model was fitted with fixed effects for treatment and patient to test the treatment effect in the trial population. This model also produced results for treatment effects in individual patients. Only in case of a significant result for an outcome parameter, a linear mixed model for these outcomes was fitted with fixed effects for treatment and patient and a random treatment effect to determine the population treatment effect, which assesses the treatment effect across the population of eligible MG patients.

Data analysis was performed using R Foundation for Statistical Computing (version 3.0.2 Vienna, Austria). P-values lower than 0.05 were considered significant.

2.6 Registration and informed consent

The study was registered under EudraCT number 2014-001355-23. The study protocol was approved by the Medical Ethics Committee of the Leiden University Medical Center, and all patients provided written informed consent.
3. RESULTS

3.1 Study population

We screened 14 patients with AChR MG for entry into the study, of which 5 did not meet the eligibility criteria and 4 declined to participate (Figure 1). We included 5 patients; one patient discontinued before the actual start of the n-of-1 trial and was replaced. All four remaining patients completed their n-of-1 trials, baseline characteristics of these patients are presented in Table 1. One patient did not complete one treatment cycle (due to an acute medical problem in a family member), this cycle was excluded and replaced by an extra randomised cycle.

3.2 Treatment effect

Add-on treatment with ephedrine compared with placebo resulted in a mean improvement in QMG score of 1.0 (95% confidence interval (CI) 0.21-1.79, Table 2), which was significant for both the trial average treatment effect (p=0.016) and the population treatment effect (p=0.024). Ephedrine treatment also showed a significant trial average treatment effect on all secondary outcome parameters; improving MG-Composite score by 2.7 (p=0.012; 95% CI 0.68-4.65), MG-ADL by 1.0 (p=0.019; 95% CI 0.19-1.81) and VAS score for individual muscle strength by 1.1 (p=0.033; 95% CI 0.10-2.07). Population average treatment effects for secondary outcomes did not differ significantly from placebo.

Individual treatment effects showed an individual response on QMG and MG-Composite scores for one of four patients and a significant improvement of MG-ADL and VAS score in another (Figure 2; see also online supplemental figure S1 for mean individual scores). Aside from the missed and replaced cycle, compliance was 100%. One VAS score was missing, constituting the only missing data point.
Treatment preference within each cycle showed that patients favoured ephedrine in 6/12 cycles, placebo in 1 cycle and had no preference in 5 cycles. Based on their individual results, three of four patients opted to continue ephedrine treatment in the open label extension phase. The fourth patient declined participation because of multiple, individually mild side effects which outweighed the small perceived treatment effect. Although no patient was officially unblinded during the crossover phase, patients correctly guessed the treatment in 68% of treatment periods and investigators in 72%.

3.3 Safety

Adverse events were limited to mild, transient symptoms (Table 3). Most adverse events were only present on a minority of treatment days. Recurring adverse events were all previously described side effects and consisted of palpitations, tremor and restlessness. None of the adverse events required escape medication or extra hospital consultation. Treatment at the current dose did not show a relevant change in blood pressure or heart rate, in these patients who were all at low risk for cardiovascular disease (see online supplement figure S2A-B). All ECGs recorded during the study were normal. Although all conduction intervals, both before and after treatment, stayed within the normal range, ephedrine significantly prolonged corrected QT (QTc) intervals at estimated maximum serum concentration on day 1 of treatment, but not at the end of treatment periods (see online supplemental Figures S2C-D).
4. DISCUSSION

Ephedrine as add-on treatment for myasthenia gravis resulted in a small but consistent reduction of symptoms and weakness. The improvement was consistently found for all primary and secondary outcome parameters, indicating a clinically relevant effect. The current study also showed that a series of n-of-1 trials can be a very effective study design to detect even a small effect in a small patient population, by replacing the large variance between patients in standard RCTs with smaller variance within individual patients.

Previous clinical trials in myasthenia gravis have reported a decrease of about 2-3.5 points on the QMG score to be clinically significant.[23-26] Our study shows an effect well below this previously defined cut-off point. However, no previous studies have tested the effect of adding a second symptomatic treatment, for which the effect can realistically be expected to be lower than for immunosuppressive drugs. In our opinion, this small effect at a limited risk can be very useful in a subset of MG patients with moderate disease severity, when current treatment does not sufficiently improve symptoms, but in whom the disease is too mild to justify a more aggressive immunosuppressive therapy at the risk of severe side effects. Treatment with ephedrine is not without risk either and is associated with cardiovascular events, as well as psychiatric, autonomic and gastrointestinal symptoms, although more severe events have mostly been described at higher doses or in combination with other stimulating drugs.[27, 28] In patients with contra-indications to ephedrine treatment risks are unlikely to outweigh the small benefit, but we expect that ephedrine treatment is suitable for a small subset of AChR MG patients with intermediate disease severity to control remaining symptoms, or prevent or postpone (higher dose) immunosuppression.
The most important limitation of the study is its small sample size. It can be difficult to extrapolate findings in four patients to all MG patients. For this reason, we extended our statistical analysis to include a population average treatment effect as well as a trial average treatment effect. The consistent improvement in QMG score for both models, as well as for the trial average treatment effect on secondary outcomes, suggests that our findings are robust. Crossover designs can be confounded by unblinding, or by a carry-over effect because of exposure to multiple treatment periods. Although we did not formally test for a carry-over effect, QMG and MG-Composite scores were actually slightly worse in placebo periods preceded by ephedrine, as compared with placebo preceded by placebo, making a relevant carry-over effect unlikely. Subjective unblinding by either treatment effect or side effects did occur in the majority of treatment cycles, as recorded by prediction of treatment periods after completed treatment periods during the trial. Correct predictions were however mainly present in the two patients with the smallest treatment effect, also limiting the potential for confounding.

Future studies should focus on the possible mechanism of action of ephedrine, for example by studying its role in innervation of the neuromuscular junction by sympathetic neurons, or correlating results with electrophysiological investigation or scales for fatigue. Ephedrine might also improve neuromuscular transmission by counteracting the destabilising effect of pyridostigmine on the neuromuscular junction. The long term effects and safety of ephedrine treatment in autoimmune MG are mostly unknown, therefore a further improvement of the treatment effect over months is still possible, as is the case in congenital myasthenic syndromes. We aim to elucidate part of this by inclusion of the patients in a 6 month open label extension phase. The effect of salbutamol, which has a
comparable method of action and is also described to have a positive effect in congenital myasthenic syndromes, could be a relevant alternative to ephedrine, which should be explored in future studies.[30] The current study also highlights the potential of a series of n-of-1 trials in rare diseases to detect a short-acting treatment effect at limited cost and sample size.

Acknowledgements

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References


FIGURE LEGENDS

Figure 1 Flow Diagram of recruitment, follow-up, and analysis.

Figure 2 Mean treatment effect per cycle for each patient.
Each patient has completed 3 treatment cycles, for which the benefit of ephedrine treatment compared with placebo is shown as dots. Error bars represent 95% confidence interval, which are equal for all patients due to the assumption of equal variances in the statistical model.

Figure A.1 Individual mean scores during ephedrine and placebo treatment.
(A) Individual mean QMG scores; (B) MG-Composite scores, (C) MG-ADL scores, (D) VAS scores of muscle group chosen by the patient.

Figure A.2 Cardiovascular effects of ephedrine compared to placebo.
(A) Systolic (solid lines) and diastolic (dashed lines) blood pressure during ephedrine (red lines) and placebo (blue lines) treatment. Mean blood pressure at outpatient visit (day 5 of treatment period) is also shown.
(B) Heart rate at baseline, 30, 60 and 120 minutes after start of ephedrine or placebo treatment. These were measured at day 1 of week 1 and 2 for all patients. Mean heart rate at outpatient visit (day 5) is also shown.
(C) Corrected QT interval 60 minutes (estimated time of maximum plasma concentration) after start of ephedrine or placebo treatment, measured at day 1 of week 1 and 2.
* Represents p<0.05 for comparison.
(D) Corrected QT interval at outpatient visit (day 5 of treatment period).
<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>33</td>
<td>46</td>
<td>53</td>
<td>35</td>
</tr>
<tr>
<td>Gender</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>Disease duration</td>
<td>6 yrs</td>
<td>21 yrs</td>
<td>7 yrs</td>
<td>5 yrs</td>
</tr>
<tr>
<td>AChR titer (nmol/L)</td>
<td>&gt;5.0</td>
<td>&gt;5.0</td>
<td>&gt;5.0</td>
<td>&gt;5.0</td>
</tr>
<tr>
<td>QMG score</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td>MGFA</td>
<td>3A</td>
<td>3B</td>
<td>2A</td>
<td>2A</td>
</tr>
<tr>
<td>MG-Composite</td>
<td>10</td>
<td>13</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Muscle group for VAS score</td>
<td>neck</td>
<td>bulbar</td>
<td>right arm</td>
<td>arms</td>
</tr>
<tr>
<td>Medication</td>
<td>pyridostigmine 120mg/d in 2 doses</td>
<td>prednisone 10mg/d; AZT 150mg/d in 3 doses</td>
<td>pyridostigmine 300mg/d in 5 doses</td>
<td>pyridostigmine 300mg/d in 5 doses</td>
</tr>
<tr>
<td>Thymectomy</td>
<td>no</td>
<td>yes (hyperplasia)</td>
<td>no</td>
<td>yes (hyperplasia)</td>
</tr>
</tbody>
</table>

AChR, acetylcholine receptor; AZT, azathioprine; MGFA, Myasthenia Gravis Foundation of America clinical classification scale; QMG, Quantitative Myasthenia Gravis score.
### Table 2 Treatment effect of ephedrine as add-on treatment

<table>
<thead>
<tr>
<th></th>
<th>Baseline scores</th>
<th>Placebo</th>
<th>Ephedrine</th>
<th>Treatment effect (± 95% CI)</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Population significance&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QMG (0-39)</td>
<td>10.0 ±4.1</td>
<td>9.5 ± 4.8</td>
<td>8.5 ± 4.5</td>
<td>1.0 (0.21-1.79)</td>
<td>p=0.016</td>
<td>p=0.024</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MG-C (0-50)</td>
<td>9.3 ±3.3</td>
<td>9.1 ±3.6</td>
<td>6.4 ± 5.3</td>
<td>2.7 (0.68-4.65)</td>
<td>p=0.012</td>
<td>p=0.149</td>
</tr>
<tr>
<td>MG-ADL (0-24)</td>
<td>3.5 ±0.6</td>
<td>2.8 ± 1.2</td>
<td>1.8 ± 0.8</td>
<td>1.0 (0.19-1.81)</td>
<td>p=0.019</td>
<td>p=0.238</td>
</tr>
<tr>
<td>VAS (0-10)</td>
<td>3.8 ±3.1</td>
<td>4.3 ± 2.4</td>
<td>3.2 ± 2.3</td>
<td>1.1 (0.10-2.07)</td>
<td>p=0.033</td>
<td>p=0.198</td>
</tr>
</tbody>
</table>

Mean primary and secondary outcomes expressed as mean ± standard deviation, treatment effect of ephedrine compared to placebo as mean ± 95% confidence interval for trial average treatment effect.

<sup>a</sup> Trial average treatment effect: fixed model assuming normality, no carry-over effects and equal variances for all patients.

<sup>b</sup> Population average treatment effect: mixed model, which additionally assumes a random treatment effect.

QMG, Quantitative Myasthenia Gravis score; MG-C, Myasthenia Gravis Composite scale; MG-ADL, Myasthenia Gravis Activities of Daily Living profile; VAS, visual analogue scale
Table 3 Adverse events reported in the study.

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Ephedrine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nervous system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tremor hands</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Nervous / restlessness</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Micturition difficulties</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Lab abnormalities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia / leukocytosis</td>
<td>2 (3.4; 11.1)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (7.4)</td>
<td>0</td>
</tr>
<tr>
<td>Bilirubinemia</td>
<td>1 (20)</td>
<td>1 (20)</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpitations / tachycardia</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Gastro-intestinal / other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Flu-like symptoms</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td>0</td>
<td>0</td>
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</table>

All reported adverse events in the study were mild and only intermittently present.