Alpha-adrenoceptor agonists for the treatment of vasovagal syncope: a meta-analysis of worldwide published data

CRD summary
This review assessed the effectiveness of alpha-adrenoceptor agonists for the treatment of vasovagal syncope and concluded: alpha-adrenoceptor agonists might be effective; and midodrine represented a better choice of treatment compared with etilefrine. This conclusion may not be reliable given the poor quality of and variation between included studies and potential publication bias.

Authors' objectives
To assess the effectiveness of alpha-adrenoceptor agonists for the treatment of vasovagal syncope.

Searching
PubMed, EMBASE, Elsevier and CNKI (dates ranged from 1968 to 2008) were searched for English- or Chinese-language publications; search terms were reported.

Study selection
Randomised placebo-controlled trials (RCTs) for the treatment of vasovagal syncope or neurocardiogenic syncope were eligible for inclusion. The included studies included etilefrine (10mg to 25mg three times a day) or midodrine (1.25mg to 15mg at differing frequencies). Patients were diagnosed with vasovagal syncope based upon the results of a head-up tilt test with or without isoproterenol or nitroglycerine; aetiologies of syncope were not defined by physical examination, electrocardiography, chest X-ray or biochemical screening. Studies with uncertain diagnosis criteria of vasovagal syncope were excluded. Outcomes included the rate of syncope recurrence during follow-up or percentage of responders in head-up tilt test. Mean age of patients in included studies was between 12 and 56 years. Frequency of syncope symptoms before treatment ranged from experienced before to two or more episodes per month.

The authors stated neither how the papers were selected for review nor how many reviewers performed the selection.

Assessment of study quality
Two reviewers independently assessed the quality of the RCTs using the criteria of Juni et al based on: methods of randomisation; allocation concealment; blinding; loss to follow-up; and use of intention-to-treat analysis. Studies were classified as: grade A when all criteria were satisfied; grade B when one or more criteria were partially satisfied; and grade C when when one or more criteria were not satisfied.

Data extraction
For each study, odds ratios (OR) were calculated for the rate of syncope recurrence and the percentage of responders. The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Pooled odds ratios and 95% confidence interval (CIs) were calculated for a combined outcome of syncope recurrence or positive head-up tilt test response using a fixed-effects model. A random-effects model was used if significant heterogeneity was present. The weighted mean percentages of responders were compared using a weighted independent t-test. Heterogeneity was assessed using the X² test with significant heterogeneity defined as p<0.05. Publication bias was assessed using a funnel plot.

Results of the review
Six RCTs (n=329, range 24 to 126) were included in the review. The duration of follow-up ranged from one week to over four years. Study quality was grade B in four studies and grade C in two. Funnel plots suggested possible publication bias.
Compared with placebo alpha-adrenoceptor agonists were significantly more effective in treating vasovagal syncope (OR 0.21, 95% CI 0.06 to 0.77, \( p=0.02 \)); significant heterogeneity was present (\( p<0.0001 \)). The weighted mean percentage of responders for midodrine was significantly greater than that for etilefrine (76.3% ± 7.7% versus 65.5% ± 15.4%; \( p < 0.001 \)).

**Authors' conclusions**

Alpha-adrenoceptor agonists can be effective treatments for vasovagal syncope, with midodrine regarded as a better treatment choice compared with etilefrine.

**CRD commentary**

The review question and inclusion criteria were clear. A small number of databases were searched for publications in English and Chinese and it was unclear whether unpublished studies were sought; therefore, language bias could have been present and some studies may have been missed. Publication bias was assessed, with evidence to support its presence. No detail was provided on how the studies were selected for the review and how the data extraction was conducted, therefore, it was unclear whether methods were used to reduce error and bias. Appropriate criteria were used to assess the quality of the included studies; no studies were of the highest quality. Most included studies were small. In the analysis, the authors appeared to combine different outcome measures (syncope recurrence and head-up test response); this may not have been appropriate. Heterogeneity was assessed and found to be present. Although the findings reflected the evidence, these were limited by a combination of publication bias, variation across studies and a lack of good-quality data. Such shortcomings mean that the authors' conclusions should be interpreted with caution.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that more studies were required to reduce bias, including large-scale, multifaceted and better designed studies.

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