Midodrine as a Treatment Option for Recurrent Vasovagal Syncope

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CLINICAL QUESTION

Is midodrine an effective treatment for recurrent vasovagal syncope?

EVIDENCE-BASED ANSWER

Midodrine can treat recurrent vasovagal syncope in adults and children. It reduces the recurrence rate by at least 30% compared with placebo (number needed to treat [NNT] = 6). (Strength of Recommendation [SOR]: A, systematic review and meta-analysis of randomized controlled trials [RCTs].) Midodrine may also delay syncope recurrence compared with placebo. (SOR: B, single RCT.) A guideline from three cardiology organizations recommends midodrine as a reasonable treatment option for adults and children with recurrent vasovagal syncope without a history of hypertension, heart failure, or urinary retention. (SOR: B, evidence-based guideline.)

EVIDENCE SUMMARY

A 2022 systematic review and meta-analysis of seven placebo-controlled RCTs (n = 319) evaluated midodrine for the treatment of recurrent vasovagal syncope.[1] Studies included in the systematic review were from Canada (one trial; n = 133), the United States (two trials; n = 83), China (two trials; n = 70), the Netherlands (one trial; n = 23), and the United Kingdom (one trial; n = 16). Patients had a mean age of 33 years and 69% were female; two trials (n = 70) evaluated children with a mean age of 11 years. Patients had at least two spontaneous syncopal episodes within 1 year of study enrollment. The daily midodrine dosage ranged from 2.5 to 30 mg administered orally as a single or repeated dose for up to 1 year (median duration = 6 months). Three trials (n = 131) were open label. The primary outcome was syncope (i.e., brief and complete loss of consciousness) observed during a tilt-table test or reported by a patient at any time during the trial. Compared with placebo, midodrine decreased the risk of tilt-table test syncope by 63% (four trials; n = 98; relative risk [RR] = 0.37; 95% CI, 0.23 to 0.59; NNT = 3) and patient-reported syncope by 49% (five trials; n = 287; RR = 0.51; 95% CI, 0.34 to 0.79; NNT = 4). In subgroup analyses of double-blind RCTs, midodrine reduced tilt-table test syncope by 61% (two trials; n = 28; RR = 0.39; 95% CI, 0.21 to 0.70; NNT = 2) and patient-reported syncope by 30% (two trials; n = 156; RR = 0.7; 95% CI, 0.53 to 0.94; NNT = 6). Heterogeneity was low in pooled analyses tilt-table test outcomes and subgroup analyses of patient-reported syncope in double-blind RCTs. However, there was moderate heterogeneity in meta-analyses of patient-reported syncope that combined blinded and unblinded studies. Other limitations included an unclear risk of selection bias and a high risk of performance bias due to the lack of information on randomization methods in the three unblinded trials.

The largest study from the 2022 systematic review was a double-blind RCT (n = 133) that compared midodrine with placebo for recurrent vasovagal syncope.[1,2] Researchers recruited patients from 25 university hospitals in North America and the United Kingdom. Patients were predominantly female (73%), had a median age of 32 years, and had been symptomatic for a median of 14 years. Patients had, on average, four syncopal episodes per year but were otherwise healthy. Exclusion criteria were significant cardiovascular disease or hypertension, liver disease, glaucoma, seizure disorder, and urinary retention. Midodrine or a matching placebo was administered at 5 mg orally three times per day, 4 hours apart, and the dosage was adjusted to tolerance (2.5 mg two times per day to 10 mg three times per day), avoiding nighttime doses. Researchers educated patients about the benign nature of vasovagal syncope and lifestyle measures (e.g., physical maneuvers, dietary advice) to prevent syncopal episodes.

The primary outcome was any episode of vasovagal syncope over 1 year, and a secondary outcome was the time to the first episode of recurrence.[2] Patients taking midodrine had a lower risk of vasovagal syncopal episodes (RR = 0.69; 95% CI, 0.49 to 0.97; NNT = 6; 95% CI, 2.8 to 48) compared with placebo.

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Author disclosure: No relevant financial relationships.

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Midodrine was also associated with a longer time until syncope recurrence compared with placebo (hazard ratio = 0.59; 95% CI, 0.37 to 0.96). In subgroup analyses, no significant interaction existed between the treatment effect and patient age, sex, number of syncopal episodes in the past year, or baseline heart rate. Midodrine appeared to be more effective than placebo at preventing syncope in patients with a systolic blood pressure above 120 mm Hg (n = 48; RR = 0.53; 95% CI, 0.32 to 0.88), but it was equivalent to placebo in those with a systolic blood pressure at or below 120 mm Hg (n = 89; RR = 0.92; 95% CI, 0.55 to 1.5). The study was limited by a high proportion of patients from a single center. In addition, 21 patients (16%) were lost to follow-up, and 27 (20%) discontinued their assigned treatments before the end of the study. However, only four patients (two from each group) stopped treatment due to adverse effects.

The 2017 consensus and evidence-based guideline from the American College of Cardiology, American Heart Association, and Heart Rhythm Society on the evaluation and management of patients with syncope recommended educating patients with vasovagal syncope about the benign nature of the disorder and focusing on symptom awareness and avoidance of possible triggers such as prolonged standing or warm environments.[3] The guideline recommended midodrine as a reasonable treatment option for recurrent vasovagal syncope in adults and children without hypertension, heart failure, or urinary retention. This guideline was approved by governing bodies from the American College of Cardiologists, American Heart Association, and Heart Rhythm Society and was endorsed by the American College of Emergency Physicians, the Society for Academic Emergency Medicine, and the Pediatric and Congenital Electrophysiology Society.

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