Effectiveness of Midodrine treatment in patients with recurrent vasovagal syncope not responding to non-pharmacological treatment (STAND-trial)

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Aims	Initial treatment of vasovagal syncope (VVS) consists of advising adequate fluid and salt intake, regular exercise, and physical counterpressure manoeuvres. Despite this treatment, up to 30% of patients continue to experience regular episodes of VVS. We investigated whether additional Midodrine treatment is effective in these patients.
Methods and results	In our study, patients with at least three syncopal and/or severe pre-syncopal recurrences during non-pharmacological treatment were eligible to receive double-blind cross-over treatment starting either with Midodrine or placebo. Treatment periods lasted for 3 months with a wash-out period of 1 week in-between. At baseline and after each treatment period, we collected data about the recurrence of syncope and pre-syncope, side effects, and quality of life (QoL). Twenty-three patients (17% male, mean age 32) included in the cross-over trial received both Midodrine and placebo treatment. The proportion of patients who experienced syncopal and pre-syncopal recurrences did not differ significantly between Midodrine and placebo treatment (syncope: 48 vs. 65%, $P = 0.22$; pre-syncope: 74 vs. 78%, $P > 0.99$). The median number of syncopes and pre-syncopes per 3 months were also not significantly different during Midodrine and placebo treatment (0 vs. 1; $P = 0.57$; and 6 vs. 8; $P = 0.90$). The occurrence of side effects was similar during Midodrine and placebo treatment (48 vs. 57%; $P = 0.75$). Also, QoL did not differ significantly.
Conclusion	Our findings indicate that additional Midodrine treatment is less effective in patients with VVS not responding to non-pharmacological treatment than reported as first-line treatment.
Keywords	Vasovagal syncope • Treatment • Midodrine • Quality of life

Introduction

According to the 2009 Syncope Management Guidelines of the European Society of Cardiology (ESC), non-pharmacological treatment is recommended as the first line of treatment for vasovagal syncope (VVS).[1] This treatment consists of maintaining an adequate fluid and salt intake, regular exercise, and the application of physical counterpressure manoeuvres.[2,3] Non-pharmacological treatment was found to be effective in about 70% of patients diagnosed with VVS.[4] In patients who do not respond adequately to this treatment,

pharmacological treatment with Midodrine, an alpha-adrenergic agonist, might be considered.[1,2,5,6] By constriction of arterioles and veins, Midodrine is thought to increase vasoconstrictor tone and reduce venous pooling of blood when standing, and thus prevent the occurrence of reflex syncope.[2,5,7]

A recent systematic review, including four studies with a total of 115 patients, evaluated the evidence of the effectiveness of Midodrine treatment compared with conventional, non-pharmacological treatment.[8] In only one of the included studies, patients were instructed to use PC.[8,9] Across different studies,

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syncopal recurrence was found to be lower during treatment with Midodrine than during conventional, non-pharmacological treatment or placebo treatment [odds ratio 0.07; 95% confidence interval (CI): 0.03–0.15].[8] In the two included studies assessing quality of life (QoL), scores were higher on Midodrine treatment than control treatment.[10,11]

However, alpha-adrenergic treatment in all studies within this review was started without prior non-pharmacological treatment.[8] Since about 70% of patients diagnosed with VVS will respond to simple, inexpensive non-pharmacological treatment,[4–6] pharmacological treatment for VVS is only relevant for patients who fail to respond to this treatment. Since it is yet unknown whether pharmacological treatment is beneficial to these patients, we determined the effectiveness of additional, alpha-adrenergic treatment with Midodrine in patients with recurrent VVS not responding to non-pharmacological treatment.

Methods

We performed a randomized cross-over trial of Midodrine against placebo in patients with VVS who responded insufficiently to non-pharmacological treatment. Midodrine or placebo was given while continuing non-pharmacological treatment measures. Each treatment period lasted for 3 months with a 1-week washout period in between.

This trial was conducted by the Syncope Treatment and Assessment network Netherlands (STAND). The protocol was approved by the Medical Ethical Committee of the Academic Medical Center in Amsterdam (project number 03/191) and the local Medical Ethical Committees of the other participating centres. The trial was registered in the Dutch Trial Register (ISRCTN29932893) and performed according to the declaration of Helsinki. All included patients gave written informed consent.

Initial phase with non-pharmacological treatment

We recruited patients between 18 and 70 years of age with a clinical diagnosis of recurrent VVS from the Emergency Department and the syncope units of four Dutch medical centres.[12] Recurrent VVS was defined as the occurrence of at least three syncopal episodes in the last 2 years. The diagnosis of VVS was based on the definition of the ESC-guidelines and defined as a self-limited complete loss of consciousness with a duration of <5 min caused by a transient global cerebral hypoperfusion.[1,13] Only patients with a clinical diagnosis of VVS with recognizable prodromal symptoms in >80% of the episodes of VVS were eligible for study participation.[12] A head-up tilt-table test (HUT test) was performed in all patients. Both patients with a clinical diagnosis of VVS based on history and physical examination and patients with highly likely VVS in combination with a positive HUT test were included. The induction of either pre-syncope or syncope in the presence of hypotension (systolic blood pressure <90 mmHg) on HUT testing was defined as a positive response.[14] Patients with transient loss of consciousness different from VVS were excluded. Patients using any medication to prevent VVS recurrence were also excluded.

After inclusion, all patients received non-pharmacological treatment consisting of reassurance regarding the benign nature of the condition, maintaining an adequate fluid and salt intake, regular exercise, and the application of PC.[1,3,12]

After at least 6 months of follow-up, patients who experienced three or more syncopal and/or pre-syncopal episodes were eligible for the cross-over trial of Midodrine against placebo. Non-pharmacological treatment was continued in all patients.

Randomized cross-over trial of Midodrine against placebo

A research physician screened eligible patients for contra-indications for Midodrine treatment by history, blood pressure measurement, and laboratory tests. Patients with one or more contra-indications for Midodrine treatment (pre-existent hypertension, cardiac and/or vascular disease, diabetic retinopathy, glaucoma, hyper-thyroidism, pheochromocytoma, renal failure, prostatism or urinary retention, or pregnancy/lactation), or patients declining pharmacological treatment were not included in the trial.

Randomization was performed by means of a computer programme to determine the sequence of Midodrine and placebo treatment. Treatment allocation was concealed, and both the patients and all research staff were blinded to the outcome of the randomization. After randomization patients received double-blind cross-over treatment starting either with Midodrine or placebo for 3 months. After the first treatment period there was a wash-out period of 1 week after which patients started their second treatment period receiving the other medication.

The Midodrine and placebo used in this trial were both manufactured by Nycomed Austria GmbH and had similar external features. A fixed dosage of 5 mg twice daily (after breakfast and lunch) was prescribed. To avoid supine hypertension, patients were instructed not to take medication after dinner.[15]

Data collection and outcome measures

After 1 week, 1 month, and 3 months of study medication, patients were asked whether they had experienced any (pre-)syncopal recurrences of VVS, trauma associated with recurrent VVS, or side effects since the start of pharmacological treatment or their previous follow-up visit during both treatment periods. Pre-syncope is defined as any condition in which patients feel as though syncope is imminent but transient loss of consciousness does not occur.[1] Only if pre-syncope was associated with near loss of consciousness, we considered pre-syncope to be present in this study. We expressed the number of (pre-)syncopal recurrences and the number of years patients were familiar with syncope by the median and interquartile range (p25–p75).

Apart from obtaining information about (pre-)syncopal recurrences and QoL, blood pressure was also checked in upright and supine position to avoid iatrogenic hypertension. Blood pressure measurements were performed using the Maxi Stabil 3 sphygmometer (Welch Allyn, NY, USA) or a similar device.

After the study period, patients returned their residual pills. Patient compliance was expressed by the actual number of pills taken divided by the expected number of pills to be taken.

Quality of life

Before treatment initiation and at the end of each pharmacological treatment period, QoL was evaluated using self-administered questionnaires [short form-36 (SF-36) questionnaire and Syncope Functional Status Questionniare (SFSQ)].

The self-administered SF-36 questionnaire is used to measure generic health concepts relevant across age, disease, and treatment groups.[16,17] After filling in the 36-item questionnaire, eight scale scores can be calculated: physical functioning, role functioning physical, bodily pain, general health, vitality, social functioning, role functioning emotional, and mental health. The scores can be summarized into two scales, the physical and mental component summaries. All raw scale scores are converted linearly to a scale ranging from 0 to 100 (maximum). The higher the scores within this range, the higher the levels of functioning or well-being. Translation, validation, and norming of the Dutch-language version were performed by Aaronson et al.[18]

The SFSQ is used to determine syncope-related QoL. This questionnaire consists of 11 yes/no questions to assess syncope interference with a patient's life and three three-point Likert-scale questions assessing fear and worry with respect to syncope.[19] The impairment score is calculated in two steps. First, the number of areas in which syncope interfered with a patients' life (range 0–11) is divided by the number of areas that are applicable to that patient. Secondly, the obtained number is multiplied by 100, resulting in a score between 0 and 100, with 100 representing impairment in all areas that are applicable to patients. The three Likert-scale questions were linearly converted to a 0–100 scale and subsequently averaged to calculate a fear/worry score scaled from 0 to 100, with 100 indicating maximum fear and worry. The Syncope Dysfunction Score represents the averaged impairment score and fear/worry score. The higher this score, the worse the syncope-related QoL. In a previous study, the validity, reliability, and responsiveness of the Dutch version of the SFSQ have been determined.[20]

Power calculation

Based on data from the Physical Counterpressure Manoeuvres Trial (PC Trial), about 10% of VVS patients were expected to experience ≥3 syncopal and/or pre-syncopal recurrences despite non-pharmacological treatment including physical counterpressure manoeuvres during 18 months of follow-up.[4] In this patient group, we expected recurrence in 60% of patients during placebo treatment and in 20% of patients in the Midodrine group based on the available literature.[4,7,10] A cross-over trial with 22 patients receiving both Midodrine and placebo treatment would have a power of 80% to detect such a difference using the McNemar's test of equality of paired proportions with a 0.05 two-sided significance level.[4,21] Taking into account loss to follow-up, we aimed at including 25 patients in the cross-over trial. This means that a total of around 250 patients needed to be included at the start of the study to obtain a total of 25 patients with a insufficient response to initial, non-pharmacological treatment.

Statistical analysis

The primary end point of the study was the proportion of patients with syncopal recurrence during each 3-month treatment period. We calculated the difference in these proportions between Midodrine and placebo together with its 95% CI using the method of Newcombe of paired data.[22] Associated P values were based on the McNemar test for paired proportions. In addition, we compared the median number of recurrences of syncope and pre-syncope during each treatment period of 3 months. For patients with a follow-up period <3 months due to drop-out, we used the actual observed rate (median number of recurrences divided by actual follow-up time) to calculate the expected number of recurrences if the follow-up would have been 3 months. The difference in median number of syncopal and pre-syncopal episodes during each treatment period of 3 months was analysed using the Wilcoxon signed rank test. We also used the Wilcoxon signed rank test to compare QoL scores at the end of each treatment period. The proportion of patients with any side effects or trauma during Midodrine or placebo treatment was analysed in the same way as the proportion of patients with recurrent VVS. We used paired t-tests to compare blood pressures and heart rates of patients during Midodrine and placebo treatment.

Because of the low power of our study, we refrained from testing for a period effect and treatment-by-period interaction effect.[23,24] All data were analysed using SPSS 16.0 (SPSS, Chicago, IL, USA), except for the calculation of CIs for differences in paired proportions for which we used StatsDirect (Statsdirect Ltd., Altrincham, Cheshire, UK). We considered two-sided P values <0.05 as statistically significant.

Results

Inclusion of patients

We included 100 patients in the non-pharmacological part of the study (Figure 1). The frequency of syncope during the first year of non-pharmacological treatment in these patients was 75% lower than during the last year before treatment (median 1 (p25–p75: 0–3) vs. median 4 (p25–p75: 2–7); P < 0.001). The frequency of severe pre-syncopal recurrence was not significantly lower during non-pharmacological treatment than before this treatment [median 7 (p25–p75: 3–25) vs. median 8 (p25–p75: 2–43)]. No patients were lost to follow-up.

A total of 84 patients were assessed for inclusion in the trial. Sixteen patients were not assessed, mainly because the pre-specified sample size of the cross-over trial was already achieved when these patients were still in their non-pharmacological phase (n = 14 patients, Figure 1). Of the 84 patients assessed, 67 patients had experienced ≥3 syncopal and/or severe pre-syncopal recurrences during follow-up and were eligible for the cross-over trial. Cross-over treatment was not started in 39 of these patients because patients were content with their partial reduction in episodes or were not willing to take medication (n = 24), had a medical contra-indication at the start of the cross-over trial (n = 12), or for other reasons (n = 3). A total of 28 patients were randomized and started pharmacological treatment (Figure 1). Follow-up information for both Midodrine and placebo treatment was available for 23 out of
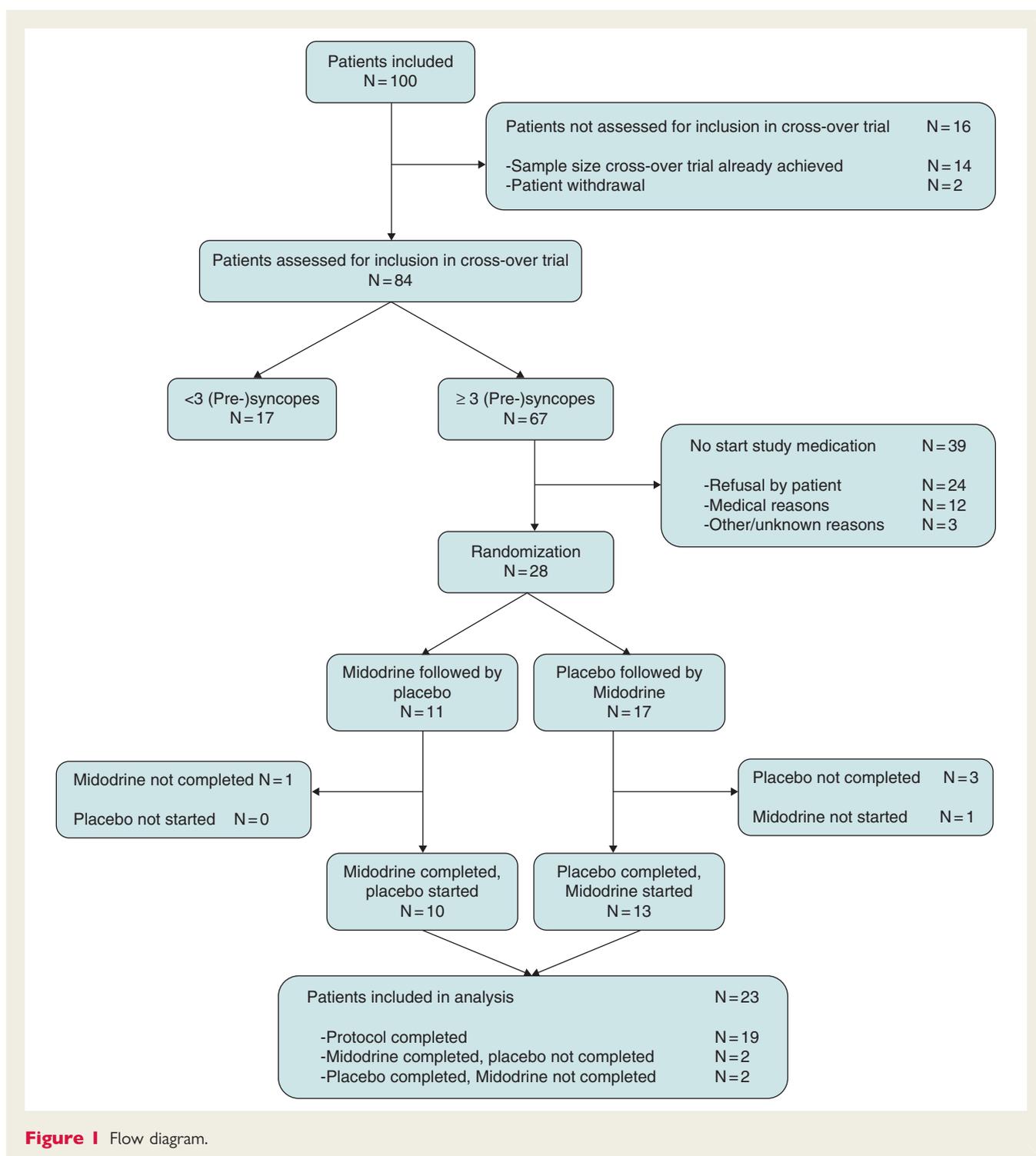
Figure 1 Flow diagram.

28 patients (*Figure 1*). The patient characteristics of the 23 patients who received pharmacological treatment did not differ significantly from those who did not receive pharmacological treatment (77 patients), except for age [mean standard deviation (SD): 31 (12) vs. 40 (14); *P* = 0.01], number of syncopal episodes during life at the start of non-pharmacological treatment (median 35 (p25−p75: 20−90) vs. 15 (p25−p75: 10−40); *P* = 0.003), and syncope burden during non-pharmacological treatment [median 6 (p25−p75: 0−18) vs. 0 (p25−p75: 0−2); *P* = 0.002] (*Table 1*). Of the 23 patients

in our analysis, 15 patients (65%) had experienced both syncopal and pre-syncopal recurrences during the initial non-pharmacological phase. The other patients (35%) had only experienced severe pre-syncopal recurrences. At baseline, in supine position the mean systolic and diastolic blood pressures (SD) in supine position were 118 (11) and 72 (8.2) mmHg. In standing position, the mean systolic and diastolic blood pressures were [SD; 118 (15) and 77 (10) mmHg, respectively), with the diastolic blood pressure being significantly different from supine (systolic *P* = 0.95 and diastolic *P* < 0.01,

Table 1 Patient characteristics

		Patients in medication trial	Patient not in medication trial
Number		23	77
Mean age (SD)		31 (12)	40 (14)
Male gender (%)		17%	39%
Race (%)			
Caucasian		91%	87%
Black		0%	6.5%
Asian		4.3%	6.5%
Hispanic		4.3%	0%
Number of syncopal episodes during life at start non-pharmacological treatment	Median (p25−p75)	35 (20−90)	15 (10−40)
Number of years with syncope at start non-pharmacological treatment	Median (p25−p75)	10 (5−17)	17 (6−27)
Syncope burden (number of syncopal episodes per year) at start non-pharmacological treatment	Median (p25−p75)	4 (2−30)	1 (1−5)
Syncope burden (number of syncopal episodes per year) during non-pharmacological treatment	Median (p25−p75)	6 (0−18)	0 (0−2)

p25, 25th percentile; p75, 75th percentile.

respectively). Heart rate in supine position was higher in standing position compared with supine position [mean (SD) 76 (14) vs. 67 (12); $P < 0.01$].

Treatment compliance was 88%. Treatment compliance did not differ significantly between Midodrine and placebo treatment (91 vs. 86%; $P = 0.17$).

Recurrences

The proportion of patients who experienced syncopal recurrence(s) was not significantly different during Midodrine and placebo treatment (48 vs. 65%; proportion difference: −17% (95% CI 36–3.8%); $P = 0.22$) (Table 2). Ten patients (43%) experienced syncopal recurrence during both Midodrine and placebo treatment, while five (22%) experienced syncopal recurrence only in the placebo period compared with one (4.3%) in the Midodrine period. The median number of syncopes per 3 months was 0 (p25−p75: 0−5) on Midodrine treatment and 1 (p25−p75: 0−7) on placebo treatment ($P = 0.57$). Nine patients (39%) experienced more syncopal episodes during 3 months of placebo treatment, while six patients (26%) experienced more syncopal episodes on Midodrine treatment. In the remaining eight patients (35%) syncopal recurrence was similar during both periods (Table 2).

Pre-syncope occurred in 74% of patients during Midodrine treatment and in 78% of patients during placebo treatment ($P > 0.99$) (Table 2). Fifteen patients (65%) experienced pre-syncopal recurrence during both Midodrine and placebo treatment. Two patients (8.7%) experienced pre-syncope recurrence only during Midodrine treatment compared with three (13%) patients only during placebo treatment. The median number of pre-syncopes per 3 months was 6 (p25−p75: 0−30) patients on Midodrine treatment and 8 (p25−p75: 1−52) patients on placebo treatment ($P = 0.90$). Nine patients (39%) experienced more pre-syncopal episodes during 3 months of placebo treatment, while 10 patients (43%) experienced more pre-syncopal

episodes on Midodrine treatment. In four (17%) patients the number of pre-syncopal recurrences was equal in both periods.

Blood pressures and heart rate in supine and standing position were similar in supine and standing position during Midodrine and placebo treatment, except for a small difference in heart rate in supine position [mean (SD) 68 (12) vs. 71 (12); $P = 0.03$] (Table 2). Patient-reported trauma due to (pre-)syncope did not differ significantly between Midodrine and placebo treatment (35 vs. 26%; $P = 0.50$) (Table 2).

Side effects

Side effects were reported by 57% of the patients during placebo treatment and by 48% during Midodrine treatment ($P = 0.75$; Table 2). During both Midodrine and placebo treatment patients reported a wide range of side effects. Headache, cold sensations, and nausea were the most frequently reported side effects during Midodrine treatment. Headache and fatigue/loss of energy were the most frequently reported side effects during placebo treatment.

Quality of life

Although QoL scores tended to be higher after Midodrine treatment, the Physical and Mental component summary of the SF-36 showed no statistically significant difference between treatments ($P = 0.24$ and $P = 0.20$, respectively; Table 3). Only the scores for the subscales bodily pain and mental health patients were significantly higher after treatment with Midodrine than after placebo treatment ($P = 0.02$ and $P = 0.01$, respectively). The Syncope Dysfunction Score of the SFSQ did not differ significantly after Midodrine or placebo treatment (mean score of 42 vs. 43; $P = 0.46$; Table 4).

Table 2 Occurrence of (pre-)syncopes, trauma and side effects during pharmacological treatment with Midodrine and placebo of the 23 patients included in the analysis

		Midodrine treatment	Placebo treatment	Difference (95% CI)	P value
Syncopal recurrence (%)		48%	65%	−17% (−36% to 3.8%)	0.22
Syncopal episodes per 3 months	Median (p25–p75)	0 (0–5)	1 (0–7)	–	0.57
Pre-syncopal recurrence (%)		74%	78%	−4.3% (−16% to 25%)	>0.99
Pre-syncopal episodes per 3 months	Median (p25–p75)	6 (0–30)	8 (1–52)	–	0.90
Supine position					
Systolic blood pressure	Mean (SD)	117 (9.9)	116 (10)	2.65 (−0.5–5.8)	0.37
Diastolic blood pressure	Mean (SD)	72 (7.4)	72 (6.4)	1.7 (− 1.8–5.1)	0.79
Heart rate	Mean (SD)	68 (12)	71 (12)	−3.4 (−7.3–0.5)	0.03
Standing position					
Systolic blood pressure	Mean (SD)	75 (7.5)	75 (8.0)	1.4 (−2.4–5.1)	0.91
Diastolic blood pressure	Mean (SD)	75 (13)	74 (12)	−1.7 (−8.1–4.6)	0.57
Heart rate	Mean (SD)	117 (9.4)	114 (8.5)	3.1 (−1.2–7.5)	0.08
Trauma due to (pre-)syncope (%)		35%	26%	−8.7% (−23% to 5.7%)	0.50
Side effects of pharmacological treatment (%)		48%	57%	−8.7% (−34% to 18%)	0.75

p25, 25th percentile; p75, 75th percentile; CI, confidence interval.

Table 3 General quality of life assessed with the Short Form-36 questionnaire after pharmacological treatment with Midodrine and placebo.[a]

SF-36 subscale	Mean score after Midodrine treatment (SD)	Mean score after placebo treatment (SD)	P value
Physical functioning	68 (28)	66 (26)	0.50
Role functioning physical	47 (42)	35 (36)	0.06
Bodily pain	69 (28)	56 (31)	0.02
General health	48 (20)	45 (20)	0.20
Vitality	46 (20)	42 (21)	0.78
Social functioning	63 (21)	57 (30)	0.43
Role functioning emotional	62 (46)	48 (44)	0.20
Mental health	66 (21)	58 (24)	0.01
Physical component summary	43 (12)	41 (11)	0.24
Mental component summary	42 (13)	38 (14)	0.20

SD, standard deviation.
[a]General quality of life can vary within a range of 0 and 100 (maximum). The higher the scores for the Physical and Mental Component Summary of the SF-36 questionnaire, the better the general quality of life.

Table 4 Quality of life assessed with the Syncope Functional Status Questionnaire after pharmacological treatment with Midodrine and placebo[a]

SF-36 subscale	Mean score after Midodrine treatment (SD)	Mean score after placebo treatment (SD)	P value
Impairment score	39 (34)	43 (35)	0.24
Fear/worry score	44 (25)	44 (25)	0.82
Syncope Dysfunction score	42 (27)	43 (27)	0.46

Abbreviations as in *Table 3*.
[a]Syncope-related quality of life can vary within a range of 0 and 100 (maximum). The lower the scores with respect to the Syncope Dysfunction Score of the SFSQ, the better the syncope-related quality of life.

Discussion

To our knowledge, this is the first study examining the effectiveness of *additional* Midodrine treatment in patients with VVS not or unsatisfactory responding to non-pharmacological treatment including physical counterpressure manoeuvres. We were unable to demonstrate the effectiveness of Midodrine treatment in these patients. Our findings differ from previous trials, where Midodrine treatment was found to be an effective treatment for reflex syncope.[7,9–11,25–30] There are several reasons that could explain the differences in results between our study and previous studies.

First, the criteria for inclusion of patients differed markedly. In our study, pharmacological treatment was only started if patients had experienced at least three syncopal and/or pre-syncopal recurrences during non-pharmacological treatment including physical counterpressure manoeuvres. This approach is in line with current recommendations in the ESC-guidelines for the diagnosis and management of syncope.[1] In previous studies, however, pharmacological treatment was started directly after presentation, usually without prior non-pharmacological treatment.[7,9–11,25,27,28,30] As pharmacological treatment was only started in patients with frequent (pre-)syncopal recurrences during non-pharmacological treatment, we

selected patients with more severe forms of VVS. Since we were unable to demonstrate the effectiveness of Midodrine treatment, our study results indicate that these patients are less susceptive to this treatment. This might be due to psychological distress associated with VVS, as syncope was found to occur more frequently in VVS patients who experienced higher levels of psychogenic distress.[31,32] However, also other factors could be involved.

There are differences across previous studies in the way the effectiveness of Midodrine treatment was determined. In some of the previous studies there was no control group.[25–30] Since, it is known that patients with VVS present themselves more often to healthcare after a recent worsening of their symptoms,[33] a return to the usual frequency of recurrence can be expected, no matter what kind of treatment is being prescribed. Placebo-controlled trials with Midodrine are, therefore, necessary to examine whether Midodrine treatment has any significant therapeutic benefit above the expected natural decrease in frequency of recurrence after diagnosis.

In three out of four studies on Midodrine, which were included in a systematic review about the effectiveness of alpha-adrenergic treatment for VVS, HUT testing was used as one of the outcome measures to determine treatment effectiveness.[7–9,11] The reliability of tilt test outcomes is, however, low and does not provide information about the effectiveness in daily life.[1,34,35] Since HUT testing is not a reliable diagnostic method to determine treatment effectiveness,[1,36] we did not use HUT tests to determine the effectiveness of treatment. Instead, we contacted patients regularly to obtain information about the recurrence of (pre-)syncope during follow-up.

Side effects

In previous studies, gastro-intestinal discomfort, nausea, pilomotor reactions (goose bumps, tingling, and chills), and headache associated with hypertension have been reported as side effects in 4–64%[9,25] of the patients.[9–11,25,28,30] Although the occurrence of side effects in our study is well within this range, surprisingly, in our study the number of patients who reported side effects was higher during placebo treatment (57%) compared with Midodrine treatment (48%). One reason for the relatively high percentage of side effects might be that we asked patients at every follow-up consultation whether they had experienced side effects. Therefore, patients were very likely to report side effects if they had experienced any complaints. If we would not have asked patients at every follow-up visit whether they had experienced any side effects, the occurrence of side effects probably would have been much lower in our study. Another reason for the relatively high occurrence of side effects might be that patients with frequent recurrences of VVS are very much concerned with their body. This concern about their body might result in a relatively high perceived severity of disease, as was shown in patients with irritable bowel syndrome.[37] Owing to disease-related fears and concerns, patients with frequent recurrences of VVS might be more likely to classify any uncomfortable feelings as side effects. Although the differences in syncopal and pre-syncopal recurrence rate are not statistically significant, the absolute values of the syncopal and pre-syncopal recurrence rate were lower during Midodrine treatment compared with placebo treatment. If patients do not experience beneficial effects of a pharmacological treatment, they might be more likely to experience side effects. This might explain why the occurrence of side effects during placebo treatment was higher than during Midodrine treatment.

Quality of life (QoL)

We observed no statistically significant differences with respect to QoL between Midodrine and placebo treatment as additional treatment measures to non-pharmacological treatment for VVS. In our view, this finding is logical, since the differences with respect to syncopal and pre-syncopal recurrence of VVS were also not significantly different between Midodrine and placebo treatment.

Limitations

A few issues have to be considered when interpreting the results of this trial. First, a low number of patients eligible for study-medication actually received pharmacological cross-over treatment (only 28 out of 67 patients). The main reason for not starting medication was that patients were content with the partial reduction in syncopal recurrences during the non-pharmacological treatment or the fear of side effects. These content patients probably have experienced a total number of ≥3 pre-syncopal and/or syncopal episodes in a relatively long time period. For this reason, these patients might be less willing to receive pharmacological treatment compared with patients who experienced this total number of episodes in a relatively short time period. Therefore, patients with more severe VVS probably were more likely to participate in our study.

In our study, syncopal and pre-syncopal recurrences were not statistically different between a Midodrine and placebo treatment period of 3 months. If the treatment periods would have been longer, we might have observed statistical differences between Midodrine and placebo treatment. However, we would also expect a higher drop-out of the study in that case. If patients have not received cross-over treatment it is impossible to compare syncopal and pre-syncopal recurrence during Midodrine and placebo treatment in a patient. Moreover, one can argue whether it makes sense to start pharmacological treatment with possible side effects if the effectiveness of this treatment might only be shown after 3 months.

In previous studies examining the effectiveness of Midodrine treatment for VVS, the daily dosage of Midodrine for adults varied between 5 and 45 mg per day.[9,10,25,26,28–30] The dosage of Midodrine in our study was 10 mg per day (5 mg twice daily). A higher dosage could have been more effective, although in earlier studies significant haemodynamic effects occurred on application of a Midodrine dosage of 5 mg, both in normal subjects and patients with reflex syncope.[7,38] In our cross-over trial, we included only a relatively limited number of patients because we expected a substantial difference in effectiveness based on earlier studies. In addition, the use of a cross-over design increases the power to detect a difference as the analysis can be based on paired data. Our results clearly indicate that the difference in effectiveness (if any) was much smaller than expected. However, small differences in effectiveness cannot be excluded based on this trial.

Conclusion

We observed no statistically significant differences between additional Midodrine and placebo treatment with respect to (pre-)syncopal recurrence, indicating that the effectiveness of Midodrine treatment in patients not responding to non-pharmacological treatment was much smaller than expected. Therefore, we do not recommend the routine use of additional treatment with Midodrine in these patients. Other treatment strategies need to be developed and examined in these patients.

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