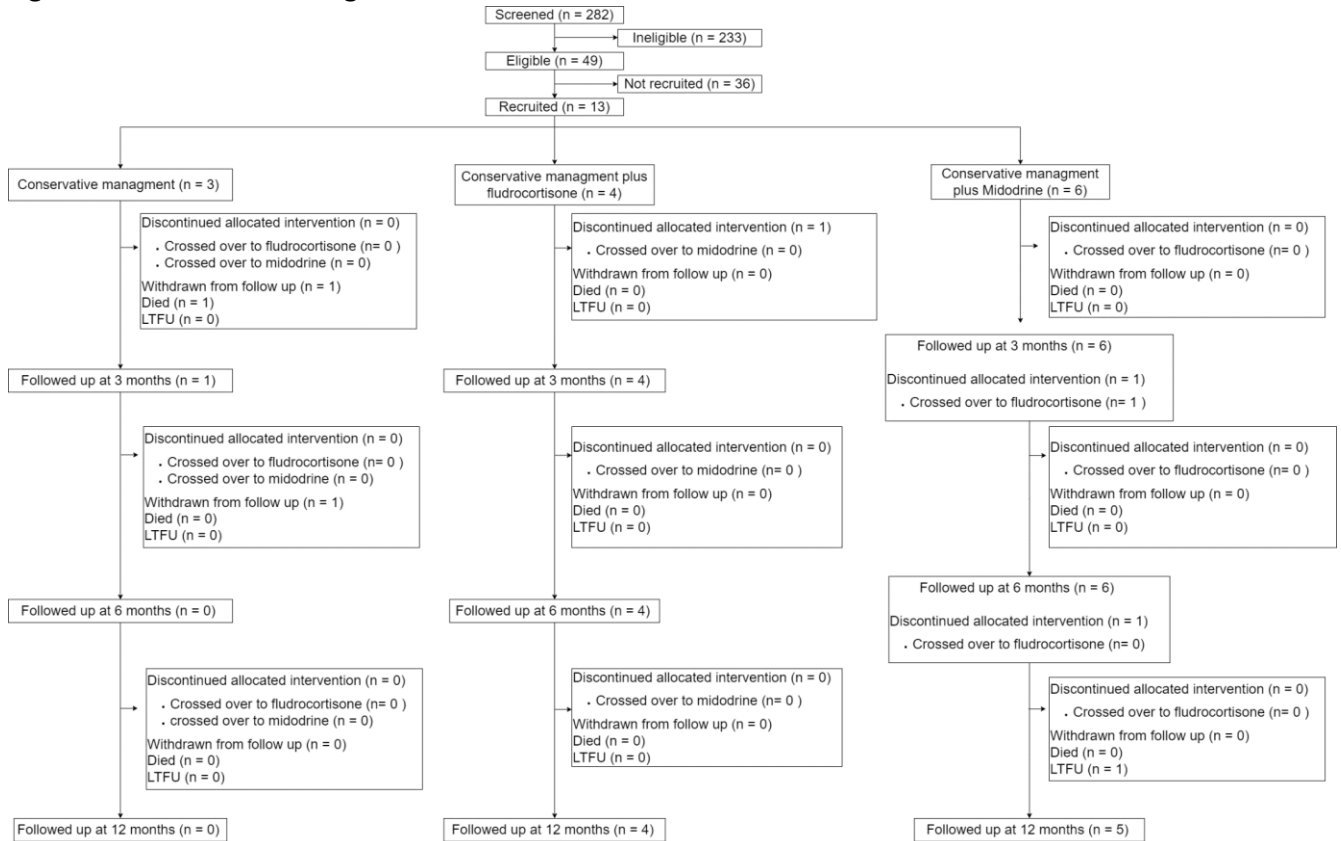


Control, Fludrocortisone or Midodrine for the treatment of Orthostatic Hypotension: A Randomised Controlled Trial

Trial registration: ISRCTN87213295

Figure 1: CONSORT flow diagram



LTFU: Lost to follow-up.

Table 1: Baseline characteristics

	Conservative management	Conservative management plus fludrocortisone	Conservative management plus midodrine	Total
	(N = 3)	(N = 4)	(N = 6)	(N = 13)
Age				
Mean (SD)	75.3 (14.6)	70.3 (12.0)	75.0 (6.0)	73.6 (9.6)
Min, Max	59, 87	53, 80	70, 84	53, 87
<80 years	1 (33%)	3 (75%)	4 (67%)	8 (62%)
≥80	2 (67%)	1 (25%)	2 (33%)	5 (38%)
Sex at birth				
Female	2 (67%)	1 (25%)	4 (67%)	7 (54%)
Male	1 (33%)	3 (75%)	2 (33%)	6 (46%)
Ethnicity				
Any white background	3 (100%)	4 (100%)	6 (100%)	13 (100%)
BMI				
No. with data	3 (100%)	3 (75%)	6 (100%)	12 (92%)
Mean (SD)	22.5 (6.1)	26.1 (2.5)	23.8 (1.5)	24.1 (3.3)
Median (Range)	22.4 (16.4, 28.7)	25.8 (23.7, 28.7)	24.2 (21.7, 26.0)	24.2 (16.4, 28.7)
OHQ score				
Mean (SD)	6.8 (1.7)	6.8 (1.6)	6.0 (1.6)	6.4 (1.5)
Median (Range)	7.5 (4.9, 8.0)	6.7 (5.1, 8.8)	5.9 (3.8, 8.7)	6.2 (3.8, 8.8)
NEADL score				
Mean (SD)	13.7 (6.0)	16.0 (9.4)	14.2 (5.3)	14.6 (6.4)
Median (Range)	13.0 (8.0, 20.0)	20.0 (2.0, 22.0)	15.0 (6.0, 21.0)	17.0 (2.0, 22.0)
Blood pressure				
How was the BP obtained?				
Study visit	2 (67%)	2 (50%)	2 (33%)	6 (46%)
Other medical records	1 (33%)	1 (25%)	4 (67%)	6 (46%)
Self-assessed at home	0 (0%)	1 (25%)	0 (0%)	1 (8%)
Supine Blood Pressure				
Systolic				
Mean (SD)	134.7 (20.7)	128.5 (26.2)	141.3 (22.9)	135.8 (22.3)
Median (Range)	131 (116, 157)	129 (96, 160)	151 (102, 160)	132 (96, 160)
Diastolic				
Mean (SD)	74.7 (4.0)	70.5 (24.6)	74.5 (10.6)	73.3 (14.3)
Median (Range)	77 (70, 77)	69 (42, 102)	79 (53, 80)	77 (42, 102)
Lowest standing BP				
Systolic				
Mean (SD)	88.3 (23.6)	88.8 (10.6)	105.0 (18.4)	96.2 (18.3)
Median (Range)	80 (70, 115)	93 (73, 96)	105 (80, 130)	94 (70, 130)
Diastolic				
Mean (SD)	60.0 (20.9)	61.5 (13.0)	65.3 (8.4)	62.9 (12.2)
Median (Range)	50 (46, 84)	62 (46, 77)	66 (55, 76)	60 (46, 84)

	Conservative management	Conservative management plus fludrocortisone	Conservative management plus midodrine	Total
	(N = 3)	(N = 4)	(N = 6)	(N = 13)
Postural blood pressure drop				
Systolic				
Mean (SD)	46.3 (4.5)	39.8 (19.6)	36.3 (18.2)	39.7 (15.9)
Median (Range)	46 (42, 51)	34 (23, 68)	34.5 (11, 64)	39 (11, 68)
Diastolic				
Mean (SD)	14.7 (19.6)	9.0 (23.6)	9.2 (10.4)	10.4 (15.9)
Median (Range)	20 (-7, 31)	-1 (-6, 44)	7.5 (-6, 22)	7 (-7, 44)
Disease aetiology				
Neurogenic OH	1 (33%)	1 (25%)	3 (50%)	5 (38%)
Non-neurogenic OH	2 (67%)	3 (75%)	3 (50%)	8 (62%)
Medical history				
Diabetes	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pure Autonomic Failure	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Parkinson's disease	1 (33%)	0 (0%)	3 (50%)	4 (31%)
<i>Disease duration</i>				
<1 year	0 (0%)	NA	0 (0%)	0 (0%)
1-5 years	1 (100%)	NA	1 (33%)	2 (50%)
>5 years	0 (0%)	NA	2 (67%)	2 (50%)
Multiple System Atrophy	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Dementia with Lewy bodies	0 (0%)	0 (0%)	0 (0%)	0 (0%)
UPDRS score	(N = 1)	(N = 0)	(N = 3)	(N = 4)
Part I				
Mean (SD)	31.0 (.)	NA	15.3 (16.2)	19.3 (15.4)
Median (Range)	31 (31, 31)	NA	7 (5, 34)	19 (5, 34)
Part II				
Mean (SD)	17.0 (.)	NA	16.3 (0.6)	16.5 (0.6)
Median (Range)	17 (17, 17)	NA	16 (16, 17)	17 (16, 17)
Part IV				
Mean (SD)	0.0 (.)	NA	5.0 (7.0)	3.8 (6.2)
Median (Range)	0 (0, 0)	NA	2 (0, 13)	1 (0, 13)

SD: Standard deviation; BMI: Body mass index; OHQ: Orthostatic Hypotension Questionnaire; NEADL: Nottingham Extended Activities of Daily Living; BP: Blood pressure; OH: Orthostatic hypotension; UPDRS: Unified Parkinson's disease rating scale

Table 2: Primary outcome – change in OHQ score from baseline

	Follow-up scores			Change from baseline		
	Conservative management	Conservative management plus fludrocortisone	Conservative management plus midodrine	Conservative management	Conservative management plus fludrocortisone	Conservative management plus midodrine
Baseline	N= 3	N = 4	N = 6	NA		
Mean (SD)	6.8 (1.7)	6.8 (1.6)	6.0 (1.6)	NA		
Median (Range)	7.5 (4.9, 8.0)	6.7 (5.1, 8.8)	5.9 (3.8, 8.7)	NA		
Month 3	N= 1	N = 4	N = 6	N= 1	N = 4	N = 6
Mean (SD)	0.6 (.)	2.6 (1.7)	3.6 (3.0)	-6.9 (.)	-4.2 (2.2)	-2.4 (3.6)
Median (Range)	0.6 (0.6, 0.6)	3.2 (0.1, 4.0)	4.2 (0.0, 7.3)	-6.9 (-6.9, -6.9)	-3.9 (-7.0, -1.9)	-2.1 (-8.5, 1.3)
Month 6	N= 0	N = 4	N = 6	N= 0	N = 4	N = 6
Mean (SD)	NA	2.3 (0.9)	4.3 (1.9)	NA	-4.5 (2.0)	-1.7 (2.0)
Median (Range)	NA	2.5 (1.2, 3.3)	4.8 (1.6, 6.3)	NA	-5.0 (-6.0, -1.8)	-2.0 (-4.4, 0.9)
Month 12	N= 0	N = 4	N = 5	N= 0	N = 4	N = 5
Mean (SD)	NA	1.9 (1.6)	4.2 (2.4)	NA	-4.9 (2.6)	-1.3 (2.7)
Median (Range)	NA	1.9 (0.0, 3.8)	3.6 (1.2, 7.5)	NA	-5.6 (-7.2, -1.3)	-0.4 (-4.8, 2.2)

Table 3: Secondary outcomes – NEADL, nadir standing blood pressure, postural blood pressure drop

	Value at follow-up visit			Change from baseline		
	Conservative management	Conservative management plus fludrocortisone	Conservative management plus midodrine	Conservative management	Conservative management plus fludrocortisone	Conservative management plus midodrine
NEADL score						
Baseline	(N = 3)	(N = 4)	(N = 6)	NA		
Mean (SD)	13.7 (6.0)	16.0 (9.4)	14.2 (5.3)			
Median (Range)	13.0 (8.0, 20.0)	20.0 (2.0, 22.0)	15.0 (6.0, 21.0)			
Month 3	(N = 1)	(N = 4)	(N = 6)	(N = 1)	(N = 4)	(N = 6)
Mean (SD)	2.0 (.)	18.3 (2.2)	13.8 (7.3)	-6.0 (.)	2.3 (9.0)	-0.3 (4.1)
Median (Range)	2.0 (2, 2)	18.0 (16, 21)	15.0 (5.0, 21.0)	-6.0 (-6.0, -6.0)	0.0 (-6.0, 15.0)	0.5 (-8.0, 3.0)
Month 6	(N = 0)	(N = 4)	(N = 6)	(N = 0)	(N = 4)	(N = 6)
Mean (SD)	NA	19.3 (1.5)	13.2 (6.6)	NA	3.3 (8.8)	-1.0 (3.2)
Median (Range)	NA	19.0 (18.0, 21.0)	14.5 (5.0, 20.0)	NA	0.5 (-4.0, 16.0)	-0.5 (-7.0, 2.0)
Month 12	(N = 0)	(N = 4)	(N = 5)	(N = 0)	(N = 4)	(N = 5)
Mean (SD)	NA	19.3 (1.0)	12.8 (7.6)	NA	3.3 (8.7)	-0.8 (3.7)
Median (Range)	NA	19.5 (18.0, 20.0)	9.0 (6.0, 22.0)	NA	0.0 (-3.0, 16.0)	-1.0 (-4.0, 5.0)
Nadir standing blood pressure						
Baseline	(N = 3)	(N = 4)	(N = 6)	NA		
Systolic						
Mean (SD)	88.3 (23.6)	88.8 (10.6)	105.0 (18.4)			
Median (Range)	80 (70, 115)	93 (73, 96)	105 (80, 130)			
Diastolic						
Mean (SD)	60 (20.9)	61.5 (13.0)	65.3 (8.4)			
Median (Range)	50 (46, 84)	62 (46, 77)	66 (55, 76)			
Month 3	(N = 1)	(N = 4)	(N = 6)	(N = 1)	(N = 4)	(N = 6)
Systolic						
Mean (SD)	59.0 (.)	112.0 (22.7)	114.2 (31.4)	-21.0 (.)	23.3 (30.5)	9.2 (29.1)
Median (Range)	59 (59, 59)	115 (83, 135)	106 (77, 171)	-21 (-21, -21)	21 (-11, 62)	10 (-33, 52)
Diastolic						
Mean (SD)	26.0 (.)	72.0 (11.0)	66.2 (14.8)	-20.0 (.)	10.5 (18.7)	0.8 (16.3)
Median (Range)	26 (26, 26)	76 (56, 80)	71 (46, 85)	-20 (-20, -20)	9 (-9, 34)	4 (-25, 18)
Month 6	(N = 0)	(N = 4)	(N = 6)	(N = 0)	(N = 4)	(N = 6)
Systolic						
Mean (SD)	NA	112.3 (23.4)	131.3 (32.2)	NA	23.5 (27.0)	26.3 (21.8)
Median (Range)	NA	110 (89, 141)	118 (99, 179)	NA	26 (-5, 48)	30 (-1, 60)
Diastolic						
Mean (SD)	NA	74.0 (18.5)	74.0 (17.7)	NA	12.5 (18.5)	8.7 (14.2)
Median (Range)	NA	71 (58, 97)	75 (53, 102)	NA	10 (-5, 35)	5 (-7, 26)
Month 12	(N = 0)	(N = 4)	(N = 5)	(N = 0)	(N = 4)	(N = 5)
Systolic						
Mean (SD)	NA	107.5 (28.3)	124.4 (33.4)	NA	18.8 (32.4)	18.4 (27.2)
Median (Range)	NA	105 (80, 140)	112 (97, 182)	NA	20 (-14, 49)	17 (-8, 63)
Diastolic						
Mean (SD)	NA	72.8 (17.3)	66.4 (10.8)	NA	11.3 (18.6)	-0.2 (10.2)
Median (Range)	NA	73 (54, 92)	66 (52, 82)	NA	7 (-4, 36)	-7 (-8, 11)

	Value at follow-up visit			Change from baseline		
	Conservative management	Conservative management plus fludrocortisone	Conservative management plus midodrine	Conservative management	Conservative management plus fludrocortisone	Conservative management plus midodrine
Postural blood pressure drop						
Baseline	(N = 3)	(N = 4)	(N = 6)			
Systolic				NA		
Mean (SD)	46.3 (4.5)	39.8 (19.6)	36.3 (18.2)			
Median (Range)	46 (42, 51)	34 (23, 68)	35 (11, 64)			
Diastolic						
Mean (SD)	14.7 (19.6)	9.0 (23.6)	9.2 (10.4)			
Median (Range)	20 (-7, 31)	-1 (-6, 44)	8 (-6, 22)			
Month 3	(N = 1)	(N = 4)	(N = 6)	(N = 1)	(N = 4)	(N = 6)
Systolic						
Mean (SD)	39.0 (.)	22.8 (28.7)	21.8 (22.2)	-12.0 (.)	-17.0 (17.8)	-14.5 (23.3)
Median (Range)	39 (39, 39)	23 (-8, 54)	22 (-7,57)	-12 (-12, -12)	-22 (-31, 7)	-15 (-46, 10)
Diastolic						
Mean (SD)	39.0 (.)	10.8 (13.5)	5.8 (15.9)	8.0 (.)	1.8 (20.2)	-3.3 (19.9)
Median (Range)	39 (39, 39)	11 (-4, 25)	5 (-14, 28)	8 (8, 8)	5 (-25, 23)	-4 (-28, 21)
Month 6	(N = 0)	(N = 4)	(N = 6)	(N = 0)	(N = 4)	(N = 6)
Systolic						
Mean (SD)	NA	35.3 (25.6)	15.2 (31.8)	NA	-4.5 (19.8)	-21.2 (31.6)
Median (Range)	NA	37 (3, 65)	25 (-31, 53)	NA	3 (-33, 9)	-13 (-61, 7)
Diastolic						
Mean (SD)	NA	11.8 (18.2)	4.5 (18.8)	NA	2.8 (15.3)	-4.7 (21.8)
Median (Range)	NA	15 (-12, 30)	8 (-28, 25)	NA	3 (-14, 19)	-7 (-32, 31)
Month 12	(N = 0)	(N = 4)	(N = 5)	(N = 0)	(N = 4)	(N = 5)
Systolic						
Mean (SD)	NA	32.0 (22.3)	18.2 (22.8)	NA	-7.8 (18.1)	-20.0 (19.6)
Median (Range)	NA	34 (4, 57)	12 (-6, 46)	NA	-4 (-32, 8)	-26 (-45, 1)
Diastolic						
Mean (SD)	NA	7.0 (12.2)	11.0 (13.2)	NA	-2.0 (13.8)	-1.2 (12.1)
Median (Range)	NA	6 (-6, 22)	13 (-3, 26)	NA	3 (-22, 9)	-7 (-10, 19)

Table 4: Adverse events, falls and syncope

	Conservative management	Conservative management plus fludrocortisone	Conservative management plus midodrine
Falls	(N = 0)	(N = 4)	(N = 6)
Number of events			
0	N/A	3 (75%)	1 (17%)
1	N/A	0 (0%)	0 (0%)
2	N/A	1 (25%)	2 (33%)
≥3	N/A	0 (0%)	3 (50%)
Event rate			
Total number of events	N/A	2	46
Total observation time (years)	N/A	4.2	5.4
Incidence rate (95% CI)	N/A	0.5 (0.1, 1.7)	8.9 (6.3, 11.4)
Fallers (≥ 1 fall)	N/A	1 (25%)	5 (83%)
Time to first fall			
< 3months	N/A	1 (100%)	4 (80%)
3-6 months	N/A	0 (0%)	1 (20%)
Syncopal events	(N = 0)	(N = 4)	(N = 6)
Number of events			
0	N/A	4 (100%)	5 (83%)
≥1	N/A	0 (0%)	1 (17%)
Total number of events	N/A	0	9
Adverse events (AEs)*	(N = 3)	(N = 5)	(N = 6)
No. of AEs reported per participant			
0	1 (33%)	1 (20%)	2 (33%)
1	1 (33%)	1 (20%)	2 (33%)
2-3	1 (33%)	2 (40%)	2 (33%)
>3	0 (0%)	1 (20%)	0 (0%)
Median (Range)	1 (0, 3)	2 (0, 11)	1 (0, 2)
Worst grade AE reported per participant			
No AE	1 (33%)	1 (20%)	2 (33%)
Mild	0 (0%)	2 (40%)	4 (67%)
Moderate	0 (0%)	0 (0%)	0 (0%)
Severe	2 (67%)	2 (40%)	0 (0%)
Adverse reactions (ARs)*	(N = 3)	(N = 5)	(N = 6)
No. of ARs reported per participant			
0	3 (100%)	5 (100%)	3 (50%)
1	0 (0%)	0 (0%)	1 (17%)
2	0 (0%)	0 (0%)	2 (33%)
Worst grade AR reported per participant			
No AR	3 (100%)	5 (100%)	3 (50%)
Mild	0 (0%)	0 (0%)	3 (50%)
Serious adverse events (SAEs)*	(N = 3)	(N = 5)	(N = 6)
Number of SAEs reported per participant			
0	1 (33%)	3 (40%)	6 (100%)
1	1 (33%)	1 (20%)	0 (0%)
≥2	1 (33%)	1 (20%)	0 (0%)
Range	0, 3	0, 4	0, 0

*Data reported out of number exposed to each treatment, allowing for crossover between interventions