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Prevalence of orthostatic hypotension in Parkinson's disease: A systematic review and meta-analysis

Daan C. Velseboer^{a,*}, Rob J. de Haan^b, Wouter Weling^c, David S. Goldstein^d, and Rob M.A. de Bie^a

^aDepartment of Neurology, Academic Medical Center, Amsterdam, The Netherlands ^bClinical Research Unit, Academic Medical Center, Amsterdam, The Netherlands ^cDepartment of Internal Medicine, Academic Medical Center, Amsterdam, The Netherlands ^dClinical Neurocardiology Section, Clinical Neurosciences Program, Division of Intramural Research, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA

Abstract

Background—Although orthostatic hypotension (OH) is recognized as one of the main non-motor symptoms of Parkinson's disease (PD), there is inconsistent evidence about the prevalence of OH in PD. To estimate the prevalence of OH in PD more precisely we conducted a systematic review of the literature.

Methods—From PubMed and Embase searches with predefined inclusion criteria, we identified studies published up till December 2009. Prevalence numbers from studies were pooled using a non-linear random-effects meta-analysis.

Results—We found 25 studies from which the prevalence of OH could be calculated. The pooled estimate of the point prevalence of OH in PD was 30.1% (95% CI: 22.9% to 38.4%). We found a large statistical heterogeneity between studies which could not be reduced by several subgroup analyses.

Conclusions—The estimated prevalence of OH in PD is 30%. However, due to the large heterogeneity between studies this pooled estimate should be interpreted with caution. More data from unselected population-based cohorts are needed.

Keywords

Autonomic diseases; Orthostatic hypotension; Parkinson's disease; Systematic review; Prevalence studies

1. Introduction

In advanced Parkinson's disease (PD), non-motor symptoms may be the major determinant of disability [1]. Orthostatic hypotension (OH) is one of the non-motor features in PD. It is

*Corresponding author. Department of Neurology, Room H2-225, Academic Medical Center, Meibergdreef 9, PO Box 22660, 1100DD Amsterdam, The Netherlands. Tel.: +31205663842; fax: +31 205669374. d.c.velseboer@amc.uva.nl (D.C. Velseboer).

thought to be the result of degeneration of the peripheral autonomic nervous system as part of the disease progress [2]. These abnormalities lead to an inadequate response to the gravitational force on the effective circulatory volume during standing due to defective vasoconstriction and excess venous pooling of blood [3]. Symptoms of OH mainly result from cerebral and retinal hypoperfusion and include dizziness, faintness, seeing black spots, and may even be accompanied by a transient loss of consciousness [4]. The occurrence of symptoms is directly related to the extent of the blood pressure drop, but autoregulation of the cerebral vasculature and baseline supine blood pressure probably also play a role. This hypothesis is supported by data showing that about one-third of patients with a systolic blood pressure drop of 60 mmHg or more during tilt-table testing are completely asymptomatic during the test [5].

By consensus, OH has been defined as a fall of 20 mmHg systolic or 10 mmHg diastolic blood pressure by 3 min of active standing or head up tilt [6]. Recently, the consensus-statement has been revised and a systolic fall of 30 mmHg was suggested for patients with an abnormally high supine blood pressure [7]. OH can be a debilitating problem and an association with increased mortality was shown for the general population [8]. Over recent decades, awareness of the impact of OH in PD has increased and consequently more research on this topic has come available. Furthermore, comprehensive reviews have been published concerning pathophysiology, diagnosis, and management of OH in PD [2,9]. Despite the increasing amount of research concerning this subject, the prevalence of OH in PD stated in the literature has a wide range; *i.e.*, 10–58% [10–12]. Accordingly, we conducted a systematic review of the literature in order to estimate the prevalence of OH in PD more precisely.

2. Methods

2.1. Literature search

We searched the electronic databases Medline and Embase using the entire time scale up to December 2009. The terms “Parkinson’s disease”, “Parkinson disease”, and “parkinsonism” were combined with “orthostatic hypotension” and “orthostatic intolerance”. The full search strategy is available in the Data supplement.

2.2. Study selection

After combining the search results, a list of titles and abstracts was evaluated by two independent reviewers (DCV and RMA dB) for eligible studies. Studies were selected according to the following inclusion criteria: (1) the study was written in English, French, German or Spanish; (2) the study investigated the number or proportion of subjects with OH in a sample of PD patients, either as a primary objective or a secondary objective; and (3) the study reported original data which were derived from retrospective, cross-sectional, or prospective cohort research. For inclusion of a paper, it was necessary that the diagnosis of OH was based on blood pressure measurements. Papers were not selected if the diagnosis was made by history taking solely. The studies that investigated the presence of OH in more than one underlying disorder (*e.g.*, idiopathic PD, Multiple System Atrophy and Progressive Supranuclear Palsy), were only included if the results for the subgroup of PD patients were

described separately. In that case, we only used the results for the PD patients. Papers that used the term Parkinsonism to describe the patient population without further specifying whether the patients had idiopathic PD were excluded.

A study was excluded if it concerned a case-report, a drug trial or if it was designed in a case-control manner, where PD patients were included on the basis of presence or absence of autonomic symptoms. In studies with overlapping data sets, we selected the study with the largest sample size. In case of doubt or disagreement between the reviewers, the full paper was retrieved.

2.3. Data extraction and assessment of methodological quality

Full reports were evaluated independently by two reviewers (DCV and RMAdB) using a standard checklist. From eligible studies the number of patients with PD and the number of PD patients with OH was extracted, as were the mean age at examination and mean duration of disease. If mean disease duration was not stated, we calculated it by subtracting the age at onset from the age at examination, where possible. For potential subgroup analyses we extracted data on type of patient population (tertiary vs. non-tertiary care) and definition of OH used, as we hypothesized that these factors would influence the prevalence of OH. We performed an assessment of study quality using a predefined set of eight criteria concerning the internal and external validity of the study. The criteria were based upon general recommendations for reporting on observational studies [13], and several methodological instruments developed for systematic reviews of prevalence studies [14–16]. Criteria were adapted and modified for the purpose of this review. If a study fulfilled the item, one point was awarded. If it was unclear whether the study fulfilled the item, no point was awarded. All items were assumed to be of equal importance and were not weighted. Studies with a score of 0–3 were classified as “low quality” reports and those with a methodological score of 4–8 as “high quality”. The exact checklist with criteria is given in the Data supplement. We used two of the eight items for separate subgroup analyses. The first item assessed whether the primary objective of the study was to investigate the prevalence of OH in PD, the second item assessed the risk of selection bias. Studies in which the patient sample was stated as random or consecutive, without the use of stringent inclusion or exclusion criteria were judged as having a low risk of selection bias. These criteria were used for separate subgroup analyses, as we hypothesized that heterogeneity between studies would be lower in unselected patient groups. Results were compared and discrepancies between the two reviewers were resolved in a meeting.

2.4. Statistical analysis

For each study, patient and study characteristics and prevalence of OH were summarized using descriptive statistics. Heterogeneity between the studies was estimated by calculating the I^2 -statistic. The I^2 index reflects the percentage of total variation across studies that is due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, and values of 25%, 50%, and 75% suggest low, moderate, and high degrees of heterogeneity [17,18]. Pooled prevalence rates accounting for interstudy variation were analyzed using a non-linear random effects model, implemented (proc nlmixed) in SAS version 9.1 (SAS

Institute Inc, Cary, NC). Statistical uncertainties were expressed in 95% confidence intervals (CIs).

3. Results

3.1. Literature search and study selection

Combining both the lists of titles and abstracts resulted in 836 records. Fig. 1 shows the results of the search and the study selection. A total of 80 full-text articles were selected for further review. Of these, 25 fulfilled our selection criteria. The other 55 articles were excluded for the following reasons: 33 studies reported a mean change of blood pressure after standing for the total patient group instead of the number of patients with OH; 8 studies used the presence or absence of autonomic symptoms as inclusion criteria; 4 studies were part of a drug trial; 4 studies did not include idiopathic PD patients; 3 studies had partially overlapping data sets; 2 studies were retracted; and 1 manuscript could not be retrieved.

3.2. Study characteristics

Table 1 summarizes the characteristics and methodological quality of the included studies. The 25 studies involved a total of 5070 PD patients. Mean age at examination ranged from 54.2 to 81.6. Mean disease duration ranged from 1.9 to 11.3 years. In eight of the 25 studies the primary objective was to report on the prevalence of OH [10,11,20,23,28,30,32,34], while in the remaining 17 studies the proportion of patients with OH was investigated as a secondary objective. In 18 studies the study population consisted of tertiary care patients. In six studies the population consisted of non-tertiary care or mixed tertiary and non-tertiary care patients. One study did not state the origin of the patient sample. The definition used to diagnose OH varied highly between studies. Only five studies [21,35,38–40] used the criteria as stated in the consensus agreement from 1996 [6]. Using the arbitrary cut-off value of four points on our quality assessment checklist, 12 studies were defined as being of high quality and 13 of low quality. There were only five studies in which the risk of selection bias was judged to be low [20,26,31,38,39].

3.3. Prevalence of OH in PD

The prevalence rate across studies ranged from 9.6% to 64.9% with an estimated pooled prevalence of 30.1% (95% CI: 22.9%–38.4%). Fig. 2 shows the forest plot for these studies. The I^2 -value was about 96%, indicating a large heterogeneity between the studies.

3.4. Subgroup analyses

Several subgroup analyses were performed in order to search for sources introducing heterogeneity between the studies and as such to explore for factors that have an impact on the prevalence of OH (Table 2). In all the subgroups the heterogeneity between studies remained high (I^2 -value ranged from 79.7% to 98.3%). The estimated prevalence in the different subgroups ranged from 25.1% to 37.6%. To assess if the study with the largest sample size (of $n = 3414$) had a significant effect on the pooled estimate, we repeated the meta-analysis leaving the study from Wüllner and colleagues [11] out. The pooled point prevalence was estimated to be 31.5% (95% CI: 24.2%–39.9%), indicating that the impact of the study on the total estimate is small.

4. Discussion

This is the first systematic review investigating the prevalence of OH in PD. The prevalence we found lies in the range stated in previous non-systematic reviews concerning this subject. We found a large heterogeneity between studies. In addition, repeated analyses for several subgroups of studies with specific characteristics—*e.g.*, sample size above 70, less risk for selection bias—also showed large heterogeneity between studies.

Though there was a large variety between studies, this is the first time a meta-analysis concerning the prevalence of OH in PD is performed, and the estimated point prevalence of 30% is the best estimate currently available in the literature. Furthermore, though subgroup analyses did not lead to a reduction of heterogeneity, the calculated prevalence in individual subgroups was always in the range of 25%–38%.

From the 25 studies in the meta-analysis, 19 gave detailed descriptions about the use of standardized criteria for the diagnosis of PD. Considering this, and given the low prevalence of MSA compared to PD, the number of MSA patients that mistakenly entered the meta-analysis is negligible.

We did not find subgroup factors that could clearly explain the large variety in results between the studies. The occurrence of OH is known to be influenced by various factors, such as medication use (*e.g.* for PD and hypertension), deconditioning, time of the day and time after meals, ambient temperature, and comorbidity [42]. Only six of the studies in our review gave detailed information about the circumstances during the blood pressure measurements [10,22,25,31,38,39]. Furthermore, in seven studies patients with concurrent treatment for diabetes mellitus or hypertension were excluded [21,23,32,33,35,37,41]. Other important factors to consider are the role of age and disease duration. Several individual studies have shown that the risk of OH in PD patients increases with higher age and longer disease duration [10–12,20]. As our systematic review lacks individual patient data, we could not analyze the impact of age and disease duration on the presence of OH.

These factors, in combination with the different definitions of OH used throughout the studies have probably caused the large variety in our results. Our review shows that data regarding the occurrence of OH in PD comes mainly from studies in tertiary care centers. Furthermore, in only five out of the 25 studies, the authors have tried to minimize the risk of selection bias. One can imagine that on one hand, this could lead to an underestimation of the prevalence, as patients with concurrent illness were often excluded from analysis. On the other hand it could lead to an overestimation, as non-consecutive patient samples might include more patients with symptoms of OH, as they are more likely to volunteer in such research. Therefore, there is still a need for studies investigating this problem in an unbiased population-based cohort, as the extent of this problem in the general PD population is still not well known.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Appendix. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi: 10.1016/j.parkreldis.2011.04.016.

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Fig. 1.
Flowchart of the reviewing process.

Fig. 2. Point prevalences of OH in PD per study and pooled prevalence rate (with their corresponding 95% Confidence Intervals).

Table 1

Characteristics of the 25 studies included in the analysis.

Study (reference)	Methodological quality Score	Sample size	Study Design	Setting	Definition of OH	Mean age at assessment	Disease duration (years)	Prevalence (95% CIs)
Kuroiwa, 1987 [19]	2	19	Cross-sectional	Tertiary Care	A drop of at least 15 mmHg in mean arterial pressure in 21 min.	59.0	Not stated	31.6% (15.4–54.0%)
Briebach, 1990 [20]	5	250	Cross-sectional	Tertiary Care	A drop of at least 20 mmHg systolic BP in 9 min.	65.9	7.3	39.6% (33.7–45.8%)
Wang, 1993 [21]	3	62	Cross-sectional	General Hospital	A drop of at least 20 mmHg systolic BP or 10 mmHg diastolic BP in 3 min.	65.6	4.7	19.4% (11.4–30.9%)
Loew, 1995 [22]	2	10	Cross-sectional	Tertiary Care	A drop of at least 20 mmHg systolic BP in 1 min.	81.6	Not stated	20.0% (5.7–51.0%)
Bellon, 1996 [23]	3	46	Cross-sectional	Tertiary Care	A drop of at least 30 mmHg systolic BP in 9 min.	64.3	Not stated	19.6% (10.7–33.2%)
Senard, 1997 [10]	4	91	Cross-sectional	Tertiary Care	A drop of at least 20 mmHg systolic BP in 10 min.	66.0	8.0	58.2% (48.1–68.3%)
Yoshita, 1998 [24]	2	48	Cross-sectional	Tertiary Care	A drop of at least 20 mmHg systolic BP or 10 mmHg diastolic BP in 10 min.	69.9	10.0	20.8% (11.7–34.3%)
Tranchant, 2000 [25]	3	19	Cross-sectional	Tertiary Care	A drop of at least 20 mmHg systolic BP. No information on standing time.	70.7	11.3	52.7% (31.7–72.7%)
Papapetropoulos, 2001 [26]	4	52	Cross-sectional	Tertiary Care	No information on definition used.	65.4	6.1	9.6% (4.2–20.6%)
Winkler, 2001 [27]	3	32	Cross-sectional	Tertiary Care	A drop of at least 20 mmHg	63.1	7.2	21.9% (11.0–38.8%)

Study (reference)	Methodological quality Score	Sample size	Study Design	Setting	Definition of OH	Mean age at assessment	Disease duration (years)	Prevalence (95% CIs)
Bonucelli, 2003 [28]	4	51	Cross-sectional	Tertiary Care	systolic BP in 5 min. A drop of at least 20 mmHg systolic BP in 3 min.	54.2	1.9	13.7% (6.8–25.8%)
Matsui, 2005 [29]	4	40	Cross-sectional	General Hospital	A drop of at least 20 mmHg systolic BP in 3 min.	71.2	9.7	62.5% (47.0–75.8%)
Nataraj, 2005 [30]	2	145	Retrospective cohort	Tertiary Care	A drop of at least 30 mmHg systolic BP or 10 mmHg diastolic BP in 3 min.	Not stated	Not stated	15.9% (10.8–22.7%)
Allcock, 2006 [31]	6	175	88 patients from a prospective cohort, 87 patients cross-sectional	General Hospital	A drop of at least 20 or a fall below 90 mmHg systolic BP in 3 min.	70.8	Not stated	49.7% (42.4–57.1%)
Chitsaz, 2007 [32]	4	150	Cross-sectional	Tertiary Care	A drop of at least 20 or a fall below 90 mmHg systolic BP in 2 min.	Not stated	Not stated	41.3% (33.8–49.3%)
Idiaquez, 2007 [33]	3	40	Cross-sectional	No information on setting	A drop of at least 20 mmHg systolic BP in 10 min.	69.0	11.2	12.5% (5.5–26.1%)
Peralta, 2007 [34]	4	10	Cross-sectional	Tertiary Care	A drop of at least 20 mmHg systolic BP or 10 mmHg diastolic BP in 10 min.	74.1	6.4	20.0% (5.7–51.0%)
Wüllner, 2007 [11]	4	3414	Retrospective cohort	Community	A drop of at least 20 mmHg systolic BP or 10 mmHg diastolic BP. No information on standing time.	66.1	9.0	10.6% (9.6–11.7%)
Adhiyaman, 2008 [35]	2	13	Cross-sectional	General Hospital	A drop of at least 20 mmHg systolic BP or 10 mmHg diastolic BP in 3 min.	69.5	5.2	46.2% (23.2–70.9%)

Study (reference)	Methodological quality Score	Sample size	Study Design	Setting	Definition of OH	Mean age at assessment	Disease duration (years)	Prevalence (95% CIs)
Goldstein, 2008 [36]	2	77	Cross-sectional	Tertiary Care	A drop of at least 20 mmHg systolic BP or 10 mmHg diastolic BP in 5 min.	65.0	9.0	64.9% (53.8–74.7%)
Shibata, 2008 [37]	2	72	Cross-sectional	Tertiary Care	A drop of at least 20 mmHg systolic BP or 10 mmHg diastolic BP. No information on standing time.	73.4	3.5	18.1% (10.9–28.5%)
Haensch, 2009 [38]	5	58	Cross-sectional	General Hospital	A drop of at least 20 mmHg systolic BP or 10 mmHg diastolic BP in 3 min.	70.9	5.1	48.3% (35.9–60.8%)
Jamnadas-Khoda, 2009 [39]	5	50	Cross-sectional	Tertiary Care	A drop of at least 20 mmHg systolic or 10 mmHg diastolic in 3 min.	57.3	Not stated	22.0% (12.8–35.2%)
Matinoli, 2009 [40]	4	120	Cross-sectional	Tertiary Care	A drop of at least 20 mmHg systolic BP or 10 mmHg diastolic BP in 3 min.	68.2	5.8	52.5% (43.6–61.2%)
Schmidt, 2009 [41]	2	26	Cross-sectional	Tertiary Care	No information on definition used.	65.0	7.0	38.0% (22.1–57.0%)

Table 2

Prevalence rates of OH in PD and heterogeneity between studies in relation to subgroups.

Subgroup	Number of studies	Estimated prevalence (%; 95 CIs)	I ² -value (%)
Estimation of prevalence was primary objective	8	25.1 (13.9–41.0)	96.9
Other primary objective	17	32.9 (23.7–43.7)	90.1
High quality studies	12	33.2 (21.3–47.7)	97.6
Low quality studies	13	26.9(18.5–37.5)	85.7
Risk of selection bias judged to be low	5	32.2 (14.9–56.3)	93.8
Risk of selection bias judged to be high	20	29.5 (21.4–39.2)	95.1
Sample size larger than 70	9	36.2 (21.8–53.6)	98.3
Sample size smaller than 70	16	26.3 (18.7–35.7)	79.7
Definition for OH: drop of systolic BP of 20 mmHg in 3 min	8	37.6(23.4–54.2)	91.2
Other definition for OH	17	26.3 (18.7–35.6)	95.3
Tertiary care population studies	18	29.6(21.6–39.1)	91.2
Non-tertiary care or mixed population studies	6	35.8 (16.8–60.7)	95.3