Quality of life following renal sympathetic denervation in treatment-resistant hypertensive patients: a two-year follow-up study

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ABSTRACT

Objective. Hypertension is a significant health burden. In the last 10 years, renal sympathetic denervation has been tested as a potential treatment option for a select group of patients with treatment-resistant hypertension. The aim of this study was to broadly assess the quality of life in patients undergoing renal sympathetic denervation with two years’ follow-up. Materials and methods. Patients with treatment-resistant hypertension being treated by hypertension specialists were eligible for inclusion in this study. Bilateral renal sympathetic denervation was performed with the Symplicity Catheter System. Quality of life was measured using standardised questionnaires (Short Form 36, 15D and a single-item question) and an open question before denervation, after six months and after two years. Results. A total of 23 patients were included. The typical participant was male, 53 years, had a mean office blood pressure of 162/108 mmHg, body mass index of 32 kg/m², and was prescribed 4.8 blood pressure lowering drug classes. At baseline, both physical and mental aspects of quality of life were affected negatively by the treatment-resistant hypertension. Over time, there were modest improvements in quality of life. The largest improvements were seen at six months. Simultaneously, the mean number of blood pressure lowering drug classes was reduced to 4.2. Conclusion. Following renal sympathetic denervation treatment, some aspects of health related quality of life showed an improved trend during follow-up. The observed improvement may reflect the impact of a reduced number of blood pressure lowering drug classes.

Clinical Trial Number registered: NCT01630928

Introduction

Hypertension is a significant global health burden that affects 30–45% of adults [1] and is responsible for about 8.5 million deaths from stroke, ischemic heart disease, other vascular diseases, and renal disease worldwide [2,3]. Hypertension can easily be detected in primary care and many drugs are available, at a reasonably low cost, for treating patients with hypertension and reducing the risk of its sequelae [3–5]. Hypertension is the leading modifiable risk factor for morbidity and mortality worldwide; thus, most international guidelines on cardiovascular disease prevention have recommended blood pressure lowering treatment for patients with hypertension [1,6].

A significant number of patients with hypertension have treatment-resistant hypertension (TRH), defined as uncontrolled blood pressure despite regular use of at least three classes of antihypertensive drugs, including a diuretic, and lifestyle changes [1]. Renal sympathetic denervation (RDN) was first reported in 2009 as a novel invasive treatment option for patients with TRH, following the rationale that increased sympathetic tone is one of the main mechanisms of TRH [7].

The first small RDN trials consistently showed significant blood pressure reduction. The optimism was overturned in 2014 by the first randomised blinded sham-controlled trial, which showed no significant treatment effect after six months but, otherwise, RDN proved to be safe [8]. Despite this, the work in the field has continued; recently, three sham-controlled trials showed that RDN reduces blood pressure in both TRH patients and in patients naïve to medication [9–11]. The success is attributed to a more careful selection of patients and a more meticulous denervation procedure [12].

Efficient treatment of hypertension is challenging because of its paradoxical nature, as quality of life (QOL) is mainly negatively affected by the awareness of a disease with...
adverse consequences and side effects of treatment, more than by the disease itself [13,14]. Adherence to hypertensive treatments is generally low and difficult to assess and manage [15]. The reported side effects of antihypertensive medication include emotional distress, reduced sexual function, nocturia, insomnia, headache, tiredness, and depression [16]. Poorer QOL is reported in patients with TRH compared to non-hypertensive patients, patients with controlled hypertension [17], and normal reference populations [18]. A review article from 2015 concluded that there is substantial evidence that TRH is associated with poorer QOL [14]. However, more research is needed on the factors explaining this association. Moreover, investigations assessing the effects of more aggressive treatment strategies, such as RDN, on health related QOL, are scarce.

Following RDN, prospective cohort studies have shown an improvement, particularly in mental health-related QOL dimensions, up to 12 months [18–21]. In the study by Krawczyk-Ozog et al., improvements in QOL followed a reduction in systolic and diastolic blood pressure [21]. However, contrasting results are reported, where the improvements in QOL were not directly associated with the magnitude of blood pressure reduction [17,20]. Similarly, in a recent pilot randomised controlled trial including 18 Belgian patients with TRH treated with RDN, the treatment resulted in a significant reduction in office blood pressure. However, no significant differences in QOL were reported at six months of follow-up [22].

In the largest prospective cohort study to date, based on data from the Global SYMPPLICITY Registry on QOL at 6 and 12 months following RDN, the results indicate an improvement in health-related QOL from baseline to 12 months [23]. The changes in QOL were not correlated with changes in blood pressure.

Although the above-mentioned studies have reported improvement in QOL up to 12 months, there are debates as to whether these improvements are related to concomitant blood pressure reduction, reduced sympathetic tone, and/or bias such as the Hawthorne effect, characterised by the effect of participating in a study with a new and innovative treatment [24]. Moreover, whether an improvement in QOL lasts beyond the first year after RDN is currently unknown.

Aims

The aims of this study were to describe QOL in patients with TRH before undergoing RDN and over two-years’ follow-up.

Materials and methods

This study is part of a larger study that aimed to examine changes in insulin sensitivity after RDN, in patients with TRH, assessed with gold standard clamp methods [25].

Patients aged 18–68 years with TRH, treated by hypertension specialists at hospitals, were eligible for inclusion and were invited to participate in this non-randomised intervention study performed in 2013–2014. Patients were recruited at the University Hospital North Norway, Norway. TRH was strictly defined as an office systolic blood pressure ≥140 mm Hg despite four or more antihypertensive drugs, to assure true TRH. The presence of TRH was verified by blood pressure monitoring after witnessed intake of the prescribed antihypertensive drugs. The exclusion criteria included known diabetes, a positive pregnancy test, cancer, hemodynamically significant heart valve disease, pacemaker or implantable cardioverter defibrillator, renal artery stenosis, and estimated glomerular filtration rate (eGFR) ≤ 45 mL/min/1.73m².

The baseline measures were performed in average 26 days before the RDN procedure, where bilateral RDN was performed with the Symplicity Catheter System. The study was completed in collaboration with the clinical trial unit at University Hospital North Norway.

The primary outcome was changes in insulin resistance from baseline to six months and two years after the intervention. Secondary outcome measures included QOL as measured by the standardised questionnaires SF-36 and 15-D, with some additional questions.

Details about the selection criteria and study procedure have been published previously and the study is registered in clinicaltrials.gov [25] (clinical trial reg. no. NCT01630928). The study was performed in accordance with the principles of the Declaration of Helsinki. The included patients provided written informed consent. Ethical approval was obtained from the Regional Committee for Medical and Health Research Ethics (2011/1296/REK Nord). Data collection and storage were in accordance with the internal storage policy of research data and was approved by the Data Protection Officer at the University Hospital of North Norway.

Quality of life

We aimed to measure QOL at three theoretical levels to include the advantage of measurements at all levels and avoid limitations by excluding levels [26]. At the global level, we measured QOL using a single-item question regarding general well-being that was previously used in national surveys in Norway, with the wording: “Thinking about your life at the moment, would you say that you by and large are satisfied with life, or are you mostly dissatisfied?” [27]. Response options were graded from 1- very satisfied to 7- very dissatisfied.

At the health-related QOL level, we used the SF-36 version 2 questionnaire [28]. The SF-36 consists of eight subscales: physical functioning, role limitation due to physical health problems, bodily pain, general health, vitality, social functioning, role limitation due to emotional health problems, and mental health, and two summary scales. The scores on the eight dimensions are transformed into scales from 0 (worst health) to 100 (best health). Thereafter, the physical component summary score (PCS) and the mental component summary score (MCS) were calculated with a norm-based scoring procedure, with each scale having a mean of 50 and standard deviation of 10, thus incorporating the 2009 US norm into the scoring algorithm [28].
To assess possible symptoms resulting from the side effects of the antihypertensive medication treatment we used the 15D scale [29]. The 15 D is a generic, comprehensive (15-dimensional) self-administered instrument to measure health-related QOL in adults complementing the SF-36. A set of utility or preference weights is used to generate the 15 D score (single index number) on a 0 (being dead) to 1 (no problems on any dimension) scale [29].

To identify possible aspects not included in the questionnaires, we included one open-ended question with the wording: “Can you please describe (up to three issues) how hypertension has affected your quality of life?” at baseline.

Analysis

Descriptive statistics are presented as means and standard deviations (SD) and as median values and inter-quartile ranges (IQR) for continuous variables with approximately normal distribution and non-normal distribution, respectively. For the standardised questionnaire scoring, missing imputation and scale calculations were performed according to the respective guidelines/manuals [28,29]. Correlation between change in medication classes and change in QOL was tested using Pearson correlation coefficient. Repeated measures ANOVA, using the General Linear Model in SPSS, was used to analyse changes in QOL over time [30]. All tests were two-tailed at a 5% significance level. Data were analysed using SPSS version 26.0. (SPSS Inc.)

The open-question responses were imported into Microsoft Word and the responses were analysed and categorised using a directed structured approach [31], informed by previous research and the categories in the 15 D instrument. The findings summarise the reported issues.

Results

A total of 23 patients were included, 19 of whom completed follow-up after two years (two withdrew, one died, and one started on antidiabetic drugs). The typical participant at baseline was male, 53 years of age, living with a spouse, started on antidiabetic drugs. The typical participant at baseline was male, 53 years of age, living with a spouse, started on antidiabetic drugs. The typical participant at baseline was male, 53 years of age, living with a spouse, started on antidiabetic drugs. The typical participant at baseline was male, 53 years of age, living with a spouse, started on antidiabetic drugs. The typical participant at baseline was male, 53 years of age, living with a spouse, started on antidiabetic drugs. The typical participant at baseline was male, 53 years of age, living with a spouse, started on antidiabetic drugs. The typical participant at baseline was male, 53 years of age, living with a spouse, started on antidiabetic drugs.

At baseline, the SF-36 MCS and PCS scores were 45.7 and 45.0, respectively, below the reported mean scores of 50 (SD 10) in the US reference population [28].

Both, the overall QOL rating and health-related QOL measured with the SF-36 showed a trend of improvements over time in all domains, with the largest improvement from baseline to six months, followed by a worsening to 24 months (Table 2). However, a statistically significant improvement over time was only found in the vitality domain (from 39.1 to 55.3, p = 0.009) and in the MCS scale of the SF-36 (45.71 to 50.9, p = 0.023).

A similar pattern was reported in the symptoms and problems reported in the 15 D, with the largest improvements occurring up to six months (Table 3). In the sum score in the 15 D, there was a significant improvement over time to 24 months (p = 0.045). The item distress reached the level of significant improvement (p = 0.002) (Table 3). Most of the domains after six months and eight of the domains after two years reached a level of improvement above 0.015 points, which is considered a minimum important change of the domains in the instrument [32]. Of note, there was deterioration above 0.015 points in the hearing, sleep, and mental domains after two years.

In the open question, three of the participants noted that they had no symptoms or problems due to TRH affecting their QOL at baseline and the other participants mentioned up to three issues each. The problems mentioned by 10 of the participants were about symptoms. In this category, most patients mentioned pain. The pain was described as pain in the chest, limbs, headache, and pain in the muscles and joints. The other symptom mentioned was dizziness. Ten participants also reported problems related to vitality. Being tired, wearing more easily, lacking energy, and feeling worn out summarise these responses. Eight of the reported problems were linked to the negative effects of TRH on usual activities. Examples of responses mentioned
Our participants had PCS and MCS scores about half a SD below the US reference population scores at baseline [28]. Our results are in accordance with previous research which has shown how TRH negatively affects QOL [17], as our participants had PCS and MCS scores about half a SD below the US reference population scores at baseline [28]. Furthermore, our results resonate with studies that demonstrated improvements in QOL after RDN may last up to six months after the procedure [19]. Regarding domains with improvements, our results are in accordance with the results reported by Lambert and colleagues, who also found the largest improvements following RDN after one year in the MCS scores of SF-36, and in mental symptoms such as sadness, tiredness, and reduced libido [20].

We are aware of only one recent study that reported one-year results on QOL in this patient group [21]. This study included 12 patients with TRH, and reported long-term improvements compared to baseline levels in the emotional reactions and sleep disturbance dimensions [21]. However, according to our knowledge, no study has previously reported QOL data two years after RDN.

Nevertheless, conflicting results have been reported from a pilot RCT indicating that RDN had no effects on QOL, despite positive effects on blood pressure reduction [22]. It has also been reported that the magnitude of blood pressure reduction after RDN is not related to the magnitude of QOL improvement [20].

To explain positive effects in blood pressure and QOL after RDN, the placebo effect of the RDN, the Hawthorne effect of participating in a clinical trial, and “regression to the mean” effects in QOL and other outcomes after RDN are proposed as possible alternative explanations for the observed improvements [24,33,34].

On the other hand, putting the modest effect of RDN on blood pressure and QOL in patients with TRH into perspective, the fact that these patients often already have developed concomitant diseases and hypertension-mediated organ damage due to persistent hypertension over years must be kept in mind. Thus, the potential for reversal of the damage, being able to reduce blood pressure and improve QOL might be difficult and could be reflected in the modest improvement [33]. In our study, although we observed a significant reduction in anti-hypertensive drug classes from 4.8 to 4.2 from baseline to six months [25], this reduction was not significant after two years [35]. Together with the fact that 12 out of 23 patients had concomitant diseases at baseline, including cardiovascular diseases, may in part explain the modest effects on long-term QOL.

Table 3. Problems/symptoms (15D) scores at baseline and during follow-up.

| 15D       | Baseline | 6 months | 24 months | p-value<sup>o</sup> |
|-----------|----------|----------|-----------|---------------------|
| n = 23    | n = 22   | n = 18   |           |                     |
| Move      | 0.86 (0.16)<sup>a</sup> | 0.90 (0.14)<sup>a</sup> | 0.87 (0.15)<sup>a</sup> | 0.637               |
| See       | 0.88 (0.18)<sup>a</sup> | 0.95 (0.13)<sup>a</sup> | 0.91 (0.17)<sup>a</sup> | 0.115               |
| Hear      | 0.95 (0.11)<sup>a</sup> | 0.95 (0.13)<sup>a</sup> | 0.93 (0.15)<sup>a</sup> | 0.238               |
| Breath    | 0.69 (0.22)<sup>a</sup> | 0.73 (0.22)<sup>a</sup> | 0.78 (0.23)<sup>a</sup> | 0.447               |
| Sleep     | 0.80 (0.26)<sup>a</sup> | 0.88 (0.23)<sup>a</sup> | 0.75 (0.27)<sup>a</sup> | 0.162               |
| Eat       | 1.00 (0.00)<sup>a</sup> | 1.00 (0.00)<sup>a</sup> | 1.00 (0.00)<sup>a</sup> |                     |
| Speech    | 0.97 (0.09)<sup>a</sup> | 0.99 (0.06)<sup>a</sup> | 0.97 (0.10)<sup>a</sup> | 0.332               |
| Usual activities | 0.77 (0.23)<sup>a</sup> | 0.90 (0.19)<sup>a</sup> | 0.81 (0.29)<sup>a</sup> | 0.062               |
| Excretion | 0.87 (0.23)<sup>a</sup> | 0.94 (0.12)<sup>a</sup> | 0.88 (0.21)<sup>a</sup> | 0.310               |
| Mental    | 0.94 (0.16)<sup>a</sup> | 0.95 (0.13)<sup>a</sup> | 0.90 (0.22)<sup>a</sup> | 0.227               |
| Symptoms  | 0.72 (0.25)<sup>a</sup> | 0.79 (0.26)<sup>a</sup> | 0.80 (0.28)<sup>a</sup> | 0.140               |
| Depression| 0.90 (0.14)<sup>a</sup> | 0.90 (0.14)<sup>a</sup> | 0.92 (0.14)<sup>a</sup> | 0.274               |
| Distress  | 0.79 (0.21)<sup>a</sup> | 0.88 (0.18)<sup>a</sup> | 0.89 (0.16)<sup>a</sup> | 0.002               |
| Vitality  | 0.71 (0.20)<sup>a</sup> | 0.82 (0.21)<sup>a</sup> | 0.82 (0.18)<sup>a</sup> | 0.278               |
| Sex       | 0.69 (0.28)<sup>a</sup> | 0.76 (0.30)<sup>a</sup> | 0.75 (0.30)<sup>a</sup> | 0.517               |
| Sum 15D   | 0.84 (0.11)<sup>a</sup> | 0.89 (0.09)<sup>a</sup> | 0.87 (0.12)<sup>a</sup> | 0.045               |

All values given as mean (SD).<sup>a</sup>Indicating a change of >0.015 from baseline.
<sup>o</sup>p-value: Test of within-subjects effects over time (Greenhouse–Geisser).

Discussion

In this study, by including carefully selected patients with TRH, we found modest improvements over time in several aspects of QOL and symptoms following RDN treatment up to six months. The improvement correlated significantly with the simultaneous reduction in number of blood pressure lowering drug classes prescribed, suggesting a possible explanation for the improved QOL. Furthermore, there were some modest long-term improvements in QOL after RDN, especially in the areas related to previously reported side effects/symptoms following antihypertensive drug treatment.

Both physical and mental aspects of QOL were affected and below the levels previously described in a reference population [28]. The domains covered by the 15D mostly affected TRH patients included breathing, sleeping, usual activities, symptoms, vitality, and sexual issues. These issues were elucidated through the participants’ descriptions in this study on how hypertension affects their QOL.

Our results are in accordance with previous research which has shown how TRH negatively affects QOL [17], as our participants had PCS and MCS scores about half a SD below the US reference population scores at baseline [28].
may be made. Furthermore, the small sample size is a substantial limitation resulting in low statistical power. The construct validity of the RDN intervention, i.e. to what extent sufficient denervation was obtained during the procedure, can be disputed as this is a new and innovative intervention where the technical aspects related to the denervation has developed following this study.

Conclusion

In this carefully selected group of patients with true TRH, we observed a modest improvement in QOL at the global, health-related, and symptom-level six months after RDN possibly reflecting a reduction in medication classes. The QOL improvement seemed sustained in the mental dimensions after two years. Based on this study, we recommend further research, preferably using randomised controlled trials including a sham intervention, on the long-term effects of RDN on blood pressure, concomitant disease development, and QOL.

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Author contributions

TAH, AM, MDS and TKS contributed to the conception or design of the work. TAH, AS, AM, MDS and TKS contributed to the acquisition, analysis, or interpretation of data for the work reported here. TAH and AS drafted the manuscript. All authors critically revised the manuscript, gave final approval, and agreed to be accountable for all aspects of this work, ensuring integrity and accuracy.

Disclosure statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Data availability statement

The datasets generated and/or analysed during the current study are not publicly available due to continued analysis and reporting of results; but are available from the corresponding author on reasonable request.

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