Limitations in current clinical trials on renal denervation

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To the editor

Renal denervation (RDN) has become a standard treatment option to lower blood pressure (BP) in patients with resistant hypertension in many countries since 2010. There is a huge interest in investigating the effect of RDN on resistant hypertension and other diseases (*e.g.* diabetes and heart failure), and 118 clinical trials have been registered at ClinicalTrials.gov. A large number of early clinical trials demonstrate that RDN lowers blood pressure. However, on 9 January 2014, Medtronic reported that RDN did not lower blood pressure in the randomized and sham controlled Symplicity HTN-3 trial. In this letter, we highlighted six major limitations of clinical trials on RDN which need to be overcome to improve our understanding of the true efficacy and safety of RDN.

1. Lack of a method to verify the completeness of RDN: RDN is thought to lower blood pressure by decreasing renal sympathetic nerve activity. However, no method to verify the completeness of RND has been established in clinical trials. The Simplicity catheter requires to be moved and rotated ≥4 times to cover the circumference of the renal artery, and this makes RDN operator-dependent. Consequently, both evaluation of the efficacy of RDN and identification of responders to the procedure in clinical trials are problematic. Therefore, research on investigating methods to verify the completeness of RDN should be emphasized.

2. Office BP measurement: Many clinical trials on RDN primarily used office BP measurement. This measurement can produce white coat effects. Consequently, a big proportion of patients undergoing RDN had white coat hypertension, which may raise ethical concerns. Ambulatory BP monitoring is regarded as the gold standard to diagnose true hypertension and to assess cardiovascular risk. Therefore, ambulatory BP should be used as one of the selection criteria and changes in ambulatory BP should be one of the primary end points.

3. Drug non-adherence: Drug non-adherence is a major problem among patients with resistant hypertension. Measuring ambulatory BP after witnessed intake of antihypertensive drugs is the best way to ensure drug adherence and should be adopted in future trials [1].

4. Low follow-up rates: The follow-up rate is generally low. For example, the 12-month follow-up rate was 20% and 38% in the Symplicity HTN-1 study [2] and the Heidelberg registry report [3], respectively. Low follow-up rates may underestimate potential side effects. Therefore, high follow-up rates should be emphasized.

5. Renal artery safety: Renal artery stenosis was not thoroughly monitored. Only a small proportion of patients underwent computerized tomographic angiography–the gold standard method to detect renal artery stenosis. Using this method, the EnligHTN I trial detected this complication in 4.3% of patients six months after RDN [4]. This suggests a necessity to use this diagnosis method in future.

6. Long-term effects: Long-term effects of RDN are not emphasized by clinical trials. For example, the ongoing randomized Symplicity HTN-3 study [5] allows patients in the randomized control group to receive RDN after completion of the six-month study. Similarly, in the Symplicity HTN-2 study, 46 of 54 patients in the randomized control group underwent RDN after completion of the six-month study. To establish the long-term effectiveness and safety of RDN, this crossover design should be discouraged.

Conflict of interest

The authors declare that they have no conflict of interest.

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