Study Protocol

Characteristics Predicting Clinically Relevant Reduction of Hypertension Following Adrenalectomy for Primary Aldosteronism: a Multicenter Analysis

University Medical Center Utrecht, Cancer Center, The Netherlands
Division of Surgical Oncology and Endocrine Surgery

W.M.C.M. Vorselaars, *MSc Student* **05-04-2016**
w.m.vorselaars@umcutrecht.nl

M.R. Vriens, *MD PhD, Prof. Endocrine Surgery*
mvriens@umcutrecht.nl

Background

Primary aldosteronism (PA) is the excessive endogenous production of the mineralocorticoid aldosterone[1]. Although various rare forms of PA exist, the vast majority of cases are accounted by either an aldosterone-producing adenoma (APA) or bilateral adrenal hyperplasia, also described as idiopathic hyperaldosteronism (IHA)[2, 3]. During the last decades the prevalence of PA has risen, predominantly due to better awareness of disease. Several studies estimated a prevalence of PA up to 17% in an unselected population of hypertensive patients. However, in a population with resistant hypertension the reported prevalence is even higher: 17-23%. This emphasizes the clinical impact of PA on morbidity and mortality due to high blood pressure[4-7]. Since both hypertension and aldosteronism are independent risk factors for cardiovascular morbidity, the aim of treatment is curation or reduction of both[8].

After an adrenalectomy for APA normalization of biochemical abnormalities is achieved in almost all cases. Nevertheless, curation of hypertension (SBP <140 and DBP <90 mmHg) without the need of antihypertensive medication is accomplished in only 35-45% of the cases[9-11]. In 2008 Zarnegar *et al.* developed the Aldosteronoma Resolution Score (ARS). This score predicts the likelihood of complete resolution of the hypertension in patients with an aldosteronoma and has been validated by others[9-11].

Reduction of hypertension is also an important clinical outcome and is reported in 90-98% of the patients after surgery[9-11]. In most studies reduction is defined as a certain decrease in blood pressure or antihypertensive medication. However, there is no consensus on the precise definition of reduction in these patients, which leads to incomparable results. Up until now only one study has analyzed the characteristics predicting clinically relevant reduction of hypertension[12]. In a study by Worht *et al*. reduction was defined as: reduction of the number of antihypertensive drugs ≥ 33% with a systolic blood pressure ≤ 130mm Hg. They showed reduction in 72% of the cases(n=58). Preoperative systolic blood pressure and serum creatinine were significantly higher in patients showing no reduction of hypertension.

Objectives

Although complete resolution of hypertension is the primary goal of unilateral adrenalectomy, reduction of hypertension leads to a lifelong decrease of cardiovascular morbidity and mortality. Moreover, reduction of hypertension can lead to decrease of antihypertensive medication and thereby improve the quality of life of the patient. Therefore, reduction of hypertension is also a favorable result of adrenalectomy. The aim of the proposed study is to determine the proportion of patients with clinically relevant reduction of hypertension after adrenalectomy in a large cohort. Furthermore, we aim to determine the characteristics predicting this clinically relevant reduction. Additionally, we evaluate the predictive value of the Aldosteronoma Resolution Score for clinically relevant reduction and aim to develop a scoring system to help clinicians predict the likelihood of reduction of hypertension after adrenalectomy so it can be used for patient counseling.

Definitions/Outcome measures

To evaluate differences between those patients who were cured versus who had reduction versus who had no reduction, patients will be stratified based on clinical response to adrenalectomy. Definitions are based on both American and European guidelines for the management of hypertension[13, 14].

Patients who were completely off antihypertensive drugs and had a postoperative systolic blood pressure < 140 mm Hg and diastolic blood pressure < 90 mm Hg are considered as ''resolution of hypertension''.

''reduction of hypertension'' is defined as: a decrease in the number of antihypertensive drugs for preoperative normotensive patients (SBP < 140 and DBP < 90 mm Hg) or a decrease of postoperative blood pressure (SBP < 140 and DBP < 90 mm Hg) with the same or less number of antihypertensive drugs for patients with preoperative resistant hypertension.

Patients who are not meeting these endpoints are stratified as ''no reduction of hypertension''.

Research Design

An international multicenter retrospective cohort study.

Inclusion Criteria

1. Patients with biochemical evidence of primary aldosteronism who underwent adrenalectomy on account of an aldosterone-producing adenoma(APA), proven by Computerized Tomography(CT) or Magnetic Resonance Imaging(MRI) or Adrenal Venous Sampling(AVS).
2. Operated between 2010-2016 in your institution.

Exclusion Criteria

1. Missing or incomplete data about preoperative blood pressure and number of antihypertensive drugs.
2. Missing or incomplete follow-up data about postoperative blood pressure and number of antihypertensive drugs. *We aim enter the blood pressure and number of antihypertensive drugs closest to 6 months after adrenalectomy.*

Study Variables

Patients demographics and preoperative disease characteristics will be queried, including age at time of operation, gender, history of cardiovascular events, BMI, mean preoperative systolic and diastolic blood pressure, preoperative number of antihypertensive drugs, duration of hypertension, family history of hypertension, smoking, hypercholesterolemia, diabetes and possible supplementation of potassium. The ARS will be calculated for each patient. Furthermore, results of imaging and AVS will be collected. Laboratory data collected include serum aldosterone, potassium and creatinine levels and plasma renin activity. The aldosterone to renin ratio will be calculated. Also operative characteristics (i.e., approach and tumor laterality) and pathologic diagnosis (i.e., aldosteronoma or hyperplasia and tumor size) will be reported.

Study Outcomes

The primary outcomes of this study are the postoperative mean systolic and diastolic blood pressure and the number of antihypertensive drugs. Secondary outcomes are postoperative serum aldosterone and potassium levels. Both primary and secondary outcomes will be measured at approximately 6 months after adrenalectomy(range 3-9 months).

Statistical analysis

To determine characteristics predicting clinically relevant reduction univariate analysis will be conducted with Pearson's chi-square test and Mann-Whitney U test. A P value of < 0.05 will be considered statistically significant. Binary logistic regression modeling will be carried out on variables demonstrating statistical significance in univariate analysis. A P value of < 0.05 will be considered statistically significant. The predictive accuracy of the ARS for reduction of hypertension will be reported as the proportion of patients with reduction in each likelihood level of the ARS: low (ARS 0-1), medium (ARS 2-3), high (ARS 4-5). When possible a new prediction model for reduction of hypertension after adrenalectomy will be developed by analyzing the receiver operator characteristics to determine the area under the curve.

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