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Random comparison of keyhole surgery versus cauterisation of aldosterone-producing adenomas in primary aldosteronism

Submission date
19/05/2022

Recruitment status
No longer recruiting

Registration date
26/05/2022

Overall study status
Ongoing

Last Edited
28/04/2025

Condition category
Nutritional, Metabolic, Endocrine

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims

In brief, aldosterone-producing adenomas (APAs) are benign tumours in the adrenal glands that produce aldosterone. There are two adrenal glands (right and left, triangle-shaped, both around 1.5cm in height and 7 cm in length) that sit on top of each kidney, right and left. Each produces a variety of hormones (chemical messengers), one of which is called aldosterone. Aldosterone is crucial in regulating the amount of sodium (salt) in the body. Too little aldosterone may be associated with a deficiency of salt, sometimes leading to dizziness from low blood pressure. Too much aldosterone often leads to an excess of salt and high blood pressure (hypertension); this study will investigate the second of these (hypertension; also known as high blood pressure). If one or both adrenal glands make too much aldosterone independent of the body's normal control mechanisms then this is called primary aldosteronism (PA). Hypertension develops and it is sometimes associated with low blood potassium levels (an important body salt). In approximately half of cases of PA, the cause is a completely benign (non-cancerous) tumour of the adrenal called an aldosterone-producing adenoma (APA). Surgical removal of an APA improves blood pressure control in almost all patients and some patients (about a third) can stop all their blood pressure tablets.

Until recently, the only way to cure PA has been an abdominal operation to remove the whole adrenal gland in which the APA has been found. However, there are now ways of potentially 'burning' or 'cauterising' just the tumour, leaving the rest of the adrenal gland intact. This study aims to establish how this less invasive cauterisation procedure compares to the removal of the whole gland by abdominal surgery as a treatment for APAs. If the APA is located within the left adrenal gland, an adapted procedure using the common endoscopy (flexible internal camera) will be used. Using a tiny needle passed through the stomach wall, the study team have developed and tested a technique in which radio-frequency energy is applied just to the APA and destroys it by heating it to a temperature at which cells die. The general term for this is 'thermal ablation'. This particular technique is possible because the left adrenal gland lies very close to the stomach wall. Radiofrequency ablation (RFA) is a commonly used technique in medicine and it has been adapted for the treatment of APAs. For APAs in the right adrenal, the team will use one of two types of thermal ablation; RFA or microwave ablation. Both involve passing a needle

through the skin from the back or side; because the patients need to be completely still this is done under general anaesthetic. The choice of microwave or radiofrequency is individualised to each patient to give every patient the maximum chance for the ablation to be successful. The study will now compare, in a clinical trial, the effectiveness of abdominal surgery to remove the whole adrenal gland vs thermal ablation of just the nodule in patients with PA.

Who can participate?
Patients aged over 18 years with primary aldosteronism

What does the study involve?
Participants will be randomly allocated into either the surgical group or the thermal ablation group. The researchers will assess any previous investigations that participants have had to make the diagnosis of aldosterone-producing adenoma (APA). If participants with a left-sided APA are randomised to radiofrequency ablation (RFA), it will usually be performed under conscious sedation (medications via a drip to make them feel drowsy and relaxed), although sometimes a general anaesthetic is required. Participants with right-sided APAs who are randomised to RFA will generally have the procedure performed under general anaesthetic. Participants will need to stay in hospital for about 24 hours following treatment. For patients allocated to the surgical group, an appointment with the surgical team will be arranged to organise an adrenalectomy. This will be performed under general anaesthetic and is usually performed as a keyhole procedure. Patients will be followed up in clinic at 6 weeks after the adrenalectomy/ablation then at 3-, 6- and 12-month study visits. The researchers will recheck blood pressure to see if the treatment has been successful with repeat blood tests. Participants in the ablation group will be invited to have a scan to see if the aldosterone-producing adenomas have gone or reduced in size.

What are the possible benefits and risks of participating?
It is hoped that the treatment (whether adrenalectomy or left/right ablation) will cure or improve the participants' high blood pressure. A cure or improvement in low blood potassium levels is also expected. If this is achieved, participants should be able to stop or greatly reduce the number of tablets they take for their blood pressure and reduce the risk of heart attacks and strokes. The information from this study will also help to improve the treatment for future patients with primary hyperaldosteronism caused by aldosterone-producing adenomas.

Where is the study run from?
Queen Mary University/St Barts NHS Trust (UK)

When is the study starting and how long is it expected to run for?
June 2021 to December 2026

Who is funding the study?
British Heart Foundation (UK)

Who is the main contact?
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Scientific

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT05405101

Integrated Research Application System (IRAS)
304174

Central Portfolio Management System (CPMS)
52429

Study information

Scientific Title
A prospective randomised trial comparing thermal ablation With laparoscopic Adrenalectomy as an alternatiVE treatment for unilateral asymmetric primary aldosteronism

Acronym
WAVE

Study objectives
Current study hypothesis as of 17/06/2024:
Brief Summary:

The primary objective of WAVE is to test the hypothesis that thermal ablation (microwave or RFA) is non-inferior to surgery in the biochemical (and if so, in the clinical) cure of unilateral PA, according to the international consensus PASO criteria.

Secondary objectives are to determine whether either intervention is superior to the other following outcomes. Where no superiority of either intervention is established, non-inferiority of thermal ablation against adrenalectomy will be sought.

Frequency and severity of adverse events
Length of inpatient stay
Patient satisfaction
Quality of life
Return to activities of daily living

An additional secondary objective in the thermal ablation group alone will be the anatomical efficacy of ablation.

Previous study hypothesis:
The primary objective of WAVE is to test the hypothesis that radiofrequency ablation (RFA) is non-inferior to surgery in the biochemical (and if so, in the clinical) cure of unilateral primary aldosteronism, according to the international consensus Primary Aldosteronism Surgical Outcome (PASO) criteria.

Secondary objectives are to determine whether either intervention is superior to the other following outcomes. Where no superiority of either intervention is established, non-inferiority of RFA against laparoscopic adrenalectomy (LA) will be sought.
1. Frequency and severity of adverse events
2. Length of inpatient stay
3. Patient satisfaction
4. Quality of life
5. Return to work

An additional secondary objective in the RFA group alone will be the anatomical efficacy of ablation.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 16/06/2022, London - Bloomsbury Research Ethics Committee (HRA RES Centre Manchester, 3rd Floor Barlow House, Manchester, M1 3DZ, United Kingdom; +44 (0)2071048285; bloomsbury.rec@hra.nhs.uk), ref: 22/LO/0243

Study design
Multicentre parallel randomized intervention study

Primary study design

Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Primary aldosteronism

Interventions
Current interventions as of 17/06/2024:
Patients will be randomised by the King's College London Clinical Trial Unit (KCL CTU) randomisation service and allocated to either the unilateral adrenalectomy arm or the thermal ablation of the aldosterone-producing adenoma arm. Patients randomised to thermal ablation of aldosterone-producing adenoma:

On the left side, Radiofrequency ablation of aldosterone-producing adenoma(s) will be undertaken via the stomach (endoscopically), under transgastric ultrasound guidance.

On the right side, either Radiofrequency or Microwave Ablation of aldosterone-producing adenoma(s) will be performed via a percutaneous approach, under CT guidance.

For patients randomised to Unilateral total adrenalectomy for aldosterone-producing adenoma. This will be laparoscopic in the vast majority of patients, with open conversion if surgically indicated (unlikely in >1-2 patients)

Other Names:
Laparoscopic adrenalectomy

Previous interventions:
Patients will be randomised by the King's College London Clinical Trial Unit (KCL CTU) randomisation service and allocated to either the unilateral adrenalectomy arm or the ablation of the aldosterone-producing adenoma arm. The ablation arm will have sedation and have ablation by radiofrequency delivered to functioning aldosterone-producing adenomas and will be a day case. The adrenalectomy arm, following current clinical intervention for aldosterone-producing adenomas, will require a general anaesthetic and keyhole surgery to remove the unilateral adrenal gland with an in-hospital stay of 2-3 days. Both arms will have seven study visits over 12 months including the procedure. The study visits will include enrolment, randomisation, surgery/ablation, and post-procedure visits at 6 weeks, 3 months, 6 months and 12 months.

Intervention Type
Procedure/Surgery

Primary outcome(s)
Current primary outcome measures as of 17/06/2024:
Complete biochemical cure of PA at 6 months post-intervention

Complete biochemical cure of PA, defined (whilst off medications that might alter serum potassium or the RAS) by both:
1. Normalisation of serum potassium, and
2. Normalisation of ARR, or

3. Elevated ARR and
4. Baseline PAC <190pmol/L, or Normal confirmatory test (as defined in the inclusion criteria)

Complete clinical cure of PA [Time Frame: 6 months post intervention]
Complete clinical cure of PA, defined as normotension without antihypertensive medication

These criteria have been defined in the international consensus PASO statement, which has become the established yardstick by which PA cure is judged. In this, normotension is defined, in accordance with the European Society of Hypertension guidelines, as <140/80 in the office, <135 /85 at home or daytime ambulatory monitoring and <130/80 for 24h ambulatory blood pressure monitoring (24hABPM).

Previous primary outcome measures:
Hierarchical primary endpoints will be adjudged at 6-12 months post-intervention and compared to the enrolment criteria or baseline visit data:
1. Complete biochemical cure of PA, defined (whilst off medications that might alter serum potassium or the RAS) by both:
1.1. Normalisation of serum potassium, and
1.2. Normalisation of aldosterone renin ratio (ARR), or
1.3. Elevated ARR and
1.3.1. Baseline plasma aldosterone concentration (PAC) <190 pmol/L, or
1.3.2. Normal confirmatory test (as defined in the inclusion criteria)
2. Complete or partial hypertension cure, defined as:
2.1. Complete = normotension without antihypertensive medication
2.2. Partial, either
2.2.1. The same blood pressure (Δ<20/10 mmHg) with less antihypertensive medications (Δ>150% baseline defined daily dosing (DDD), or
2.2.2. A reduction in blood pressure (Δ>20/10 mmHg) with the same or less antihypertensive medications (Δ<150% baseline DDD)

Measurements at baseline, 6 weeks, 3 months, 6 months and 12 months post intervention procedure.

Key secondary outcome(s))

Secondary outcome measures as of 17/06/2024:
1. Adverse events are directly sought at each study visit through history and physical examination throughout the study period of approximately 2 years. Subjects will be encouraged to report between study visits and will have a mechanism to do so. Events will be classified by system, seriousness, causal relationship and expectedness according to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE)
2. Anaemia measured using a blood test and full blood count [FBC], requirement for blood transfusion at 6, 12, 24 and 36 months post-intervention
3. Renal dysfunction and electrolyte abnormalities (U&Es) measured using a blood test at 6, 12, 24 and 36 months post-intervention
4. Liver dysfunction (LFTs) measured using a blood test at 6, 12, 24 and 36 months post-intervention
5. Pancreatitis (lipase/amylase) measured using a blood test at 6, 12, 24 and 36 months post-intervention
6. Hypertensive urgency (physiological parameters, plasma metanephrines) measured using a blood test at 6, 12, 24 and 36 months post-intervention
7. Length of inpatient stay (hospital episode data) measured using data reported by the patient at 6 weeks post-intervention

8. Patient satisfaction (Freiburg index of patient satisfaction) measured using data completed by patients, using the FIPs score values to rate the treatment they have received at 6 weeks post-intervention
9. Quality of life questionnaire measured using the - EQ-5D 5L and SF-36 questionnaires at 6 months post-intervention
10. Return to usual activities of daily living measured using self-reported data at 6 weeks post-intervention
11. Anatomical efficacy of ablation measured in the ablation group only; post-ablation Metomidate/CETO PET-CT appearances at 6, 12, 24 and 36 months post-intervention

Other pre-specified outcome measures:
Hierarchical analysis testing applied to sequential testing of the following hypotheses at 6 months post-intervention. Each positive outcome permits the next limb to be tested as a co-primary hypothesis. A negative outcome converts subsequent limbs to secondary hypotheses.
1. Complete biochemical cure for left ablation vs all surgery (positive if non-inferiority (NI) margin <45%)
2. Complete biochemical cure for all ablation vs all surgery (positive if NI margin <45%)
3. Complete clinical cure for all ablation vs all surgery (positive if NI margin <30%). The first limb of the hierarchy will be tested if sufficient patients have been recruited on the left.

Previous secondary outcome measures:
1. Adverse events will be directly sought at each study visit through history and physical examination where appropriate. Subjects will be encouraged to report between study visits and will have a mechanism to do so. Adverse events will be classified by system, seriousness, causal relationship and expectedness according to the Common Terminology Criteria for Adverse Events v6.0 (CTCAE)
2. Pre-specified post-intervention safety aspects will be systemically evaluated and, where appropriate, compared between the two interventions:
2.1. Anaemia (full blood count [FBC], requirement for blood transfusion)
2.2. Renal dysfunction and electrolyte abnormalities (urea and electrolytes [U&Es])
2.3. Liver dysfunction (liver function tests)
2.4. Pancreatitis (lipase/amylase)
2.5. Hypertensive urgency (physiological parameters, plasma metanephrines RFA only)
3. Length of inpatient stay measured using hospital episode data
4. Patient satisfaction measured using the Freiburg index of patient satisfaction or equivalent
5. Quality of life measured using EQ-5D 5L, SF-36
6. Return to work (self-reported)
7. Anatomical efficacy of ablation in the radiofrequency ablation group; post-RFA metomidate /CETO PET-CT appearances

Measurements at baseline, 6 weeks, 3 months, 6 months and 12 months post intervention procedure.

Completion date
01/12/2026

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 17/06/2024:
All of the following Participant inclusion criteria:

1. Age > 18 years
2. Primary aldosteronism diagnosed according to international guidelines
3. Unilateral disease by AVS or PET-CT criteria
4. Ipsilateral radiological abnormality with benign imaging characteristics and technically amenable to both thermal ablation and surgery
5. Able and willing to give informed consent
6. Randomisation approved by MDT

Previous participant inclusion criteria:
1. Age >18 years
2. Primary aldosteronism according to international guidelines:
2.1. An elevated aldosterone renin ratio (according to local reference ranges), and at least one of the following (when measured off confounding medications):
2.1.1. Spontaneous or diuretic-induced hypokalaemia
2.1.2. A positive saline infusion test (SIT)
3. Four-hour aldosterone >190 pmol/L
4. A positive captopril suppression test (CST), either:
4.1. Failure to suppress two-hour aldosterone by >30% and persistent suppression of plasma renin activity/mass
4.2. Two-hour aldosterone >300 pmol/L14
4.3. Unilateral PA, defined by at least one of the following criteria:
5. ACTH-stimulated AVS24
5.1. Selectivity index (SI) >3, and
5.2. Lateralisation index (LI) >4
6. Non-ACTH-stimulated AVS24:
6.1. SI > 2, and
6.2. LI > 3, and
6.3. Contralateral suppression index (CSI) < 0.5/1
7. Metomidate/CETO PET-CT scan
7.1. >25% higher PET signal (maximum standardised uptake value) over an adenoma compared to the contralateral adrenal
8. Age <35 years, unilateral adrenal lesion with normal contralateral gland
9. Radiological abnormality ipsilateral to the side of lateralisation, which is:
9.1. Benign:
9.1.1. Unenhanced CT attenuation <20HU, or
9.1.2. Post-contrast CT absolute washout >60%, or
9.1.3. Post-contract CT relative washout >40%, or
9.1.4. Signal drop-out on out-of-phase MRI
9.2. Technically amenable to both RFA and surgery (determined at MDT review)
10. Able and willing to give informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit

18 years

Sex
All

Total final enrolment
122

Key exclusion criteria
Current participant exclusion criteria as of 17/06/2024:
1. Absolute contraindication to α- or β-adrenoceptor antagonist therapy or CT contrast
2. Contraindication or unwillingness for either surgery or thermal ablation
3. Inability to withdraw β-adrenoceptor antagonist therapy for 2 weeks
4. Unwilling to undergo either LA or thermal ablation
5. Unwilling to comply with study visit schedule
6. Pregnancy or unwillingness to undertake secure contraception for the study duration (female participants only)
7. Life-limiting comorbidity (at the discretion of the PI)
8. Clinical and/or biochemical evidence of autonomous cortisol secretion sufficient, in the opinion of the patient's physician, to mandate a unilateral adrenalectomy independent of autonomous aldosterone secretion

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1. Absolute contraindication to α- or β-adrenoceptor antagonist therapy or CT contrast
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Date of first enrolment
01/09/2022

Date of final enrolment
28/04/2025

Locations

Countries of recruitment
United Kingdom

England

Study participating centre

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Study participating centre
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Sponsor information

Organisation
Queen Mary University of London

ROR
https://ror.org/026zzn846

Funder(s)

Funder type
Charity

Funder Name
British Heart Foundation

Alternative Name(s)
The British Heart Foundation, the_bhf, BHF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study will be published as a supplement to the results publication

IPD sharing plan summary
Published as a supplement to the results publication