# The HubBLe Trial: haemorrhoidal artery ligation (HAL) versus rubber band ligation (RBL) for symptomatic second- and third-degree haemorrhoids: a multicentre randomised controlled trial and health-economic evaluation

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# Scientific summary

## The HubBle RCT

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# Scientific summary

## Background

Anal cushions are a normal component of the anal canal and are composed predominantly of vascular tissue, supported by smooth muscle and connective tissue. Pathological changes in the anal cushions with enlargement of the vascular plexus result in haemorrhoidal development. Haemorrhoids are common, affecting as many as 1 in 3 of the population, and result in a significant burden to the UK NHS. Over 20,000 haemorrhoidal operations are carried out in England each year. Prevalence may be even higher in professionally active people. Repeated visits to hospital for therapy represent a significant disruption to the personal and working lives for this population in particular.

Treatment is dictated by the degree of symptoms and the degree of prolapse, and ranges from dietary advice to rubber band ligation (RBL) in the outpatient department, to an operation under anaesthetic. Although RBL is cheap, it has a high recurrence rate and often needs repeating. Failure may require surgical intervention, commonly the traditional 'open' haemorrhoidectomy (OH) or a stapled haemorrhoidopexy (SH), both requiring anaesthetic. OH is associated with considerable postoperative discomfort and a delay in return to normal activity, but has a low recurrence rate. SH has a slightly higher recurrence rate, but potentially shorter recovery. An alternative treatment is haemorrhoidal artery ligation (HAL), which, although it also requires an anaesthetic, is thought to enable an even quicker return to normal activity. Recurrence rates are reportedly similar to SH, but complication rates are lower.

There are substantial data in the literature concerning the efficacy and safety of RBL, including multiple comparisons with other interventions. Recurrence varies from 11% to > 50%, the broad range probably reflecting the definition of recurrence, severity of the disease, number of treatments and/or the intensity and length of follow-up. In most studies, the incidence of recurrence is > 30% and appears greatest for grade III (third-degree) haemorrhoids (prolapsing piles requiring manual reduction). Significant complications are rare after RBL.

Although HAL requires an anaesthetic, evidence suggests a recovery that is similar to RBL, but an effectiveness that approaches the more intensive surgical options. There are significant data about the effectiveness of HAL, including four systematic reviews, 11 randomised controlled trials (RCTs), seven non-randomised trials and > 60 case series. All of these reviews highlight the lack of good-quality data as evidence for the advantages of the technique. There are no existing RCTs that compare HAL with RBL.

## Objectives

The aim of this study was to establish the clinical effectiveness and cost-effectiveness of HAL compared with conventional RBL in the treatment of people with symptomatic prolapsing haemorrhoids (second or third degree).

The primary objective was to compare patient-reported symptom recurrence at 12 months following the procedure. Recurrence was defined using a simple dichotomous outcome that was derived from a previously published systematic review, and supplemented with general practitioner (GP) and hospital notes.

The secondary objectives were to compare postoperative:

- symptom severity score
- health-related quality of life [using the European Quality of Life-5 Dimensions (EQ-5D)]

- continence (using the validated Vaizey incontinence score)
- pain [using a 10-cm visual analogue scale (VAS)]
- surgical complications
- need for further treatment
- clinical appearance of haemorrhoids at proctoscopy following recurrence
- health-care costs
- cost-effectiveness.

## Methods

This was a multicentre, parallel-group RCT involving 18 centres throughout England and Scotland. Delegated study staff located at individual centres identified and consented potential participants.

These participants fell into two basic groups:

1. Patients presenting to the surgical outpatient clinic (SOPC) with symptomatic haemorrhoids, for which alternative diagnoses had been excluded either clinically or after investigation.
2. Patients with symptoms – due to haemorrhoids – confirmed, who returned to SOPC following one unsuccessful RBL.

After consent, participants were individually randomised to HAL or RBL in equal proportion at all centres using a web-based randomisation system.

Sheffield Clinical Trials Research Unit (CTRU) coordinated follow-up and data collection in collaboration with the UK centres. Participant study data were collected and recorded on study-specific case report forms and patient questionnaires, and then entered on to a web-based data capture system, transferring data to Sheffield CTRU for analysis.

Data were collected to establish which patients had further treatment for recurrent symptoms or complications following their initial procedure. This was achieved at a clinic visit around 6 weeks following the intervention and by reviewing hospital records, asking the patients' consultants, writing to patients' GPs and questioning the patient via telephone interview at 12 months.

## Setting

Sheffield Teaching Hospitals NHS Foundation Trust was the 'clinical coordinating centre' housing the Chief Investigator. A further 17 centres screened patients and delivered the trial; one centre did not recruit, so 17 centres recruited participants. Recruitment took place in outpatient clinics, RBL took place in outpatient clinics or theatre (depending on the Trust's current practice) and HAL took place in theatre.

## Participants

The target population was patients who were referred to collaborating centres for treatment of haemorrhoids.

### *Inclusion criteria*

- Adults aged $\geq$ 18 years with symptomatic second- or third-degree (grade II/III) haemorrhoids.

### *Exclusion criteria*

- Patients who have had previous surgery for haemorrhoids (at any time).
- Patients who have had more than one injection treatment for haemorrhoids in the past 3 years.
- Patients who have had more than one RBL procedure in the past 3 years.
- Patients with known perianal sepsis, inflammatory bowel disease, colorectal malignancy or pre-existing sphincter injury.
- Patients with an immunodeficiency.
- Patients who were unable to have general or spinal anaesthetic.
- Patients who were currently taking warfarin or clopidogrel bisulfate (clopidogrel) or who had any other hypocoagulability condition.
- Patients who were currently taking nicorandil.
- Pregnant women.
- Patients who were unable to give full informed consent (this may be because of mental capacity or language barriers).
- Patients who were previously randomised to this trial.

## Sample size

We assumed that the proportion of patients who experience recurrence following RBL was 30% and following HAL 15%. Therefore, the sample size required to detect a difference in recurrence rates with an odds ratio (OR) of '2', with 80% power and 5% significance, was 121 individuals per group. In order to account for any between-surgeon variation and loss to follow-up, we increased this to 175 per group.

## Interventions

The intervention was either RBL or HAL – both established and well-documented procedures, considered as standard care by the National Institute for Health and Clinical Excellence.

Rubber band ligation is a basic surgical skill with which all senior staff are familiar and are competent in performing.

Haemorrhoidal artery ligation is a simple procedure that uses existing surgical skills and has a short learning curve. All of the surgeons involved in the study had completed the required training and, in addition, had carried out the manufacturer's recommendation of five procedures before commencing the study.

## Statistical and health-economic analyses

Differences in the primary outcome of recurrence were analysed using logistic regression, adjusting for gender, age and history of previous intervention as fixed effect covariates and surgeon as a random effect. This allows the calculation of ORs with confidence intervals (CIs) for the effect of RBL relative to HAL, adjusting for the effects of covariates and the clustering by surgeon. The secondary outcomes of pain, symptoms and incontinence were analysed at each time point using a random-effects, generalised least squares model, adjusting for the same covariates. Procedural complications and serious adverse events (SAEs) were summarised as numbers and percentages.

A full economic evaluation, focusing on estimating the incremental cost per quality-adjusted life-year (QALY) of HAL compared with RBL over the 12-month follow-up period, was also carried out. A secondary cost-effectiveness analysis (CEA) was performed in terms of the incremental cost per recurrence avoided. Long-term cost-effectiveness was estimated by extrapolating the analyses beyond the trial time horizon.

## Results

In total, 372 participants were randomly assigned to receive RBL or HAL; 187 patients were allocated to receive RBL, and 185 were allocated to receive HAL. Two of these participants (both randomised to RBL) were removed from the trial completely, as they were ineligible at the time of consent, and, therefore, a total of 370 participants were entered into the trial. The recurrence rate for HAL was significantly lower than for RBL at 12 months (30% vs. 49%, adjusted OR = 2.23, 95% CI 1.42 to 3.51; $p = 0.0005$). Further treatment was required in 31% of the RBL group and 15% of the HAL group (adjusted OR for further procedure = 2.86, 95% CI 1.65 to 4.93; $p = 0.0002$). Eighteen per cent of the RBL group received a second banding session within the year. In these cases, because the initial haemorrhoids were incompletely treated, excluding these RBLs as recurrence resulted in a larger reduction of our recurrence rate for RBL and no statistical difference between the groups (HAL 30% vs. RBL 37.5%, adjusted OR 1.35, CI 0.85 to 2.15; $p = 0.20$).

At 6 weeks following the procedure, 13 (9%) of patients in the HAL group and 44 (29%) of patients in the RBL group reported their haemorrhoidal symptoms as 'unchanged' or 'worse' (adjusted OR 4.35, 95% CI 2.19 to 8.65; $p < 0.001$).

The haemorrhoid symptom severity score improved in both arms compared with scores prior to procedure. At 6 weeks, the mean scores reduced from 6.5 [standard deviation (SD) 3.3] to 4.0 (SD 3.5) for RBL and from 6.4 (SD 3.0) to 3.0 (SD 3.1) for HAL. There was a statistically significant difference between groups at 6 weeks in favour of HAL (adjusted mean difference 1.0, 95% CI 0.3 to 1.8; $p = 0.01$) but no difference was apparent at 1 year (difference in means 0.0, 95% CI –0.8 to 0.8; $p = 0.98$). Applying the definition used by Nyström *et al*., in which a score of 0 or 1 points indicates symptomatic cure, the two interventions were similar at both 6 weeks (HAL 38% vs. RBL 31%; adjusted OR 0.73, 95% CI 0.44 to 1.22; $p = 0.23$) and 1 year (HAL 31% vs. RBL 27%; adjusted OR 0.79, 95% CI 0.46 to 1.38; $p = 0.42$) (Nyström PO, Qvist N, Raahave D, Lindsey I, Mortensen N. Randomized clinical trial of symptom control after stapled anopexy or diathermy excision for haemorrhoid prolapse. *Br J Surg* 2010;**97**:167–76).

Haemorrhoidal artery ligation was associated with a short-term reduction in mean health utility (European Quality of Life-5 Dimensions, 5-level version) at 1 and 7 days postoperatively, whereas for RBL the mean had reverted back at 1 week. The adjusted difference in means were 0.08 (95% CI 0.04 to 0.13; $p = 0.001$) at 1 day and 0.08 (95% CI 0.05 to 0.12; $p = 0.001$) at 7 days in favour of RBL. The two arms were similar (and above baseline values) at all time points from day 21 onwards.

There was a small reduction of about 1–2 points in the mean Vaizey faecal incontinence score 6 weeks after both interventions. There was no evidence of a difference in incontinence score between the two interventions. The majority of patients reported increased pain, measured by VAS, following both procedures (56% RBL vs. 71% HAL). For RBL, this pain was usually of low intensity (median VAS score on day 1: 3.0) and resolved rapidly to below baseline values (median VAS score on day 7: 1.0); about 50% of patients required analgesics for the first few days after treatment. For HAL, the pain was significantly greater, with moderate pain at day 1 (median VAS score 5.0, mean difference from RBL –1.2, 95% CI –1.8 to –0.5; $p < 0.001$) and mild pain on day 7 post procedure (median VAS score 3.0, mean difference from RBL –1.5, 95% CI –2.0 to –1.0; $p < 0.001$). Pain had resolved in almost all patients by the 3-week assessment (median VAS score 0.0 RBL vs. 1.0 HAL, mean difference from RBL –0.1, 95% CI –0.6 to 0.3; $p = 0.44$). Analgesia was required by the majority after a HAL procedure on a daily basis for the first week, but tailed off such that at 3 weeks 72% of patients had stopped taking medication.

Twelve patients (7%) reported a SAE (in all cases entailing hospitalisation) following HAL procedure, compared with two (1%) in the RBL arm. In the HAL arm there were six admissions due to pain, two for urine retention, and one each of bleeding, wound infection, nausea/vomiting and a reaction to anaesthetic. For RBL, both events related to prolonged hospitalisation: one for severe pain and one for bleeding 12 days following banding.

The main findings of within-trial cost–utility analysis suggest that HAL procedure appeared not to be cost-effective compared with RBL at a cost-effectiveness threshold of £20,000–30,000 per QALY. In the base-case results, the difference in mean total costs was £1027 higher for HAL than RBL. QALYs were higher for HAL; however, the difference was very small (0.01), resulting in an incremental cost-effectiveness ratio (ICER) of £104,427 per additional QALY. At the threshold of £20,000 per QALY, HAL has zero probability of being cost-effective; at the threshold of £30,000, it has 0.05 probability of being cost-effective.

The base-case CEA suggests that the incremental cost per recurrence avoided was estimated as £4882. In a sensitivity analysis scenario using recurrence from the consultant questionnaire only, the incremental cost per recurrence was estimated as £6346. The extrapolation for 3 years beyond the trial time horizon generated an ICER of £21,887 per QALY, and HAL has 0.34 probability of cost-effectiveness.

## Conclusions

Haemorrhoidal artery ligation is a more clinically effective procedure than a single RBL intervention. However, if HAL is compared with repeat RBL the procedures become equivalent in terms of recurrence. Similarly, symptom severity score, complications, quality of life and continence score were no different between interventions, and patients had more pain in the early postoperative period after a HAL procedure. The HAL procedure is significantly more expensive than RBL and not cost-effective in terms of cost per QALY.

## Trial registration

This trial is registered as ISRCTN41394716 (UKCRN database ID 12486).

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