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ORIGINAL RESEARCH ARTICLE

Cost-Effectiveness of Haemorrhoidal Artery Ligation versus Rubber Band Ligation for the Treatment of Grade II–III Haemorrhoids: Analysis Using Evidence from the HubBLe Trial

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Abstract

Aim Haemorrhoids are a common condition, with nearly 30,000 procedures carried out in England in 2014/15, and result in a significant quality-of-life burden to patients and a financial burden to the healthcare system. This study examined the cost effectiveness of haemorrhoidal artery ligation (HAL) compared with rubber band ligation (RBL) in the treatment of grade II–III haemorrhoids.

Method This analyses used data from the HubBLe study, a multicentre, open-label, parallel group, randomised controlled trial conducted in 17 acute UK hospitals between September 2012 and August 2015. A full economic evaluation, including long-term cost effectiveness, was conducted from the UK National Health Service (NHS) perspective. Main outcomes included healthcare costs, quality-adjusted life-years (QALYs) and recurrence. Cost-effectiveness results were presented in terms of incremental cost per QALY gained and cost per recurrence avoided. Extrapolation analysis for 3 years beyond the trial follow-up, two subgroup analyses (by grade of haemorrhoids and recurrence following RBL at baseline), and various sensitivity analyses were undertaken.

Results In the primary base-case within-trial analysis, the incremental total mean cost per patient for HAL compared with RBL was £1027 (95% confidence interval [CI] £782–£1272, $p < 0.001$). The incremental QALYs were 0.01 QALYs (95% CI −0.02 to 0.04, $p = 0.49$). This generated an incremental cost-effectiveness ratio (ICER) of £104,427 per QALY. In the extrapolation analysis, the estimated probabilistic ICER was £21,798 per QALY. Results from all subgroup and sensitivity analyses did not materially change the base-case result.

Conclusions Under all assessed scenarios, the HAL procedure was not cost effective compared with RBL for the treatment of grade II-III haemorrhoids at a cost-effectiveness threshold of £20,000 per QALY; therefore, economically, its use in the NHS should be questioned.

Key Points for Decision Makers

Because of its significant high cost compared with RBL, with very small additional health benefits, the HAL procedure is unlikely to be cost effective for the treatment of grade II–III haemorrhoids.

The long-term cost-effectiveness result is uncertain due to the lack of good-quality evidence on long-term recurrence, and therefore further research is needed to resolve this issue.

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1 Introduction

Haemorrhoids are a common condition affecting as many as one in three of the population [1], with nearly 30,000 procedures carried out in England in 2014/15 [2]. The degree of symptoms and prolapse (protrusion of the haemorrhoids outside the anal canal) are key determinants of the current standard treatment choice, ranging from dietary advice to rubber band ligation (RBL) in the outpatient department, to an operation under general anaesthetic [3]. Although RBL is cheap, it has a high reported recurrence rate and often needs further procedure(s) to alleviate discomfort caused by residual tissue, which may be repeat RBL or surgical intervention such as excisional haemorrhoidectomy (EH) or a stapled haemorrhoidopexy (SH).

Haemorrhoidal artery ligation (HAL) has been introduced as an alternative treatment option. Although HAL requires an anaesthetic, evidence suggests a recovery similar to RBL but an effectiveness that approaches the more intensive surgical options such as EH. Despite four systematic reviews [4–7] and an overview by the UK National Institute for Health and Care Excellence (NICE) [8], there is a lack of good-quality data as evidence for the advantages of the HAL; however, a recent trial (the HubBLe trial) [9] comparing the effectiveness of HAL with RBL goes some way to providing these data.

Using the data from HubBLe, we conducted a full economic evaluation to establish the cost effectiveness of HAL compared to RBL for the treatment of early-grade haemorrhoids. The headlines of the health economic analyses were provided as part of the clinical effectiveness paper published by Brown et al. [9]. The main trial results are described later in this paper (see Sect. 2.2), which describes the methods used for the economic evaluation and provides detailed results for both trial-based and long-term cost effectiveness. Methods used to undertake various subgroup analyses and sensitivity analyses to address uncertainty associated with the primary cost-effectiveness results are well-described and their results are reported in this paper.

2 Methods

2.1 Overview

As recommended by the UK NICE [10], the economic evaluation was undertaken from the National Health Service (NHS) and Personal Social Services perspective for a 1-year time horizon (the trial follow-up). In the primary within-trial analysis, cost effectiveness was expressed in terms of incremental cost per quality-adjusted life-years (QALY) gained. A secondary within-trial cost-effectiveness analysis (CEA) was performed where the result is expressed in terms of the incremental cost per recurrence avoided. Long-term cost effectiveness was estimated by extrapolating the analyses to a 4-year time horizon.

2.2 The HubBLe Trial

The HubBLe trial is a multicentre, open-label, parallel group, randomised controlled trial (RCT) conducted in 17 acute UK hospitals from September 2012 to August 2015. The study design, protocol, consort diagram and full clinical effectiveness results have been published elsewhere [9, 11]. In brief, the trial enrolled 372 patients with grade II or early grade III haemorrhoids (piles that prolapse but either spontaneously reduce or require minimal manual replacement). Patients were randomly assigned to either the HAL group ($n = 185$) or the RBL group ($n = 187$) and followed for up to 12 months. The primary outcome of this study was recurrence at 1-year post-procedure, which was found to be 49% in the RBL group and 30% in the HAL group (adjusted odds ratio 2.23, 95% confidence interval [CI] 1.42–3.51, $p = 0.0005$). Data for health-related quality of life (HRQoL), resource use and clinical outcomes used for CEAs come from the HubBLe trial. Table 1 shows the clinical data inputs used in the analysis, including the mean costs of each clinical event, standard deviation, and sample size for both treatment groups. The clinical events data include the procedures events, procedural and post-procedural complications, hospital admissions, and medications on discharge.

2.3 Resource Use and Costs

The costing approach followed the standard stages used in economic evaluation and involved identification of resource use, measurement and valuation [12]. The use of the following types of resources during RBL or HAL procedures were identified and recorded: procedure event, procedural and post-procedural complications, hospital admissions, and medications on discharge. Post-discharge resource use included outpatient treatments, surgical treatments, emergency admissions, contact with healthcare professions, follow-up treatments and procedures.

Data on measurement of resource use were collected in HubBLe using the procedure details form completed on the procedure day (day 0), clinical assessment form at 6 weeks, and consultant and general practitioner (GP) questionnaires at 12 months. The participant questionnaire at 1 year was also used as a sense-check for the consultant and GP responses. All resource-use data collection forms and questionnaires are provided as electronic supplementary materials (ESM) 1–5. For the HAL procedure, measurements of resource use include the type of anaesthetic (general and local, spinal, or sedation only), grade of

Table 1 Health services resource use and costs

	RBL			HAL		
	Mean costs (£)	SD	*N* (%)*	Mean costs (£)	SD	*N* (%)*
Medications	2.04	8.4	187 (100)	7.59	8.4	185 (100)
RBL procedure	109.00	0.0	187 (100)	0.00	0.0	185 (100)
Excisional tag removal	0.00	0.0	187 (100)	10.02	31.6	185 (100)
HAL procedure	0.00	0.0	179 (96)	732.56	299.7	151 (82)
Admissions for surgery	0.00	0.0	187 (100)	23.01	80.5	158 (85)
Proctoscopy	5.02	5.5	149 (80)	4.71	5.5	140 (76)
Other elective procedure	0.00	0.0	187 (100)	7.23	98.4	185 (100)
Post-discharge admissions	41.73	253.0	150 (80)	65.66	314.9	143 (77)
Other procedures	0.00	0.0	150 (80)	0.76	9.1	143 (77)
Repeated RBL	82.45	276.3	187 (100)	32.05	148.0	185 (100)
Further HAL	203.76	587.6	187 (100)	18.72	179.6	185 (100)
Excisional haemorrhoidectomy	16.14	155.6	187 (100)	24.47	191.1	185 (100)
Stapled haemorrhoidopexy	26.51	255.6	187 (100)	0.00	0.0	185 (100)
RBL in the theatre	21.47	218.4	187 (100)	14.47	138.8	185 (100)
Admissions in 1 year	17.78	166.4	176 (94)	68.04	320.1	161 (87)
Emergency procedure	29.53	284.8	187 (100)	29.85	286.3	185 (100)
Consultant visits	88.59	131.2	175 (94)	86.39	151.2	161 (87)
GP visits	10.93	27.8	122 (65)	16.54	35.2	114 (62)
Nurse visits	0.56	6.2	122 (65)	0.85	3.8	113 (61)

RBL rubber band ligation, *HAL* haemorrhoidal artery ligation, *SD* standard deviation, *GP* general practitioner

* The numbers in parentheses represent the percentages of complete cases, as a proportion of the total number of patients randomised for each treatment group, which were used for estimating the mean cost for each resource use item

operating surgeon, consultant supervision time, timing for surgery and overall time spent in the operating theatre. Types of hospital admissions were recoded and the length of stay was measured based on the NHS average estimates [13]. All visits to consultants, GPs and GP nurses were recorded and resource use during each visit was calculated using the average estimates based on the NHS [13] or Personal Social Services Research Unit (PSSRU) of the University of Kent approaches, where relevant [14].

Valuation of resource use followed different approaches for procedure events and post-discharge events. A micro-costing approach was applied for the HAL procedure event as cost per minute in procedure, recovery time and theatre overhead based on actual time spent during the procedure. Unit costs for surgical kits used in the HAL procedure were obtained from the NHS supply system. Unit costs for resource use in 2014/15 prices were obtained, where relevant, from routinely published national reference costs sources. The NHS reference costs [13], the PSSRU's report on unit costs for health and social care [14] and the British National Formulary (BNF) [15] were used. Other unit costs were obtained from other sources, i.e. costs for the SH procedure were obtained from McKenzie et al. [16] and adjusted for inflation; blood transfusion costs were obtained from the costing statement issued by NICE [17]; and costs for repeated RBL and HAL procedures were calculated using average costs within HubBLe. All unit costs are provided in Table 2. Discounting was not used for trial-based analyses as it was carried out for a 1-year time horizon.

2.4 Health Outcomes

QALY was used as an outcome measure for the primary cost-utility analysis (CUA) as per NICE recommendations [10]. The individual patient-level QALYs were calculated using the 5-level version of the EuroQol 5-Dimension HRQoL questionnaire (EQ-5D-5L) [18]. The utility scores applied in calculating the QALYs were obtained using recently published EQ-5D-5L tariffs based on the English general public preferences [19]. The EQ-5D-5L measurements used were taken in HubBLe at baseline, 1 day, 7 days, 21 days, 6 weeks and 12 months. Recurrence at 1 year was used as an outcome for a secondary CEA in terms of additional cost per recurrence avoided.

2.5 Analysis

The economic evaluation involved CUA within the trial time horizon as a primary analysis, whereas trial-based CEAwas

Table 2 Unit costs applied for valuation of resource use

Event	Description	Unit cost (£)	Source	Notes
RBL procedure				
Procedure cost	RBL procedure	109.00	NHS reference costs 2014/15 [13]	Outpatient procedure
	Blood transfusion	170.14	NICE 2015 [17]	Blood transfusion costing statement
Hospital admission	In-patient bed day	303.00	NHS reference costs 2014/15 [13]	–
Medication prescribed post-procedure	Paracetamol	1.27	BNF 2015 [15]	500 mg, 32-tablet pack
	Co-codamol	6.73	BNF 2015 [15]	30/500 mg, 100-tablet pack
	Codeine	1.23	BNF 2015 [15]	15 mg, 28-tablet pack
	NSAIDs	3.50	BNF 2015 [15]	Ibuprofen 200 mg, 84-tablet pack
	Tramadol	14.10	BNF 2015 [15]	100 mg, 30-tablet pack
	Laxative	3.82	BNF 2015 [15]	Bisacodyl 5 mg, 100-tablet pack
	Antibiotic	5.03	BNF 2015 [15]	Augmentin 375 mg, 21-tablet pack
HAL procedure				
Anaesthetic	General and local anaesthetic	100.08	NHS reference cost 2014/15 [13]	
	Spinal anaesthetic	200.00		
HAL procedure	Consultant cost per minute	2.30	PSSRU 2015 [14]	Includes costs of qualifications
	Associate specialist cost per minute	2.13	PSSRU 2015 [14]	Includes costs of qualifications
	Surgical trainee cost per minute	2.13	PSSRU 2015 [14]	Includes costs of qualifications
	Fellow cost per minute	2.13	PSSRU 2015 [14]	Includes costs of qualifications
	Specialist nurse cost per minute	1.52	PSSRU 2015 [14]	Includes costs of qualifications
	Research nurse cost per minute	1.52	PSSRU 2015 [14]	Includes costs of qualifications
	Registrar cost per minute	1.20	PSSRU 2015 [14]	Includes costs of qualifications
	Scrub nurse cost per minute	1.52	PSSRU 2015 [14]	Includes costs of qualifications
	Cost per minute in recovery	0.41	McKenzie et al., 2009 [16]	Adjusted for inflation
	Cost per minute for theatre overheads	13.74	McKenzie et al., 2009 [16]	Adjusted for inflation
Operating event	Outpatient procedure	109.00	PSSRU 2015 [14]	
	Surgical kit for the HAL procedure	432.00	NHS supply system	
	Excision of skin tags	109.00	NHS reference costs 2014/15 [13]	Outpatient procedure
Procedure cost	Cost of HAL surgery (used in sensitivity analysis)	1128.00	NHS reference costs 2014/15 [13]	Intermediate anal procedure (FZ22B (EL)
Hospital admission	Inpatient bed day	303.00	NHS reference costs 2014/15 [13]	
	Need for blood transfusion	170.14	NICE 2015 [17]	Blood transfusion costing statement

Table 2 continued

Event	Description	Unit cost (£)	Source	Notes
Medication on discharge	Paracetamol	1.27	BNF 2015 [15]	500 mg, 32-tablet pack
	Co-codamol	6.73	BNF 2015 [15]	30/500 mg, 100-tablet pack
	Codeine	1.23	BNF 2015 [15]	15 mg, 28-tablet pack
	NSAIDs	3.50	BNF 2015 [15]	Ibuprofen 200 mg, 84-tablet pack
	Tramadol	14.10	BNF 2015 [15]	100 mg, 30-tablet pack
	Laxative	3.82	BNF 2015 [15]	Bisacodyl 5 mg, 100-tablet pack
	Antibiotic	5.03	BNF 2015 [15]	Augmentin 375 mg, 21-tablet pack
	GTN paste	39.30	BNF 2015 [15]	GTN ointment 0.4%, 30 g
	Diltiazem paste	73.83	BNF 2015 [15]	2% diltiazem cream
Post-discharge (RBL or HAL)				
Outpatient treatment	Outpatient visit	114.00	NHS reference costs 2014/15 [13]	
	Injection sclerotherapy	4.79	BNF 2015 [15]	Phenol 5% injection 5-ml amp
	Excisional haemorrhoidectomy	1508.72	NHS reference costs 2014/15 [13]	FZ22E (EL)
	Stapled haemorrhoidopexy	2478.42	McKenzie et al., 2009 [16]	Adjusted for inflation
	Rubber band ligation (in theatre)	1338.45	NHS reference costs 2014/15 [13]	FZ22E (EL)
	Other elective procedure	1338.45	NHS reference costs 2014/15 [13]	FZ23A
Emergency admissions	Emergency admission for symptoms related to RBL/HAL	1565.00	NHS reference costs 2014/15 [13]	NEL
	Blood transfusion	170.14	NICE 2015 [17]	Blood transfusion costing statement
	Emergency operation	2761.00	NHS reference costs 2014/15 [13]	FZ23A
Contact with health professionals	GP visit	46.00	PSSRU 2015 [14]	
	Nurse visit (GP practice)	13.70	PSSRU 2015 [14]	Based on 15.5 min per visit
	Consultant visit	114.00	NHS reference costs 2014/15 [13]	
Further treatments	GTN paste	39.30	BNF 2015 [15]	GTN ointment 0.4%, 30 g
	Diltiazem paste	73.83	BNF 2015 [15]	2% diltiazem cream
Recurrence treatment costs	Proctoscopy at 6-week assessments	10.99		
	RBL after recurrence	523.16	Mean RBL cost within the HubBLe trial	
	Admissions with complications	1565.00	NHS reference costs 2014/15 [13]	NEL

RBL rubber band ligation, *HAL* haemorrhoidal artery ligation. *NSAIDs* nonsteroidal anti-inflammatory drugs, *NHS* National Health Service, *NICE* National Institute for Health and Care Excellence, *BNF* British National Formulary, *PSSRU* Personal Social Services Research Unit, *GP* general practitioner, *GTN* glyceryl trinitrate, *EL* elective, *NEL* non-elective

conducted as a secondary analyses. A long-term CUA was conducted by extrapolating the primary analysis to a 4-year time horizon. All analyses involved differences in costs and outcomes (QALYs and recurrence at 1 year, respectively). Analyses of trial data were undertaken using Stata® version 13.1 (StataCorp LLC, College Station, TX, USA).

The base-case primary analysis was based on imputed data. The Multiple Imputation Chained Equations (MICE) method with predictive mean matching was used for imputing missing values of costs, QALYs and baseline utilities [20, 21]. Age, sex, grade of haemorrhoids, centre and randomisation group were used as imputation variables

in the imputation model. A seemingly unrelated regression (SUR) model was fitted for estimating differential mean total costs and QALYs between HAL and RBL [22]. The SUR model assumes normal distribution for both costs and QALYs. It was controlled for imbalance in baseline utility at the QALY equation [23], and took into account the correlation between costs and QALYs [22]. The incremental cost-effectiveness ratio (ICER) was estimated from the SUR regression results, which gives the cost per additional QALY gained. To assess cost effectiveness, the estimated ICER was then compared with the NICE cost-effectiveness threshold of £20,000–30,000 per QALY [10]. Another advantage for using the SUR model was that it provided the estimation of the full variance–covariance matrix, which was used for addressing uncertainty, as described in the next paragraph.

Uncertainty around the primary CUA estimates was addressed using a number of approaches based on the parametric method [24, 25]. Five key parameters from the SUR regression output were used for conducting a fully parametric analysis. These parameters were difference in mean costs, standard error of differential mean costs, difference in mean QALYs, standard error of differential QALYs, and covariance between costs and QALYs. From these parameters, the cost-effectiveness acceptability curve (CEAC) was produced. The higher bound of the NICE cost-effectiveness threshold of £30,000 per QALY was used as the standard decision rule in these analyses. The cost-effectiveness threshold was then varied from £0 to £140,000 to address uncertainty across different levels of willingness to pay.

A subgroup analysis was conducted for patients with new haemorrhoids and patients with recurrence following RBL at baseline (those who had a previous unsuccessful RBL procedure). An additional regression analysis was conducted by controlling for the grade of haemorrhoids (II/III) on both cost and QALY equations, together with baseline utility within the SUR model. The latter analysis allowed us to assess the effect of the grade of haemorrhoids on the ICER estimate, and hence on cost-effectiveness. A secondary CEA was conducted for estimating the additional cost per recurrence avoided.

A number of sensitivity analyses were performed to assess the robustness of estimates from the base-case analysis. Three scenarios were considered. First, a CUA using complete cases only was carried out, and, second, analysis using the NHS reference cost for the HAL procedure rather than the micro-costing approach described earlier was carried out. In this analysis, HAL was considered as a day case intermediate anal procedure and the national average cost associated with this Health Resource Group (HRG) was applied [13]. A third scenario assumed QALY losses for each subsequent procedure performed during the trial follow-up. Since the EQ-5D-5L questionnaire was completed at particular follow-up time points that did not coincide with any subsequent procedure, estimated QALY decrements were applied. QALY decrements for subsequent HAL or RBL procedures were estimated using mean utility scores from the HubBLe trial measured at baseline and days 1 and 7. For EH and SH, utility decrements were taken from a published UK study [26].

A secondary analysis explored the extrapolation beyond the trial time horizon for estimating the long-term cost effectiveness. Costs, utilities and recurrence data collected within the HubBLe trial were used in combination with external evidence [3, 27] on long-term recurrence for analyses over a 4-year time horizon. The choice of time horizon was driven by evidence from the external studies where recurrence rates for both HAL and RBL were available over this time horizon.

A three-health-state Markov model was constructed for extrapolating within-trial analysis to long-term cost effectiveness. To maintain consistency with the trial analyses, health states were chosen based on the primary outcome measure of the HubBLe trial, i.e. recurrence. Health states modelled were new haemorrhoids, recurrence and no recurrence. Patient transition from the recurrence or no recurrence health states to new haemorrhoids was restricted in the model, assuming that any new haemorrhoids after the first year is not associated with condition at baseline. The UK Treasury discount rate of 3.5% per year was used for discounting all future costs and QALYs to their present values [10]. A probabilistic sensitivity analysis (PSA) was run on 1000 Monte Carlo simulations to address uncertainty around the model parameters. The main parameters used in the PSA analysis over 4 years were based on the deterministic analysis, and their values were as follows. For RBL, the mean total cost was £1205 (standard error [SE] = 351), and the mean QALY was 3.48 (SE = 0.20). For HAL, the mean total cost was £2322 (SE = 848), and the mean QALYs was 3.53 (SE = 0.25). Normal distribution was assumed for both costs and QALYs in the extrapolation PSA to maintain consistency with the within-trial analysis. The transition probabilities deriving patients' movement between the modelled health states is provided as ESM 6.

3 Results

3.1 Healthcare Costs

The mean total healthcare costs per patient, and 95% CIs, are reported as descriptive statistics based on the complete case analysis. For the RBL group, the mean total cost per patient was £709 (n = 103, 95% CI £522–£896), and for

the HAL group, the mean total cost was £1767 ($n = 99$, 95% CI £5568–£1965). Within-trial cost data were right skewed, with only a few patients incurring very high costs in both arms of the trial.

3.2 Health-Related Quality of Life

The mean baseline utilities and QALYs for RBL and HAL are descriptively reported based on complete case analysis. The mean baseline EQ-5D-5L utility score was 0.90 ($n = 149$, 95% CI 0.88–0.92) in the RBL group and 0.89 ($n = 152$, 95% CI 0.87–0.92) in the HAL group. The mean QALYs for the RBL group was 0.91 ($n = 85$, 95% CI 0.89–0.94), and 0.92 ($n = 92$, 95% CI 0.90–0.95) for the HAL group.

3.3 Trial-Based Cost Effectiveness

The primary base-case cost-effectiveness results, together with results from all subgroup analyses and sensitivity analyses, are presented in Table 3. In the primary base-case analysis, the incremental total mean cost per patient for HAL compared with RBL over a 1-year time horizon was £1027 (95% CI £782–£1272, $p < 0.001$). The adjusted estimates of differential QALYs, after controlling for imbalance in baseline utility, showed that HAL gained an average of 0.01 QALYs (95% CI −0.02 to 0.04), although the difference was not statistically significant ($p = 0.49$). This generated an ICER of £104,427 per QALY, suggesting that HAL is highly unlikely to be cost effective at the £20,000–30,000 threshold. The cost per recurrence avoided was estimated to be £4882 (95% CI £3628–£6135).

The CEAC generated from the parametric analysis applied on imputed data is presented in Fig. 1. This graph shows the probability that HAL is cost effective under a range of cost-effectiveness threshold values (£0–£140,000). At £20,000 per QALY threshold, HAL had zero probability of being cost effective; at the £30,000 threshold, it had a 0.05 probability of cost effectiveness.

3.4 Subgroup and Sensitivity Analyses

Results from subgroup analysis for patients with recurrence following RBL (at baseline) led to an ICER of £246,959 per QALY, suggesting that QALY gains were more costly for this group compared with new patients (£89,972 per QALY). This result was driven by the smaller difference in QALYs for patients with recurrence following RBL at baseline (Table 3). The second subgroup analysis conditional on patients with grade III haemorrhoids (at baseline) generated an ICER of £108,478 per QALY after adjusting for baseline grade of haemorrhoids.

Results from all sensitivity analyses are reported in Table 3. These did not materially change the base-case result and HAL remained non-cost-effective in all scenarios. The first sensitivity analysis based on complete cases led to an ICER of £90,688 per QALY. The second sensitivity analysis, based on using the NHS reference cost for HAL, generated an ICER of £152,479 per QALY. Finally, the third analysis, which accounted for QALY decrements

Table 3 Cost-effectiveness results for base–base, subgroup and sensitivity analyses

Analysis	Incremental cost [£]: HAL–RBL (95% CI); *p* value	Incremental QALYs: HAL–RBL (95% CI); *p* value	ICER £ per QALY gained	Probability that HAL is cost effective at the threshold 20,000/QALY (£30,000/QALY)
Base-case analysis: trial based analysis based on imputed data	1027 (782–1272); <0.001	0.01 (−0.02 to 0.04); 0.49	104,427	0.00 (0.05)
Subgroup analysis: patient with recurrence following RBL at baseline	1091 (623–1558); <0.001	0.004 (−0.049 to 0.058); 0.87	246,959	0.05 (0.13)
Subgroup analysis: patient with grade III haemorrhoids	999 (760–1239); <0.001	0.01 (−0.09 to 0.037); 0.52	108,478	0.00 (0.07)
Sensitivity analysis: complete case analysis	1073 (700–1447); <0.001	0.01 (−0.019 to 0.04); 0.50	90,688	0.00 (0.00)
Sensitivity analysis: using the NHS reference cost for HAL	1498 (1262 – 1735); <0.001	0.01 (−0.018 to 0.038); 0.49	152,479	0.00 (0.00)
Sensitivity analysis: applying QALY decrements for subsequent procedures	1030 (760–1300); <0.001	0.01 (−0.02 to 0.036); 0.56	125,076	0.00 (0.05)
Long-term extrapolation analysis	1125 (1117–1133)	0.05 (0.048–0.055)	21,798	0.66 (0.78)

HAL haemorrhoidal artery ligation, *RBL* rubber band ligation, *QALYs* quality-adjusted life-years, *ICER* incremental cost-effectiveness ratio, *CI* confidence interval, *NHS* National Health Service

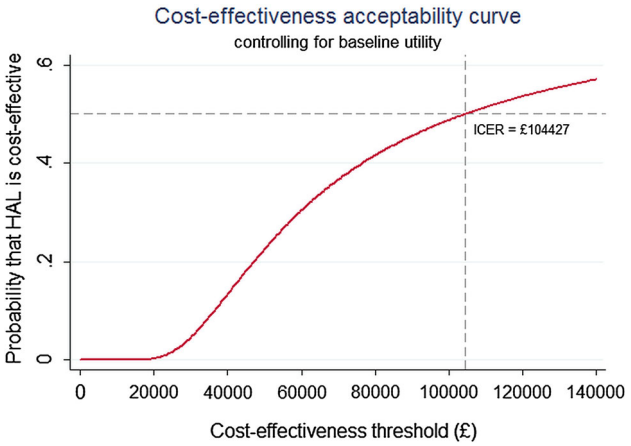

Fig. 1 Cost-effectiveness acceptability curve showing the probability that HAL is cost-effectiveness at different thresholds (within trial analysis)

for subsequent procedures, had an ICER estimate of £125,076 per QALY.

3.5 Long-Term Cost Effectiveness

In the extrapolation analysis, the estimated cost per QALY for HAL compared with RBL for a 4-year time horizon was lower compared with the analysis within the trial. The probabilistic ICER was estimated at £21,798 per QALY, produced from an incremental total mean cost of £1125 (95% CI £1117–£1133) and incremental mean QALYs of 0.05 (95% CI 0.048–0.055). Figure 2 shows the CEAC based on 1000 PSA simulations from the extrapolation analysis. The PSA revealed that HAL has a 0.66 probability of being cost effective at the £20,000 threshold when long-term cost effectiveness was considered. At the £30,000 threshold, HAL has a 0.78 probability of being cost effective.

4 Discussion

The main findings of the within-trial analysis of this study suggest that the HAL procedure is highly unlikely to be cost effective compared with RBL under the cost-effectiveness threshold of £20,000–£30,000 per QALY. In the base-case trial-based CUA, HAL was £1027 more costly compared with RBL, and the additional health benefit generated was very small (0.01 QALYs). The incremental total mean cost per QALY was £104,427. All sensitivity analyses did not materially change the base-case results and HAL remained non-cost-effective in all scenarios, indicating the robustness of the primary base-case analysis. When different population subgroups were considered, analysis of patients with recurrence following RBL (at baseline), as well as new patients, was broadly consistent with the overall study population, although the incremental cost per QALY was higher for patients with recurrence compared with new patients (£246,959 compared with £89,972). Similarly, results from another subgroup analysis based on the grade of haemorrhoids (II/III) generated fairly similar cost-effectiveness results.

Trial-based cost effectiveness in terms of additional cost per recurrence avoided was estimated at £4882. This indicates that HAL could only be considered as worthwhile

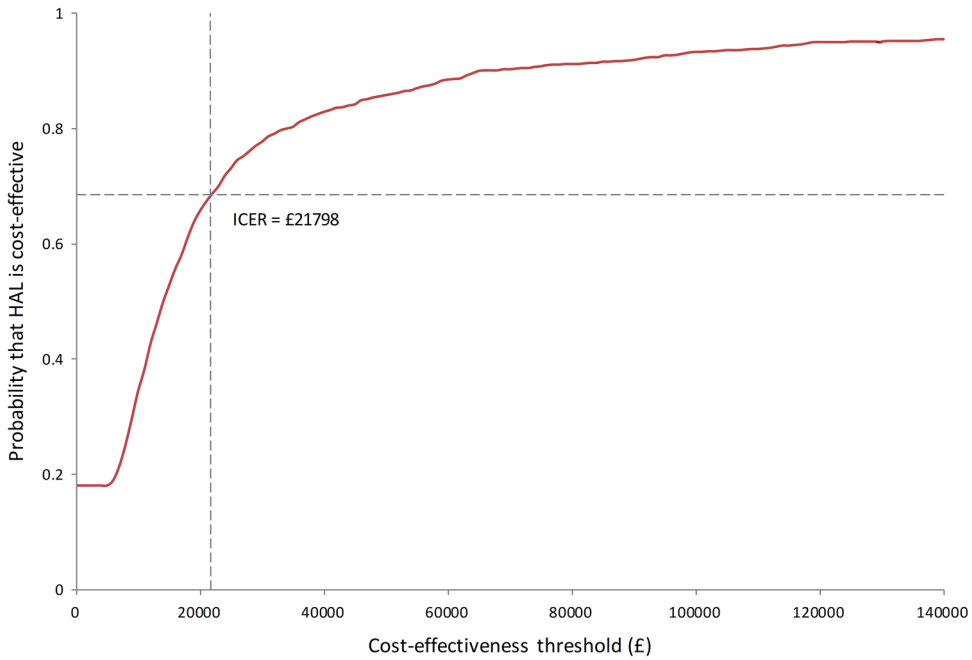

Fig. 2 Cost-effectiveness acceptability curve showing the probability that HAL is cost-effectiveness at different thresholds (extrapolation analysis)

economically if the healthcare system is willing to pay approximately £5000 per each case of recurrence avoided as a result of introducing the HAL procedure. However, this approach is not generally used within the NICE decision-making framework, where cost per QALY is the preferred measure used to establish cost effectiveness. The long-term cost effectiveness generated from extrapolating the analyses beyond the trial time horizon suggested a lower cost per QALY compared with the short-term trial-based analyses. The probability of HAL cost effectiveness remained low at the £20,000 threshold based on the extrapolation analysis (but more likely than the within–trial analysis).

Additional evidence on healthcare cost from the literature is sparse for this condition. Cost analysis is available in one trial comparing SH with RBL for the treatment of grade II haemorrhoids [16]. The results from this study are consistent with the findings in HubBLe. The mean total cost for RBL was estimated at £273 with the difference in mean total cost of SH versus RBL being substantially higher (£1483), generated negative difference in QALYs (−0.014), and SH was unlikely to be cost effective compared with RBL at a 1-year time horizon [16]. Interestingly, the study found that RBL was associated with a higher recurrence rate compared with SH, with an estimated additional cost of £4945 per recurrence avoided. Another multicentre RCT comparing HAL with SH has estimated the incremental cost per averted complication at €7192 [28]. The study concluded that HAL was more expensive, was a lengthy procedure, and provided inferior outcomes, suggesting an increased risk of recurrence [28].

Among the strengths of this study is that it is based on a pragmatic, multicentre RCT design using a mix of teaching and district general hospitals across the UK, ensuring that the results could be generalisable to all patient populations seeking treatment for grade II/III haemorrhoids. The numbers of patients recruited are such that there can be considerable confidence in the conclusions drawn from the trial-based cost-effectiveness analyses. We used a three-pronged approach for resource use data collection within the trial, which was based on hospital records (procedure form, clinical assessment form, and consultant 1-year questionnaire), GP records (GP 1-year questionnaire), and patient self-reported 1-year questionnaire. The latter was used as a sense check for hospital and GP records, which might be expected as rather more complete. This approach would limit the impact of recall bias because patient-reported data were largely secondary.

The main limitation of this study is that the long-term cost-effectiveness result is subject to uncertainty. This should be interpreted with caution due to uncertainty around long-term recurrence rates emanating from the poor quality of external evidence used in the extrapolation model. However, the findings of this study add to the growing body of evidence base that proposes various interventions for management of grade II–III haemorrhoids. Among this, the HubBLe and eTHoS trials [9, 29] include four interventions for this patient population: RBL, HAL, SH and EH. Pooling of data from these studies with existing datasets [30] in a network meta-analysis should be considered. This will allow comparison of all four principal procedures and provide robust cost-effectiveness evidence to inform treatment guidelines.

5 Conclusions

Based on all scenarios assessed in this study, the HAL procedure is unlikely to be cost effective compared with RBL for the treatment of grade II–III haemorrhoids; therefore, from an economic perspective, its use for these particular patients should be questioned.

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Compliance with ethical standards

Availability of data The datasets generated and/or analysed during the current study are not publicly available due to ethical restrictions but may be available from the corresponding author on reasonable request.

Conflicts of interest Abualbishr Alshreef, Allan J. Wailoo, Steven R. Brown, James P. Tiernan, Angus J.M. Watson, Katie Biggs, Mike Bradburn and Daniel Hind declare that they have no conflicts of interest.

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Ethical approval This study was approved by an NHS Research Ethics Committee (NRES Committee Yorkshire and The Humber—South Yorkshire [REC reference 12/YH/0236]) and has been performed in accordance with the ethical standards of the Declaration of Helsinki. Fully informed written consent was obtained from all individual participants included in the study.

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