Hydrogel-coated coils versus bare platinum coils for the endovascular treatment of intracranial aneurysms (HELPS): a randomised controlled trial

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Summary

Background Coated coils for endovascular treatment of cerebral aneurysm were developed to reduce recurrence and retreatment rates, and have been in clinical use for 8–9 years without robust evidence to determine their efficacy. We assessed the efficacy and safety of hydrogel-coated coils.

Methods This randomised trial was undertaken in 24 centres in seven countries. Patients aged 18–75 years with a previously untreated ruptured or unruptured cerebral aneurysm of 2–25 mm in maximum diameter were randomly allocated (1:1) to aneurysm coiling with either hydrogel-coated coils or standard bare platinum coils (control). Randomisation was done with a computer-generated sequence, stratified by aneurysm size, shape, and dome-to-neck ratio; intention to use assist device; and by region. Participants and those assessing outcomes were masked to allocation. Analysis was by modified intention to treat (excluding missing data). Primary outcome was a composite of angiographic and clinical outcomes at 18-month follow-up. We also did prespecified subgroup analyses of characteristics likely to be relevant to angiographic outcome. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN30531382.

Findings 249 patients were allocated to the hydrogel coil group and 250 to the control group. In 44 of 467 patients for whom an 18-month composite primary outcome was unavailable, 6-month angiographic results were used. 70 (28%) patients in the hydrogel group and 90 (36%) control patients had an adverse composite primary outcome, giving an absolute reduction in the proportion of adverse composite primary outcomes with hydrogel of 7·0% (95% CI −1·6 to 15·5), odds ratio (OR) 0·73 (0·49–1·1, p=0·13). In a prespecified subgroup analysis in recently ruptured aneurysms, there were more adverse composite primary outcomes in the control group than in the hydrogel group—OR 2·08 (1·24–3·46, p=0·014). There were 8·6% fewer major angiographic recurrences in patients allocated to hydrogel coils—OR 0·7 (0·4–1·0, p=0·049). There were five cases of unexplained hydrocephalus in not-recently-ruptured aneurysms in the hydrogel coil group and one case in the control group.

Interpretation Whether use of hydrogel coils reduces late aneurysm rupture or improves long-term clinical outcome is not clear, but our results indicate that their use lowers major recurrence.

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Introduction

After the international subarachnoid aneurysm trial (ISAT), which showed better outcomes with endovascular coiling than with neurosurgical clipping for the treatment of intracranial aneurysms, endovascular coiling is the preferred treatment for many patients.[1–3] The technique for endovascular coiling is described in the webappendix (p 1); see also webvideos 1–4). Although aneurysm clipping is a much more invasive procedure, aneurysm remnants or recurrences and the need for retreatment are more common after endovascular coiling than after clipping.[2,4–6] Major aneurysm recurrences (aneurysm incompletely occluded on follow-up imaging) occur after coiling in 15–19%[4,6,7] of patients by 3–6 months after treatment, rising to 21% at a mean of 16 months after treatment.[4] Therefore, follow-up imaging beyond 6 months is mandatory and important for the ongoing management of patients.[8]

The risk of haemorrhage from an aneurysm after coiling is very low at 0·12–0·4% per year.[3,9,10] Retreatment rates after coiling are also low at 9–11% per year.[3,9] This low event rate means that randomised trials to assess whether a refinement of technology improves outcomes (especially haemorrhage) would need an unfeasibly large study population for what is, compared with cardiological interventions, a relatively low volume procedure. A surrogate endpoint for coiling outcome is therefore needed to assess whether technical advances improve outcomes.[11] Major (angiographic) recurrence is a clinically relevant surrogate because angiographic follow-up directly affects management of patients. Major recurrence is associated with an increased risk of bleeding, and can lead to retreatment and more intense or extended imaging surveillance.[6,10,11] An intervention that substantially reduced major recurrence rate would be expected to reduce the already low rebleed and retreatment rates[10] and

See **Online** for webappendix and webvideos

reduce the intensity and duration of imaging surveillance, which would be of clear benefit to patients and health-care systems.[11] The externally validated angiographic scale (Montreal scale) used to assess recurrences in the Hydrocoil Endovascular aneurysm occLusion and Packing Study (HELPS) trial has high reproducibility and good to very good interobserver agreement (with mean κ for 3 point Montreal scale of 0·67).[4,12]

Coated coils for aneurysm treatment have been in clinical use for 8–9 years at a much increased cost compared with bare platinum coils, and without robust evidence of their safety and effectiveness.[13] The hydrogel-coated coil we used in HELPS was designed to improve aneurysm packing by coils, aiming to improve aneurysm stability and aneurysm neck healing,[14,15] with the added advantage of the use of substantially shorter coil length (webappendix p 3). We aimed to establish whether use of hydrogel-coated coils for treatment of intracranial aneurysms improves outcomes compared with use of bare platinum coils.

Methods

Patients

Patients were enrolled into HELPS, a pragmatic, multicentre, randomised controlled trial from 24 centres in seven countries (UK, USA, Brazil, Germany, Australia, France, and Argentina). Patients were eligible for inclusion if they presented with a previously untreated cerebral aneurysm measuring 2–25 mm in maximum diameter, were aged 18–75 years, were deemed by the neurovascular team to need coiling, were not pregnant, had a World Federation of Neurosurgeons grading between 0 and 3,[16] had anatomy such that endovascular occlusion was judged possible, had not previously been enrolled into the trial, and if the neurointerventionalist who would do the surgery was content to use either bare platinum or HydroCoil Embolic System (HES; MicroVention Inc, Tustin, CA, USA) coils. Patients were excluded if they had more than one aneurysm requiring treatment at one procedure. All patients gave written informed consent or, if they could not give consent, written assent was obtained from their next of kin. This trial had UK Multicentre Research Ethics Committee approval and all centres had local ethics approval.

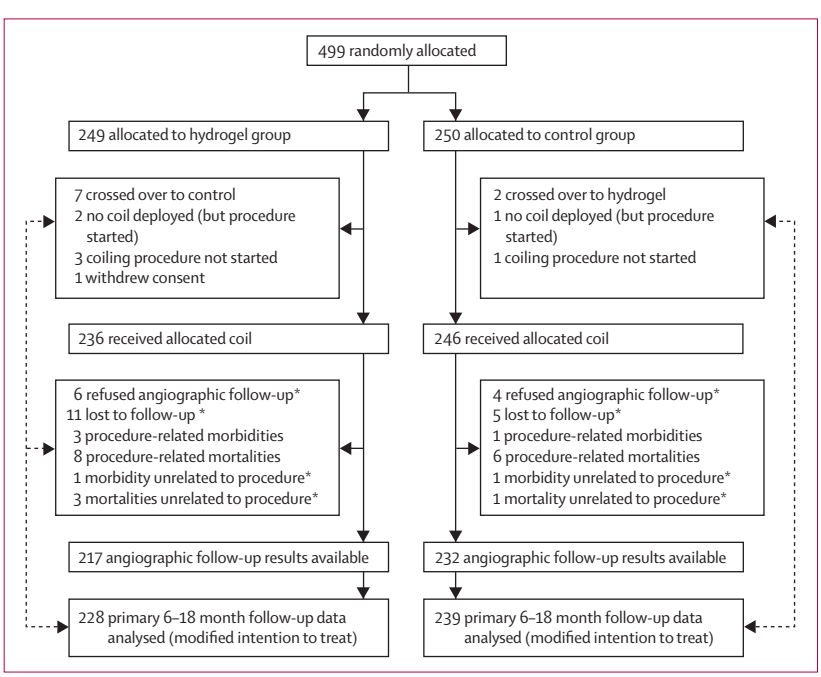

Figure 1: **Trial profile**
Only 12 of 24 centres kept a comprehensive eligibility log. These 12 centres randomly allocated 355 of 499 participants, assessing 1785 patients for eligibility and excluding 1430 for the following reasons: 563 did not meet inclusion criteria, 48 declined to participate, 819 for other reasons. *Excluded from the modified intention-to-treat analysis.

Randomisation and masking

The online, computer-generated random allocation schedule was run from the coordinating centre (Edinburgh, UK) and was stratified by aneurysm size, shape, and dome-to-neck ratio; intention to use assist device; and by region. The information technology manager at the University of Edinburgh Division of Clinical Neurosciences developed the website and randomisation programme under instruction of trial statistician. The online system ensured allocation was concealed before the decision to randomise. Groups were balanced with minimisation criteria.[17] For information about minimisation criteria and assist devices see webappendix (p 4).

Masking of the interventional team to the randomly allocated treatment was not possible. Patients were masked to allocation unless they specifically requested otherwise. Digital copies of angiogram images were sent to the trials office for collation then sent in batches to assessors at the independent core laboratory (CHUM Research Centre, Notre-Dame Hospital, Montreal, Canada) for analysis, who were masked to both treatment allocation and treatment received. The core laboratory assessed angiograms according to the revised three-point Montreal scale (complete, near complete, or incomplete occlusion) with a major remnant or recurrence defined as one sufficiently large enough to technically allow placement of further coil(s).[4] Because the smallest coils available were 2 mm in diameter, not every incomplete occlusion would be large enough to be classed as major recurrence.

Procedures

Detailed information about the coiling procedure is reported elsewhere.[17] For patients allocated to the HES group, a guideline target hydrogel usage was prespecified (webappendix p 5). Detailed information about baseline demographics, data handling, and coiling are shown elsewhere.[17] To check validity of these data, the trial manager compared case records with patients' original

medical notes in a random 10% sample (selected with a computer-generated programme) and detected no substantial discrepancy.

The primary outcome measure was the proportion of patients with major aneurysm recurrence on follow-up angiography at 18 months after treatment. Procedure-related deaths and morbidity that resulted in patients not having follow-up angiography were also counted as adverse primary outcomes, making the primary trial endpoint a composite of angiographic and clinical outcomes. A composite angiographic and clinical endpoint was used rather than an angiographic endpoint alone because some patients die or are left so disabled after coiling or subarachnoid haemorrhage that follow-up angiography is not appropriate. When angiographic results at 18 months were not available, a patient's angiographic result at 6 months was used instead.

Secondary outcomes were clinical outcome at 3 months and 18 months after treatment (as measured by the modified Rankin Scale [MRS]), rebleed and retreatment rates, and aneurysm packing density. Calculation of aneurysm packing density was done with aneurysm volume (as calculated by the core laboratory) and the online angiocalc programme. MRS assessment at 3 months and 18 months was by a postal questionnaire completed by patients or, if patients were unable to complete the questionnaire themselves, by their main carer, and was independent of the interventional team. Rebleed was defined as any bleed from a target aneurysm that occurred after completion of the initial coiling procedure (including first bleeds occurring after treatment in previously unruptured aneurysms). Retreatment was classified as any further treatment procedure on a target aneurysm. We also did a post-hoc analysis of the frequency of hydrocephalus in unruptured aneurysms, a possible complication of coiling that emerged after the trial started.[18–21]

Statistical analysis

The planned study size was 500 patients, which we calculated assuming that the proportion of patients with major aneurysm recurrence on follow-up angiography would be 20%[22] in the bare platinum group and 10% in the HES group; a 10% reduction in major recurrence rate being regarded as of clinical significance. This size provided an 80% chance of detecting this treatment difference at the 5% level. Clinical experience and the very few randomised trials done suggested that some patients would be lost to follow-up or would refuse imaging follow-up. To allow for these losses, we assumed a worst-case scenario of 10% for dropout from angiographic follow-up, crossovers to the other treatment group, and non-compliance for other reasons. Data were analysed by the trial statistician and reviewed in strict confidence by the independent data monitoring committee (Hull, UK) three times during the trial (webappendix p 6).

Primary analysis was a comparison between treatment groups of the proportion of patients who had a primary outcome adverse event (composite of angiographic and clinical), with logistic regression adjusted for aneurysm size, neck size, rupture status, aneurysm shape, and planned use of assist device. Data were analysed according to the groups in which patients were originally allocated, irrespective of the treatment they actually received. We removed patients with missing outcome data from the primary outcome analysis (modified intention-to-treat analysis) but did a sensitivity analysis to assess the effect of missing data. The proportion of patients who had a major aneurysm recurrence at the end of follow-up (angiographic outcome) was compared between the two treatment groups. A per-protocol analysis was also done, excluding patients who were enrolled into the trial but did not meet the inclusion criteria, who crossed over to the other treatment group, or in whom the coiling procedure was not done. We did

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	Modified intention-to-treat analysis		Per-protocol analysis	
	Hydrogel-coated coils (n=249)	Control (n=250)	Hydrogel-coated coils (n=234)	Control (n=247)
Good				
No major aneurysm recurrence on angiographic follow-up	158 (64%)	149 (60%)	151 (65%)	149 (60%)
Adverse				
Major angiographic aneurysm recurrence	59 (24%)	83 (33%)	57 (24%)	83 (34%)
No angiographic follow-up because of procedural morbidity	3 (1%)	1 (<1%)	3 (1%)	1 (<1%)
No angiographic follow-up because of procedural mortality	8 (3%)	6 (2%)	8 (3%)	5 (2%)
Total composite adverse outcome	70 (28%)	90 (36%)	68 (29%)	89 (36%)
Other				
No angiographic follow-up because of morbidity unrelated to procedure	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
No angiographic follow-up because of mortality unrelated to procedure	3 (1%)	1 (<1%)	3 (1%)	1 (<1%)
Missing				
Refused or lost to angiographic follow-up	17 (7%)	9 (4%)	11 (5%)	7 (3%)

Data are n (%). In 44 patients, 6-month angiographic results were used because 18-month angiogram was not done or available.

Table 1: **Angiographic and clinical composite outcomes at 18 months**

	18-month outcomes only		6-month outcomes used when 18-month outcomes were missing	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Unadjusted (missing excluded)	0·70 (0·47–1·05)	0·08	0·73 (0·50–1·08)	0·11
Adjusted* (missing excluded)	0·69 (0·45–1·05)	0·08	0·73 (0·49–1·10)	0·13
Unadjusted (missing counted as adverse)	0·88 (0·62–1·26)	0·50	0·85 (0·59–1·22)	0·38
Adjusted* (missing counted as adverse)	0·88 (0·62–1·27)	0·50	0·85 (0·58–1·23)	0·38
Unadjusted (missing counted as good)†	0·66 (0·44–0·97)	0·03	0·70 (0·48–1·01)	0·06
Adjusted* (missing counted as good)†	0·63 (0·42–0·95)	0·03	0·68 (0·46–1·01)	0·05

*Adjusted for aneurysm size, neck size, rupture status, aneurysm shape, and planned use of assist device. †Good primary outcome is defined as patient having no major angiographic recurrence on follow-up imaging at 18-months.

Table 2: **Sensitivity analyses on the composite primary outcome**

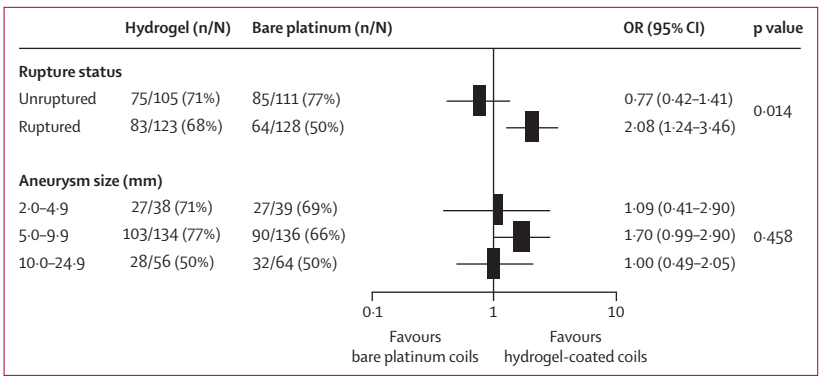

Figure 2: **Subgroup analysis of angiographic and clinical composite outcomes at 18 months after treatment**

prespecified subgroup analyses of characteristics likely to be relevant to angiographic outcome. The primary outcome was compared for subgroups by aneurysm size and rupture status, meeting of target HES use (versus not meeting target HES use), and use of an assist device. Subgroup analyses were done with logistic regression, by examining the change in log likelihood when an interaction term was added. SAS version 9.2 was used for statistical calculations.

This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN30531382.

Role of the funding source

Neither sponsor nor funder had any part in trial design, data collection, analysis, or reporting, which were organised by the steering committee. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Patients were randomly assigned to treatment between September 13, 2004, and February 21, 2007 (figure 1). 12 centres kept detailed eligibility logs, which showed that 20% of screened patients were included in this trial, which is consistent with similar trials.[1–3] One patient was inadvertently enrolled twice, and the second entry is not included in analyses. Patients' baseline characteristics and clinical demographics and protocol deviations, including crossovers and withdrawals, are presented elsewhere.[17] One patient with a giant aneurysm included in allocation analysis was excluded from the per-protocol analysis. 467 (94%) of 499 patients had their composite primary outcome analysed. Angiographic follow-up was available for 449 (91%) of 491 patients who received a coil; median angiographic follow-up was 17·4 months (IQR 12·6–19·6) in the HES group and 17·5 months (IQR 15·2–20·0) for controls; 6-month results were used for 44 patients.

An adverse composite primary outcome was more likely in the control group than in the HES group, but the difference was not statistically significant. Primary outcome data were not available for 32 patients (21 in the HES group and 11 controls; table 1). Exclusion of these patients gave an absolute difference in the proportion experiencing the primary outcome of 7·0% (30·7% in the HES group *vs* 37·7% in controls; 95% CI –1·6% to 15·5%. The adjusted odds ratio [OR] for adverse composite primary outcome was 0·73 (95% CI 0·49–1·13, p=0·13; table 1). Unadjusted sensitivity analyses gave very similar results to adjusted results (table 2). Patients with ruptured aneurysms in the HES group had better primary outcomes at 18 months than did such patients in the control group (figure 2). Analysis of the medium-sized aneurysm subgroup showed a non-significant trend towards reduced adverse composite primary outcome in the HES group (figure 2).

Fewer patients in the HES group had a major recurrence (59 of 217 patients with follow-up data) than did control patients (83 of 232 patients with follow-up data), giving an absolute difference in the proportion of 8·6% (OR 0·7, 0·4–1·0, p=0·049; table 1).

We recorded no statistical difference in the proportion of patients who were dead or dependent (MRS ≥3) at 18 months between the HES group (39 [15·7%]) and control group (32 [12·8%] (table 3); the difference was 2·9% (–3·3% to 9·0%, p=0·36). Three deaths occurred in the subgroup with a not-recently-ruptured target aneurysm (ie, not ruptured within 30 days of randomisation; one in the HES group and two controls), all of which were related to complications during or after the procedure. 21 patients in the not-recently-ruptured subgroup had poor clinical outcomes (MRS 3–5). Of these, 12 were in the HES group (six were unrelated to coiling of target aneurysm, four were definitely or probably related to coiling or persisting symptoms from aneurysm, one was possibly related to coiling or persisting symptoms from aneurysm, and one was of unknown cause) and nine were controls (four were unrelated to coiling, four were definitely or probably related to coiling or persisting symptoms from aneurysm, and one was possibly related to coiling or persisting symptoms from

	All patients		Target aneurysm ruptured within 30 days		Target aneurysm not ruptured within 30 days	
	Hydrogel-coated coils (n=249)	Control (n=250)	Hydrogel-coated coils (n=132)	Control (n=133)	Hydrogel-coated coils (n=117)	Control (n=117)
0	87 (35%)	79 (32%)	39 (30%)	33 (25%)	48 (41%)	46 (39%)
1	60 (24%)	70 (28%)	33 (25%)	39 (29%)	27 (23%)	31 (26%)
2	46 (19%)	54 (22%)	28 (21%)	34 (26%)	18 (15%)	20 (17%)
3	20 (8%)	17 (7%)	12 (9%)	11 (8%)	8 (7%)	6 (5%)
4	5 (2%)	4 (2%)	3 (2%)	2 (2%)	2 (2%)	2 (2%)
5	3 (1%)	3 (1%)	1 (1%)	2 (2%)	2 (2%)	1 (1%)
6*	11 (4%)	8 (3%)	10 (8%)	6 (5%)	1 (1%)	2 (2%)
Missing	17 (7%)	15 (6%)	6 (5%)	6 (5%)	11 (9%)	9 (8%)

Data are n (%). *Death.

Table 3: **Independently assessed modified Rankin score at 18 months**

aneurysm). Therefore, combined MRS 3–6 in patients with not-recently-ruptured target aneurysms with coiling-related symptoms or persisting aneurysm symptoms was between 11 and 14 of 234 (4·7–6·0%) with no difference between treatment groups.

We noted two cases of rebleeds or bleeds from target aneurysms, one in each treatment group (webappendix p 7). No target aneurysm rebleeds were recorded in the recently ruptured subgroup. There were two cases (both controls) in which a patient presented with subarachnoid haemorrhage and only one aneurysm was identified on digital subtraction angiography. The target aneurysm was coiled uneventfully in both cases. However, both patients had another subarachnoid haemorrhage within 2 weeks and on further imaging a second, recanalised, aneurysm was seen, which was presumed to have been the actual source of haemorrhage in both cases.

In the per-protocol analysis, 7 (3%) of 236 patients in the HES group and 8 (3%) of 246 patients in the control group had retreatment. One patient who crossed over from the HES group to the control group was re-treated (with inclusion of crossovers, the re-treatment rate in the control group was nine [4%] of 253 patients). The median time to re-treatment was 212 days (IQR 182–287) in the HES group and 229 days (IQR 183–284) for controls.

Greater aneurysm packing density was achieved in the HES group (median 63·9%, IQR 43·2–89·4) than in controls (23·2%, 16·8–32·8; p<0·0001). Table 4 shows the relation between composite primary outcome and whether or not target use of hydrogel to coil aneurysm was reached in the hydrogel group. It indicates that when this guideline target was met, good outcome was significantly more likely than in control group (OR 1·6, 95% CI 1·0–2·5).

Overall, use of an assist device did not affect the composite primary outcome (table 5). Complications relating to assist devices are presented elsewhere.[17]

We recorded six cases of unexplained hydrocephalus in not-recently-ruptured target aneurysms; five in the HES group and one in the control group. Mean time to presentation was 13·2 months (SD 4·1). Four of five HES cases were large aneurysms as was the sole control. Five were basilar tip aneurysms (all >8 mm diameter; four of five >12 mm in maximum diameter). One patient (in the HES group) had a posterior communicating artery aneurysm (>12 mm). Four further cases of hydrocephalus in not-recently-ruptured target aneurysms were explicable: two by procedural rupture (control), one by bleed from another aneurysm (control), and one by stroke with mass effect (HES). Overall, the risk of unexplained hydrocephalus in not-recently-ruptured target aneurysm was 4·5% (five of 110) in the HES group and 0·9% (one of 112) in the control group, HES seemed to increase hydrocephalus risk, but not significantly so (OR 5·3, 95% CI 0·6–46).

	Good outcome*	Odds ratios (95% CI) compared with controls
HES, target met	120/165 (73%)	1·6 (1·0–2·5)
HES, target not met	31/54 (57%)	0·8 (0·4–1·5)
HES, final coil used was a hydrogel-coated coil	102/151 (68%)	1·2 (0·8–1·9)
HES, target met and final coil used was hydrogel coated	84/120 (70%)	1·4 (0·9–2·2)
Controls	149/238 (63%)	N/A

Data are n/N (%). N/A=not applicable.

Table 4: **Composite primary outcome by hydrogel treatment achieved (per-protocol analysis)**

	Hydrogel-coated coils (%)	Control (%)	Absolute difference (95% CI)
Assist device used	70/102 (69%)	69/109 (63%)	5·3% (–7·4 to 18·1)
No assist device used	87/125 (70%)	80/130 (62%)	8·1% (–3·6 to 19·7)
Assist device (acutely ruptured aneurysm)	20/30 (67%)	16/34 (47%)	19·6% (–4·2 to 43·4)
No assist device (acutely ruptured aneurysm)	63/93 (68%)	48/94 (51%)	16·7% (2·8 to 30·5)
Assist device (unruptured aneurysm)	50/72 (69%)	53/75 (71%)	–1·2% (–16·0 to 13·6)
No assist device)unruptured aneurysm)	24/32 (75%)	32/36 (89%)	–13·9% (–32·1 to 4·3)

Data are n/N (%), unless otherwise stated. *Good primary outcome is defined as "patient has no major angiographic recurrence on follow-up imaging at 18-months" (with 6-month data for missing values).

Table 5: **Composite primary good outcomes by use of assist device**

Hydrocephalus rate in ruptured aneurysms was 18·7% in the HES group and 15·2% in controls, with no late delayed cases reported.[17]

Discussion

We recorded no significant difference between patients in the HES and control groups when assessing the primary outcome—a composite of major angiographic recurrence and clinical status. However, when assessing only angiographic recurrence (on which the trial was powered), we recorded fewer angiographic recurrences in the HES group than in controls.

We noted little difference in clinical outcomes, bleed or rebleed, and re-treatment rates between the two treatment groups. As expected, the number of rebleed or re-treatment events within the short follow-up was small. We recorded two significant findings in subgroup analyses: reduced adverse composite primary outcome in the HES group compared with controls in ruptured aneurysms, and reduced adverse composite primary outcome when target use for HES was met. The medium-sized aneurysm (5–9·9 mm) subgroup seemed to have reduced adverse composite primary outcome in the HES group, but this was not significant (figure 2). Significantly greater aneurysm packing density was achieved with HES, though the volumetric packing density calculation assumes full hydrogel expansion, which might not occur in vivo, so packing density results should be viewed cautiously.

Clinical outcomes in patients with ruptured aneurysms were encouraging, with good outcome (MRS 0–2) at 18 months in 81% of patients. Before HELPS, no randomised trial of coiling of unruptured intracranial aneurysms was reported (panel). We recorded low mortality in patients with a not-recently-ruptured target aneurysm at 18 months. In HELPS, adverse clinical outcomes attributable to the coiling procedure in patients with not-recently-ruptured target aneurysms are very similar to a systematic review,[9] which showed 4–5% procedural morbidity and mortality, although the review used data from self-assessed, non-randomised studies. The overall all-cause clinical adverse outcome rate in not-recently-ruptured target aneurysms in HELPS at 18 months (24 of 234 [10·3%]), is similar to the adverse outcome rate in the endovascular cohort of the International Study of Unruptured Intracranial Aneurysms (ISUIA) at 1 year (43 of 451 [9·5%]).[23] However, outcomes in ISUIA are not directly comparable with outcomes in HELPS because ISUIA assessments were done by investigators from recruiting centres[23] and self-assessment of outcomes (as done in ISUIA) can result in lower morbidity and complication rates.[9,24]

In HELPS, there were more missing primary outcomes in the HES group than in the control group on an allocated-treatment basis. Although some of these outcomes were missing for reasons unrelated to treatment, reasons are not known for all patients. Some patients could have had long term adverse effects from hydrogel coils that we are unaware of. Sensitivity analyses (table 2), however, indicated that these missing data would not have affected the overall trial outcome.

Major angiographic recurrence rate was higher than has been reported in other studies[4–7,22]—36% in HELPS controls (27% in the HES group) versus 20% expected (10% predicted for the HES group). If the absolute difference remains constant as the proportion of outcomes rises (from 0·2 to 0·36), which seems to be the case, there is a loss of power on the odds scale used in the regression analyses. Had the relative difference remained constant as outcome rate rose, the difference between groups would have been significant (for primary composite outcome). This effect has resulted in an underpowered trial.

We noted a non-significant difference in the number of unexplained cases of hydrocephalus in patients with unruptured intracranial aneurysms between the HES group and the controls. HELPS indicates that risk of hydrocephalus could be more related to the site and size of an aneurysm than to any other factor—unexplained hydrocephalus in our trial occurred mostly in unruptured basilar tip aneurysms of more than 12 mm in maximum diameter, but these data should be interpreted cautiously because assessment of hydrocephalus was not a prespecified analysis. For such aneurysms coiling is preferable because of the perceived neurosurgical risk of clipping.[22,23] But in view of these data, risk of hydrocephalus should be considered before coiling large unruptured posterior circulation aneurysms. The underlying cause for such hydrocephalus is unclear. A mechanical effect from

Panel: Research in context

Systematic review

We did a systematic review of studies of coated coils for cerebral aneurysm treatment from 2002 to 2007.[13] We searched for full papers reporting case series, randomised clinical trials, and meta-analyses. Prespecified quality criteria were used to critically appraise reports. We identified no previous meta-analysis or randomised controlled trial that assessed either the safety or efficacy of coated coil technologies.

Interpretation

Pre-existing studies of coated coil technologies were of poor quality but did not show any safety concerns. Conversely, there was no clear evidence for improved effectiveness to justify their introduction into routine clinical practice. Our results are consistent with the findings of a systematic review with respect to safety, with no evidence recorded of worse clinical outcomes in patients treated with hydrogel-coated coils compared with patients treated with control bare platinum coils. The HELPS trial provides evidence for increased efficacy for hydrogel-coated coils, with a lower major angiographic recurrence rate and improved composite primary outcome in the subgroup of acutely ruptured aneurysms with hydrogel coiling.

basilar artery dolichoectasia impressing into the floor of the third ventricle was postulated in the 1960s as a cause of hydrocephalus.[25] Coiling of a large basilar tip aneurysm could possibly cause a similar effect, because coiling can cause aneurysm expansion.[14,15] An alternative hypothesis is that an inflammatory response is generated by thrombus within a coiled aneurysm, causing local swelling and mechanical obstruction (again potentially explaining predilection for the basilar tip) or a communicating hydrocephalus.[18,20] The larger the aneurysm and the more complete the occlusion, the more thrombus is trapped within the aneurysm and thus the greater the inflammatory response generated.[25] The cause of such hydrocephalus certainly merits investigation.

Because the procedures were done in HELPS without constraints on type of bare platinum coil or assist device, patients with ruptured and unruptured aneurysm were included, and the trial inclusion criteria were broad, the results of this trial are generalisable to the wide range of patients and aneurysms encountered in routine practice. More high-quality data on coiling assist techniques and unruptured aneurysms are urgently needed.

Contributors

PMW and SCL shared first authorship. JMW and RJS assisted with the writing and decisions on content. SCL was responsible for all statistical aspects and analysis. LF and SCL were responsible for data cleaning, editing, table preparation, and checking. Additional input into content and editing were provided by AG, HN, and CC.

HELPS trial collaborators

The HELPS trial collaborators are listed in the order that participating centres joined the HELPS trial, with the number of patients recruited in each centre given in parentheses. Principal investigators (PI) were responsible for obtaining local institutional review board and ethics approval, provision of care for study patients, and, in some units, collection of data. Local coordinators had the major data-collection responsibility. Western General Hospital, Edinburgh, UK: PI, Robin Sellar; Trial chief investigator, Phil White; coordinator and trial manager, Lynn Forrester (105 patients). Queens Medical Centre, Nottingham, UK: PI, Norman McConachie; Coordinator, Alison Southam (35 patients). University Hospital of Wales, Cardiff, UK: PI, Shawn Halpin (22 patients); Newcastle General Hospital, Newcastle, UK: PI, Anil Gholkar; Coordinator, Nicola Hind (12 patients). Oregon Health and Science University, Portland, OR, USA: PI, Stan Barnwell; Coordinator, Sarah Ross (79 patients). Hope Hospital, Salford, UK: PI, Roger Laitt; Coordinator, Elaine Wilkins (13 patients). Queen Elizabeth Hospital, Birmingham, UK: PI, Sal Lamin; Coordinator, Beverley Hudson (11 patients). Walton Centre, Liverpool, UK: PI, Hans Nahser; Coordinator, Sam Saminaden (54 patients). Cleveland Clinic, Cleveland, OH, USA: PI, David Fiorella; Coordinator, Terese Wheeler (28 patients). Southampton General Hospital, Southampton, UK: PI, John Millar; Coordinator, Sarah Halcrow (12 patients). Hospital Das Clinicas, São Paulo, Brazil: PI, Jose Guilherme Caldas (10 patients). University of Essen, Essen, Germany: PI, Isabel Wanke; Coordinator, Sophia Goricke (13 patients). St Joseph's Hospital, Phoenix, AZ, USA: PI, Cameron McDougall; Coordinator, Mary Harrigan (19 patients). The Methodist Hospital, Houston, TX, USA: PI, Richard Klucznik; Coordinator, Denise Meyer (20 patients). Henry Ford Hospital, Detroit, MI, USA: PI, William Sanders (2 patients); Royal Prince Alfred Hospital, Sydney, Australia: PI, Geoffrey Parker; Coordinator, Victoria Dunne (13 patients). Neuroradiologie Hôpital Purpan, Toulouse, France: PI, Christophe Cognard (5 patients); University of Virginia Health Science Center, Charlottesville, VA, USA: PI, Mary Jensen; Coordinator, Patty Schweickert (10 patients). Hôpital Henri Mondor, Creteil Paris, France: PI, Andre Gaston; Coordinator, Raphael Blanc (8 patients). ENERI, Buenos Aires, Argentina: PI, Pedro Lylyk; Coordinator, Carlos Miranda (7 patients). Royal Victoria Hospital, Belfast, UK: PI, Ian Rennie (2 patients); Hôpital Gui de Chauliac, Montpellier, France: PI, Alain Bonafe; Coordinator, Marinette Moynier (11 patients). University of Texas Southwestern, Dallas, TX, USA: PI, Lee Pride; Coordinator, Kim Dutton (3 patients). Leeds General Infirmary, Leeds, UK: PI, Tony Goddard (5 patients).

HELPS trial steering committee: AG (chair), PMW (PI), SCL (statistician), JMW, HN, RJS, CC, MF (representative for patients). HELPS data *monitoring committee*: RJ Bartlett (chair), PAG Sandercock, N Anderson (statistician).

Conflicts of interest

PMW has done consultancy work for MicroVention Inc and Micrus (both companies manufacture coils for aneurysm treatment); holds an unrestricted research grant from MicroVention for HELPS as the Chief Investigator; has received financial support to attend conferences during the past 5 years from Micrus, Codman (a manufacturer of coils for aneurysm treatment), and MicroVention; had MicroVention stock options from 2001–02, which were bought out when Terumo took over Microvention in 2006; and is the co-organiser of an educational meeting (Brainstorm), which is sponsored by Siemens Medical and MicroVention Terumo. SCL had some of her salary paid from the grant from Microvention Terumo for HELPS. AG has received travel support to conferences from MicroVention Inc and Codman, and has done consultancy work for Codman. RJS has done consultancy work for MicroVention and Micrus and is the co-organiser of an annual educational meeting (Brainstorm), which is sponsored by Siemens Medical and Microvention Terumo. HN has done consultancy work for Boston Scientific (a manufacturer of coils for aneurysm treatment) and has received support to attend conferences during the past 5 years from Boston, Codman, and Microvention. CC has done consultancy work for Boston Scientific, Codman, eV3 (a manufacturer of coils for aneurysm treatment), and MicroVention Terumo Inc. LF was employed as the trial manager of HELPS, funded by MicroVention Terumo Inc. JMW declares that she has no conflicts of interest.

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