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ORIGINAL RESEARCH

HydroCoil Endovascular Aneurysm Occlusion and Packing Study (HELPS Trial): Procedural Safety and Operator-Assessed Efficacy Results

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BACKGROUND AND PURPOSE: Coated coils have been in clinical use for several years without robust evidence to determine their safety/efficacy. The HydroCoil Endovascular Aneurysm Occlusion and Packing Study (HELPS) addresses this deficiency for the HydroCoil embolic system. This article reports periprocedural safety/operator-assessed angiographic results from HELPS.

MATERIALS AND METHODS: Patients were randomized to the hydrogel coil or control arms by using concealed allocation with minimization matching groups. Any bare platinum coils were allowed in the control arm, and assist devices could be used as clinically required. Both recently ruptured and not recently ruptured/unruptured aneurysms were included. Analysis was on an intention-to-treat basis.

RESULTS: Four hundred ninety-nine patients were recruited. Coiling was successful in 98.6%. Mean aneurysm size was 6.5 mm (26% were ≥10 mm), 53% were recently ruptured aneurysms, and an assist device was used in 46%. Seventy procedural adverse events were reported in hydrogel coils and 86 in control arms. The 3-month mortality rate was 3.6% in hydrogel coils and 2.0% in control arms; the difference was not significant ($P = .6$). There was a lower 2-month mortality rate in the HELPS subarachnoid hemorrhage cohort (4.1%) than would be anticipated from the International Subarachnoid Aneurysm Trial (7%). There was a trend toward increased adverse events when assist devices were used, which was substantial for stents deployed in recently ruptured aneurysms. Ninety-six percent of patients discharged were World Federation of Neurosurgeons grade 0–2 at discharge. No difference was found between arms in the operator assessment of angiographic occlusions ($P = .3$).

CONCLUSION: These HELPS results reinforce coiling as an effective treatment for aneurysms, with an excellent technical success rate. Hydrogel coils can be used in a wide spectrum of aneurysms with a risk profile equivalent to that of bare platinum.

EXPEDITED PUBLICATION

ORIGINAL RESEARCH

Endovascular treatment is now the preferred treatment option for many intracranial aneurysms,[1-3] but aneurysm recurrences and rebleeds are more frequent after endovascular treatment than neurosurgical clipping.[2,4-6] Major aneurysm recurrences are found in 15%[4,7] to 19%[6] of patients by 3–6 months, rising to 21% at a mean of 16 months of follow-up.[4] Follow-up imaging beyond a few months is mandatory and important to the ongoing patient management.[8]

An endovascular treatment that substantially reduced the major recurrence rate would be expected to reduce both the rebleed and the retreatment rate and would be beneficial to patients and health care systems. The HydroCoil Embolic System (MicroVention, Aliso Viejo, Calif) was designed to improve volumetric filling with an expansile hydrogel that should fill more of the aneurysm lumen than standard platinum coils—thus aiming to improve aneurysm stability and durability—and it might provide a better scaffold to initiate neointima formation and healing.[9] Early experience demonstrated that hydrogel coils substantially improved calculated packing of the aneurysm lumen relative to standard platinum coils (72% versus 32%).[10] The more important issue of whether major recurrence in aneurysms is reduced remains unknown. In the early data from the HydroCoil for Endovascular Aneurysm Occlusion (HEAL) prospective registry, the recurrence rate at 12–18 months was only 3% for aneurysms <25 mm (1/35) (Cloft, personal communication, June 2003), but the evidence from the full HEAL registry results was less impressive. The overall recurrence rate was 28%, though 0% where the aneurysm was coiled >75% by length with hydrogel coils (a small minority of cases) or 11% where the hydrogel coil was the final coil placed.[11] However, coated coils of several types have been in widespread clinical use for several years without a robust preferably independently assessed randomized trial providing evidence to determine their safety and efficacy.

Therefore, a prospective randomized trial of HydroCoil versus bare platinum in the endovascular treatment of intracranial aneurysms was performed to determine whether hydrogel coils do indeed influence major aneurysm recurrence (primary outcome) and clinical outcome, rebleed, and retreatment rates (secondary outcomes). This article is a report of periprocedural complications and operator-assessed immediate efficacy (angiographic results at end of the coiling procedure). An article with the primary and secondary outcomes of the trial will be reported once follow-up is complete.

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The trial was sponsored (on behalf of the UK National Health Service) by Lothian Health University Hospitals Division. The sponsors had no part in data collection, analysis, or reporting. This was organized by the Steering Committee. The study was funded by MicroVention Terumo Incorporated, the manufacturers of the hydrogel coils. However, they have had no direct or indirect access to the data or source documents.

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Methods

Patients and Techniques

HELPS is a pragmatic multicenter international randomized controlled trial of a policy of HydroCoil versus bare platinum in the endosaccular treatment of intracranial aneurysms. The trial has UK Multicenter Research Ethics Committee approval, and all trial centers have local institutional review board approval. The trial was sponsored by Lothian University Hospitals Division. The International Standardised Randomised Controlled Trials Number (ISTCRN) is 30531382. Any bare platinum coils with controlled detachment were permitted, as were any assist devices believed necessary by the operator, provided they had local regulatory approval. Randomization allocation was via a Web-based process run from the Coordinating Centre (Edinburgh), ensuring that allocation was concealed before the decision to randomize a patient. From the moment of randomization, the patient was in the trial and accounted for in the analysis (intention to treat). Groups were matched (minimization criteria) according to aneurysm size (2–4.9, 5–9.9, and 10–24.9 mm), neck size (dichotomized by dome-to-neck ratio <1.5 or ≥ 1.5), rupture status, aneurysm shape (multilobulated or not), planned use of an assist device, and whether randomized in the Americas (North and South combined).

Inclusion and Exclusion Criteria

Patients presenting with a previously untreated cerebral aneurysm measuring 2–25 mm in maximal diameter deemed to require endovascular treatment by the neurovascular team (typically comprising a neurosurgeon, neurointerventionalist, plus or minus a neurologist) were eligible for inclusion if they were 18–75 years of age and not pregnant, were World Federation of Neurosurgeons (WFNS) grade 0–3,[12] had anatomy such that endovascular occlusion was deemed possible, had not previously been randomized into the trial, and the neurointerventionalist was content to use either bare platinum or hydrogel coils. Patients were excluded if they had >1 aneurysm requiring treatment, unless the treatment was to be staged with only 1 aneurysm being treated at 1 sitting. All patients gave written informed consent, or if they could not consent for themselves, appropriate written assent was sought from their next of kin. The accumulating data were analyzed by the trial statistician and reviewed in strict confidence by the Data Monitoring Committee (DMC) once per year (3 times during the course of the trial so far). All members of the DMC were totally independent.

Embolization Procedure

Standard local procedures for the coiling of aneurysms were followed. With both HydroCoil and bare platinum, the aim was to coil to angiographic occlusion whenever possible. Patient safety was the paramount consideration at all times. In the HydroCoil arm, for aneurysms 2–9.9 mm, it was recommended that HydroCoil constitute at least 50% of the total coil length deployed or $>50\%$ of the aneurysm packing achieved and that the total aneurysm packing should exceed 50%. For aneurysms ≥ 10 mm, it was recommended that HydroCoil should constitute at least two thirds of the total coil length deployed, or at least 70% of the aneurysm packing achieved, and the total aneurysm packing should exceed 40%. These recommendations were for guidance only and not a rigid requirement. More detail on packing attenuation calculation can be found in prior publications.[10,11] Other technical considerations such as steaming of hydrogel coils and type of bare platinum coil were left entirely to the operator's discretion. As a result of a pragmatic approach, the results will be widely applicable because we have compared the outcome of coiling by using either HydroCoil or bare platinum in a real clinical setting in a large number of centers across the world where procedures were performed without any constraints on the type of bare platinum coils or assist devices used and with patients with both ruptured and unruptured aneurysms well represented.

Data Collection and Analysis

The following parameters were obtained at the time of randomization: sex and age, aneurysm presentation as ruptured (including date of rupture) or unruptured (and specified as symptomatic, additional, or incidental), WFNS grade at randomization, number of aneurysms, aneurysm size in millimeters (in 3 orthogonal planes), neck size in millimeters and dome-to-neck ratio, aneurysm location, aneurysm shape (regular or multilobulated), and planned use of assist devices. Following the coiling procedure, data were obtained on coils used, aneurysm occlusion grade (on the Montreal grading system)[4] as judged by the operator (the Core Laboratories independent analysis on this will be presented in a subsequent publication), assist devices used, and any neurologic deterioration at the end of the procedure. For every patient, a form was completed on disease- and procedure-related complications, including rebleed, delayed ischemic neurologic deficit, hydrocephalus, cardiorespiratory problems, aneurysm rupture, coil migration, parent artery occlusion, or other thromboembolic event. Further data on the management of complications that occurred and the use of antiplatelets/thrombolytic agents were also obtained. At time of discharge, WFNS grade and location of discharge (home, other hospital, rehabilitation unit, or other) were recorded.

Case record forms were completed locally then faxed/e-mailed to the coordinating center. They were entered by a professional data puncher into the purpose-designed encrypted password-protected trial SQL data base with the use of a drop-down list selection and audit checks built in, to ensure accuracy of both data provided and entered. All statistical analyses were performed by the trial statistician.

The absolute difference in the proportion of outcome events between the 2 treatment arms was calculated and expressed as a percentage, with 95% confidence intervals. Subgroup analyses were performed by using logistic regression, by examining the change in log-likelihood when the interaction term was added.

Results

Recruitment started in late September 2004 and ended in mid-February 2007. The part of the data base containing baseline and early safety information was locked on July 31, 2007, but we are still collecting 3- to 6- and 18-month follow-up data. Four hundred ninety-nine unique patients were randomized by 24 centers in 7 countries. One patient was inadvertently randomized twice, but data from the first randomization only has been used in this analysis. One patient was randomized, then withdrew consent to participate, so no further data could be collected. Two hundred fifty patients were randomized to receive bare platinum coils, and 249, hydrogel coils. Coiling was attempted in 495/499 (99.2%) patients and was "successful"—defined as coils deployed in the aneurysm—in 492/495 (99.4%) patients. Table 1 delineates randomization allocation and the treatment actually received.

The reasons for not starting the procedure were the following: 1) additional angioviews showed that the posterior com-

Table 1: Treatment allocated and treatment received

	Randomized Treatment			
	Hydrogel		Bare Platinum	
	No.	%	No.	%
No. of patients randomized	249		250	
Received coil as allocated	236	94.8	246	98.4
Crossed over*	7	3.2	2	0.8
Procedure started but no coil inserted	2	0.8	1	0.4
Procedure not started	3	1.2	1	0.4
Consent revoked	1	0.4	0	

* "Crossed over" in HydroCoil arm means that the patient was allocated HydroCoil but only bare platinum coils were deployed. In the control arm, it means that the patient was allocated bare platinum but some HydroCoil was deployed.

municating artery arose from distal neck and could not be confidently protected (HydroCoil), 2) only a stent was placed (HydroCoil), 3) only a stent was placed (platinum), 4) previous stent and coiling of the aneurysm on the opposite side 3 months earlier and at angiography for coiling of the target randomized aneurysm. Flow patterns had changed with an in-stent stenosis, so that treatment was postponed (HydroCoil). The reasons for starting the procedure but not deploying any coils were that the aneurysm was catheterized but the patient had unsuitable anatomy (1 HydroCoil and 1 bare platinum) and failure to catheterize the target aneurysm (1 HydroCoil). Four hundred eighty-two patients (96.6%) received the treatment as allocated. There were 3 small aneurysms in which, on balance, the operator had attempted but failed to deploy hydrogel coils and used bare platinum only, and in another 4 patients (all with very small aneurysms), the operators decided they were, in fact, not comfortable with deploying hydrogel coils after catheterizing the target aneurysm and used bare platinum.

For the sake of clarity and conciseness, the results are mainly presented in a series of tables. As outlined in Table 2, the baseline age/sex data are very comparable in the 2 treatment arms, and for the categories in which minimization was used, matching was expected and was achieved, as shown.

Mean aneurysm size was 6.5 mm, and the median was 5.9 mm (range, 2–22 mm). The mean dome-to-neck ratio was 1:8, and the median was 1:6. During the start-up phase of the trial, a forced response on "planned use of assist device" was not required to randomize a patient, but this was subsequently changed after the first 29 patients when it became clear that a substantial proportion of cases were likely to involve an assist device—hence the "missing data" row in this section of Table 2. The median coil length used in the hydrogel coil arm was 37 cm (interquartile range [IQR], 18–70) compared with 46 cm (IQR, 26–98) in the bare platinum arm—a relative reduction of 19.6%. This was statistically significant ($P = .002$, Wilcoxon 2-sample test). (Data on coil length used was not available in 4/498 patients [2 from each arm].)

The periprocedural and disease-related complications are summarized in Table 3 and early deaths, in Table 4 (early was defined as within 3 months, so before any clinical or angiographic follow-up was obtained). The mortality case record forms provided data on whether the death was regarded as procedure-related (or at least exacerbated by coiling procedure). Data on hydrocephalus from randomization to 3 months are presented separately in Table 5. There were a variety of disease-related complications, which are listed under the "other" category, as follows: postprocedural seizures, 2 reported in the hydrogel coil arm, 1 in the control arm; postprocedure cranial nerve palsy or other focal new neurologic symptoms/signs, 4 reported in the hydrogel coil arm and 6 in the control arm; meningitic presentation in an unruptured aneurysm, 2 reported in the hydrogel coil arm and zero in the control arm; worsening headache with no clear explanation (such as vasospasm or hydrocephalus), 3 reported in the hydrogel coil arm and 2 in the control arm; organ failure (worsening postprocedure), 2 reported in the hydrogel coil arm and zero in the control arm. A total of 88 procedure-related adverse events were reported in the hydrogel coil arm and 103 in the control arm; a total of 67 disease-related adverse events were reported in the hydrogel coil arm and 73 in the control arm (Table 3). Of course, some of these adverse events, especially procedural ones, did not result in permanent clinical sequelae.

Table 2: Baseline data on randomization

	Randomized Treatment			
	Hydrogel		Bare Platinum	
	No.	%	No.	%
Total No. patients randomized	249		250	
Sex				
Female	176	70.7	174	69.6
Male	73	29.3	76	30.4
Age (years)				
<45	80	32.1	78	31.2
46–55	68	27.3	75	30.0
>55	101	40.6	97	38.8
Target aneurysm size (maximal dimension)				
2–4.9 mm	42	16.9	41	16.4
5–9.9 mm	144	57.8	144	57.6
10–24.9 mm	63	25.3	65	26.0
Dome-to-neck ratio				
<1.5	83	33.3	81	32.4
>1.5	166	66.7	169	67.6
Baseline rupture status				
Yes, in previous 30 days	132	53.0	133	53.2
Yes, >30 days ago	5	2.0	4	1.6
Yes, but date unknown	2	0.8	1	0.4
No	110	44.2	112	44.8
Aneurysm shape				
Irregular (multilobulated)	76	30.5	77	30.8
Not multilobulated	173	69.5	173	69.2
Planned use of assist device				
Yes	112	45.0	115	46.0
No	122	49.0	121	48.4
Missing (see "Results")	15	6.0	14	5.6
Assist device actually used*	116	46.6	115	46.0
Balloon	65	26.1	60	24.0
Stent	46	18.5	52	20.8
Other (TriSpan† double microcatheter techniques)	3	1.2	3	1.2
Assist device attempted but failed	2	0.8	0	0
Not known (consent withdrawn)	1	0.4	0	0
None	131		137	
Randomized Americas‡				
Yes	89	35.7	89	35.6
No	160	64.3	161	64.4

* More than 1 assist device may have been used in any individual case.
† Boston Scientific, Natick, Mass.
‡ This is North and South America combined.

Table 3: Procedure- and disease-related adverse events*

	Randomized Treatment			
	Hydrogel		Bare Platinum	
	No.	%	No.	%
Procedural aneurysm rupture	9	3.6	8	3.2
Coil migration	15	6.0	10	4.0
Parent artery occlusion	4	1.6	8	3.2
Thromboembolic complication	14	5.6	25	10.0
Other procedure-related adverse events	8	3.2	9	3.6
Intra-arterial thrombolysis used	20	8.0	26	10.4
Neurologic deterioration immediately after coiling	18	7.2	17	6.8
Rebleed before discharge	0	0	2	0.8
Delayed ischemic neurologic deficit	34	13.7	38	15.2
Cerebral hematoma	9	3.6	11	4.4
Cardiorespiratory	11	4.4	13	5.2
Other disease-related†	13	5.2	9	3.6

* Events, especially procedural ones, may not have resulted in clinical sequelae.
† See "Results" for explanatory notes.

The rate of procedure-related adverse events reported in patients with stents was 19.6% (9/46) in the hydrogel coil group and 23.1% (12/52) in the control group. By comparison, the rate of procedure-related adverse events reported in balloon/other assist-device groups combined was 24.3% (17/70) in the hydrogel coil group and 30.2% (19/63) in the control group. These rates are not that dissimilar to the procedure-related adverse event rates reported in the nonassisted group, 17.4% and 25.2% in the hydrogel coil and control arms, respectively. However, 10/14 deaths occurred in the assist-device-used group (10/161; 4 patients with stents, 6 with balloons; 6.2%); 68/161 (42.2%) of these assist-device procedures were in patients with acutely ruptured aneurysms. The mortality rate at 3 months in the unassisted coiling cohort was extremely low at 1.5% (4/267), even though 205/267 (76.8%) were patients with acutely ruptured aneurysms. This comparison is weighted by 4 deaths in which stents were used in patients with acutely ruptured aneurysms (67% mortality rate). Table 6 provides more detail on use of assist devices.

Of the 14 deaths within 3 months of randomization, 12 were in recently ruptured aneurysms, and 11 of these were within 2 months of randomization. In almost half of the deaths after recent subarachnoid hemorrhage (SAH), a procedural adverse event occurred that contributed to the eventual demise of the patient. Of the 2 deaths in the unruptured arm, 1 was due to rupture of a different aneurysm from the treated target aneurysm 10 days after stent placement and coiling, possibly related to antiplatelet regimen post-stent placement (hydrogel coil arm). The other was due to a bleed from the previously unruptured target aneurysm post-stent placement and coiling, also while the patient was on an antiplatelet regimen postprocedure (control arm). These were included in the procedure-related/exacerbated subgroup in Table 4. Regarding thrombotic events, an antiplatelet regimen was used during/immediately postprocedure in 131 patients in the hydrogel coil arm (52.6%) and 140 in the control arm (56.0%), and intravenous heparin was given as per institutional protocol during the coiling procedures.

The patient's condition, assessed by crude WFNS grading at the time of discharge, is given in Tables 7 and 8, and the data on the initial outcome of the endovascular procedure (operator's self-assessment) are given in Table 9. Discharge location was as follows: discharged home, 190 in the hydrogel coil arm (76.3%) and 190 the control arm (76.0%); discharged to another hospital, 42 in the hydrogel coil arm (16.9%) and 46 in the control arm (18.4%); discharged to a rehabilitation unit, 6 in the hydrogel coil arm (2.4%) and 9 in the control arm (3.6%); discharged other, 2 in the hydrogel coil arm (0.8%) and 2 in the control arm (0.8%); and unknown (consent withdrawn), 1 in the hydrogel coil arm (0.4%) and zero in the control arm.

In a later article, the more scientifically reliable clinical outcome data assessed by the modified Rankin Scale score at 6 and 18 months and the unbiased independent Core Laboratory angiographic results (baseline and follow-up at 3–6 and 15–18 months) will be presented (these analyses are ongoing). Median time overall to discharge after admission was 7 days (IQR, 2–11 days), and in patients with recent aneurysm rupture, it was a median of 9 days (IQR, 7–15 days).

Discussion

HELPS has provided the first robust randomized controlled trial data on endovascular aneurysm treatment since the International Subarachnoid Aneurysm Trial (ISAT), which stopped recruiting in May 2002.[1,2] The technical success rate was commendably high, with coils deployed in the aneurysm in 491/498 (98.6%) recruited patients in whom data could be used and in 491/494 (99.4%) in whom coiling was actually attempted. In ISAT, in the endovascular arm, coiling was attempted but failed in 6% and not attempted in a further 1.4%, a technical success of 92.6%.[1,2] This probably reflects a raft of improvements in imaging technology (especially 3D digital subtraction angiography and multidetector CT angiography), microcatheters/wires and coils themselves, as well as greater operator experience. It is reassuring that most patients were discharged in a good-to-reasonable clinical condition as assessed by the WFNS scale: 96% of survivors were WFNS grade 0–2 on initial discharge and >75% were discharged home.

The control and hydrogel coil arms were well matched by age and sex as well as on the specified minimization criteria. Combined with concealed allocation, this good matching means that there can be confidence that between-group comparisons are really comparing like with like. The assist-device usage overall is very similar between groups, with a handful more balloon remodelling cases and a handful fewer stent cases in the hydrogel coil arm. Rather as might be expected from the proposed action of hydrogel, less coil length was deployed in the hydrogel coil arm than in the bare platinum arm, a 20% reduction (statistically significant, $P = .002$).

One of the concerns with any new device is whether it will actually cause more problems. It is reassuring that the HELPS data on reported procedural adverse events are overall lower in the hydrogel coil arm. In total, 110 procedural adverse events were reported in HELPS, a rate of 22%. This seems high compared with other reported series in which rates of 8%–18% have been reported.[13-20] However, one would anticipate a higher complication/adverse outcome rate within the context of a rigorous randomized controlled trial (RCT) than in self-reported/assessed series,[21] and these types of data were not presented in either ISAT *Lancet* article, the only previous large randomized controlled dataset on coiling.[1,2]

Table 4: Deaths within 3 months of endovascular procedure

	Randomized Treatment				
	Hydrogel		Bare Platinum		Absolute Difference
	No.	%	No.	%	(95% CI)
Total no. patients randomized	249		250		
Died within 3 months of procedure*†	9	3.6	5	2.0	1.6% (−1.5% to +4.9%)
Procedure-related/exacerbated (eg, rupture, rebleed)	5	2.0	2	0.8	1.2% (−1.2% to +3.9%)
Disease-related	4	1.6	3	1.2	0.4% (−2.1% to +3.0%)
Deaths by target aneurysm rupture status†					
Aneurysm ruptured <30 days before randomization	8/132	6.1	4/133	3.0	3.1% (−2.3% to +8.8%)
Did not rupture <30 days before randomization‡	1/117	0.9	1/117	0.9	0.0% (−3.9% to +3.9%)

Note:—CI indicates confidence interval.
* All these 14 patients were coiled on the day of randomization.
† Test for interaction (to find whether the effect of treatment differs between subgroups); $P = .6$ from logistic regression.
‡ The patient in the hydrogel coil arm "not recently ruptured" who died was baseline WFNS 1 but died before discharge. The patient in control arm "not recently ruptured" who died was WFNS 0 and was discharged the day after the procedure but bled 9 days later and died. The intracerebral bleed was not thought to be from the target aneurysm.

Table 5: Occurrence of hydrocephalus in HELPS trial to 3 months postrandomization*

	Randomized Treatment				
	Hydrogel		Bare Platinum		Absolute Difference
	No.	%	No.	%	95% CI
Total no. patients randomized	249		250		
Ruptured aneurysm; no hydrocephalus	112	80.6	117	84.8	
Ruptured aneurysm; hydrocephalus present	26	18.7	21	15.2	+3.5% (−5.4% to +12.4%)
Consent withdrawn	1	0.7	0		
Not recently ruptured; no hydrocephalus	108	98.2	109	97.3	
Not recently ruptured; hydrocephalus present	2	1.8	3	2.7	−0.9% (−5.9% to +4.1%)

Note:—CI indicates confidence interval; TA, target aneurysm (the one on which randomization was based).
* Test for interaction (to find out whether the effect of treatment differs between subgroups), $P = 0.5$, from logistic regression (ie, there is no evidence that the effect of treatment on hydrocephalus is different in ruptured and unruptured aneurysms).

Table 6: Procedure-related adverse events and mortality: comparison of assist device versus unassisted coiling cases

	Randomized Treatment				
	Hydrogel		Bare Platinum		Absolute Difference
	No.	%	No.	%	(95% CI)
Procedure-related adverse event					
Stent used in acutely ruptured aneurysm	2/3	66.7	2/3	66.7	0% (−53% to +53%)
Stent used in unruptured aneurysm	7/43	16.3	9/49	18.4	−2.1% (−17% to +14%)
Balloon/other assist used in acutely ruptured aneurysm	9/32	28.1	8/30	26.7	+1.5% (−20% to +23%)
Balloon/other assist used in unruptured aneurysm	9/38	23.7	6/31	19.4	+4.3% (−16% to +23%)
No assist device, acutely ruptured aneurysm	18/104	17.3	22/101	21.8	−4.5% (−15% to +6.4%)
No assist device, unruptured aneurysm	2/28	7.1	6/34	17.6	−10.5% (−27% to +7.6%)
Mortality rate (0–3 months)					
Stent used in acutely ruptured aneurysm	2/3	66.7	2/3	66.7	0% (−53% to +53%)
Stent used in unruptured aneurysm	0/43	0	1/49	2.0	−2% (−11% to +6.3%)
Balloon/other assist used in acutely ruptured aneurysm	4/32	12.5	1/30	3.3	+9.2% (−6.1% to +25%)
Balloon/other assist used in unruptured aneurysm	1/38	2.6	0/31	0	+2.6% (−8.6% to +14%)
No assist device, acutely ruptured aneurysm	2/104	1.9	1/101	1.0	+0.9% (−3.7% to +5.8%)
No assist device, unruptured aneurysm	0/28	0	0/34	0	0% (−10% to +12%)

Note:—CI indicates confidence interval.

Total procedural adverse events are not comprehensively reported in many case series. It is, therefore, more meaningful to compare HELPS results for specific complications. For example, the aneurysm perforation rate overall in HELPS was 3.4% (17/498). In a meta-analysis from 2002,[16] the aneurysm perforation rate was 4.1% for ruptured and 0.5% for unruptured aneurysms, and in an earlier systematic review, it was 2.4% for a controlled detached-coil series but 4.5% in high-quality studies.[15] Moreover, perforation was as high as 8.7%–8.8% in 2 more recent articles specifically evaluating the complications of endovascular coiling.[18,19] There is evidence that

Table 7: Condition at the time of initial postprocedural discharge: hydrogel coil arm

Randomization WFNS	Discharge WFNS						
	0	1–2	3	4–5	Dead	Missing	Total
0	90	15	3	0	0	1	109
1	4	106	3	1	7	0	121
2	0	15	1	0	1	0	17
3	0	1	1	0	0	0	2
6	0	0	0	0	0	0	0
Total	94	137	8	1	8	1	249

Table 8: Condition at time of initial postprocedural discharge: bare platinum arm

Randomization WFNS	Discharge WFNS						
	0	1–2	3	4–5	Dead	Missing	Total
0	94	14	1	0	0	0	109
1	2	107	2	1	1	0	113
2	1	18	2	2	1	0	24
3	0	0	2	0	1	0	3
6	1	0	0	0	0	0	1
Total	98	139	7	3	3	0	250

small acutely ruptured aneurysms have a higher than average procedural rupture risk.[19,22] Thromboembolic complications (including parent artery occlusion) occurred in HELPS in 10.2% (51/498). By comparison, rates in previous non-RCT series varied from as low as 5%[14] up to 28%,[20] with most somewhere in between,[13,17] and the rate was 9% in the systematic review.[15]

Even comparisons like these can be difficult because end points used can be ill-defined and differ between case series. For instance, Pelz et al[20] reported a thromboembolic rate of 28% but only a 5% permanent deficit rate, whereas others have only included permanent thromboembolic deficits. Death related to/exacerbated by procedural complications is perhaps more consistently defined, and in HELPS, it was 1.4% (7/498). Comparative figures in the literature range from 1.2%,[18] 1.7%,[17] 2.6%,[14] up to 3.4%[19]; and in the early systematic review of coiling, overall the rate was 1.1% but 2.1% in the subgroup of high-quality studies.[15] Therefore, the findings in HELPS are comparable with the existing literature, despite higher complication/adverse outcome rates often being demonstrated within the context of rigorous RCTs than in self-assessed case series literature.[21]

HELPS is the first RCT to include a sizeable number of patients with stents (98), and in due course, it will be possible to compare this subgroup with a matched nonstent subgroup from the trial to assess if stent deployment has a major impact on angiographic aneurysm recurrence rates and medium-to-long-term clinical outcomes. There are overall trends toward greater procedural adverse events reported when assist devices are used than in unassisted coiling cases, but of course, the groups are not so directly comparable, with complex "difficult" wide-necked aneurysms concentrated in the assist-device-used groups. However, a trend was seen toward greater mortality in ruptured aneurysms when an assist device was used in an acute situation, but absolute numbers are small and confidence intervals wide (Table 6). This trend toward increased complications with assist-device usage has already been reported in the literature but remains controversial.[13,14]

The cohort of HELPS patients with recently ruptured aneurysm (total 268, of which 3 had an unknown ictal date) were all WFNS grades 1–3 (and 1 was grade 6) and, as such, can be reasonably compared with the ISAT endovascular cohort (total, 1073; 95% grades 1–3 and 6). In ISAT, the 2-month mortality rate in the endovascular arm was 7.0%; in the HELPS SAH cohort, the 2-month mortality rate was 4.1% (11/268), a relative risk reduction of 41%. Of course, the small number of very poor-grade patients in ISAT (11 patients with WFNS grade 5 in the endovascular arm, 1%) will have weighted the ISAT mortality figure a small amount. Nevertheless, HELPS seems to provide RCT evidence for improving outcomes in endovascular treatment. Furthermore, anatomically difficult aneurysms, which would not have been enrolled by many units in ISAT, are routinely now tackled endovascularly in many units worldwide, including those participating in HELPS; and anatomically difficult aneurysms are well represented in HELPS. Such challenging aneurysms are more prone to complications. The challenging anatomy of many aneurysms included in HELPS is demonstrated by the fact that almost one third of the target aneurysms in HELPS were truly wide-necked (dome-to-neck ratio, $<$1:5), a quarter were large (compared with only 8% in ISAT), and almost one third were multilobulated or very irregular in shape. A number of the very small and distal acutely ruptured aneurysms in patients enrolled in HELPS are again not altogether typical of the ISAT enrolled aneurysms.

Hydrocephalus related to unruptured aneurysm treatment was an issue that arose after HELPS had commenced randomization, so the trial was not designed to specifically investigate this problem. However, data on hydrocephalus were recorded. For ruptured aneurysms in HELPS, periprocedural (randomization to 3 months) hydrocephalus rates of 15.2%–18.7% are comparable with those reported in the literature: 6%–63%,[23] though more commonly in the range of 15%–20%.[24] No difference between the hydrogel coil and control arms has been identified in HELPS, in either recently ruptured or unruptured aneurysms (Table 5), with cases of hydrocephalus occurring in unruptured aneurysms in both arms. However, all 3 cases of hydrocephalus in baseline unruptured target aneurysms in the control arm were explicable. Two were converted by procedural rupture to a ruptured aneurysm, and 1 previously unruptured aneurysm bled several days after stent placement and coiling, whereas the 2 cases in the hydrogel coil arm are unexplained. Of more interest with respect to hydrocephalus will be the longer term follow-up data on adverse events when available. Another randomized trial of hydrogel coils in aneurysms prone to recurrence (Patients Prone to Recurrence after Endovascular Treatment) has commenced, and this has been designed to investigate further the relationship between coil type and hydrocephalus.

The operator-assessed angiographic results indicate very similar findings for the 2 arms, with widely overlapping confidence intervals and χ^2 test for trend results of $P = .3$. Some of the small variation in near-complete versus complete between arms might be technical. With hydrogel coils, some operators wait a full 20 minutes after the last hydrogel coil is deployed for full gel expansion before performing a final end-of-procedure angiography, whereas others will not routinely wait. One can predict that in some cases had a 20-minute delayed control been performed, some of the incomplete cases in the hydrogel coil arm would have become near-complete or even complete. This possibility is merely a refinement of the argument propounded in an earlier work by Raymond et al[4] on their angiographic grading system with respect to early improvements in angiographic grade from 3 to 2 and 2 to 1. They suggested that heparin maintains aneurysm patency at the end of a procedure, but that once this has stopped, an improvement in occlusion grade can be anticipated in a number of aneurysms if very early control angiography is performed after heparin is

Table 9: Initial outcome of endovascular procedure: operator self assessment

	Randomized Treatment				
	Hydrogel		Bare Platinum		Absolute Difference
	No.	%	No.	%	(95% CI)
Total no. patients randomized	249		250		
No coiling done	5	2.0	2	0.8	
Consent withdrawn	1	0.4	0	0	
Degree of occlusion (operator opinion)*					
Complete	115/243	47.3	118/248	47.6	−0.3% (−9.0% to +8.5%)
Nearly complete	76/243	31.3	94/248	37.9	−6.6% (−14.9% to +1.8%)
Incomplete	52/243	21.4	36/248	14.5	+6.9% (+0.1% to 13.7%)

Note:—CI indicates confidence interval.
* χ^2 test for trend, $P = .3$.

stopped. The follow-up angiographic Core Laboratory data may subsequently shed light on this hypothesis.

Conclusions

The HELPS periprocedural data are encouraging. They underpin coil embolization as an effective safe treatment for intracranial aneurysms, with a very high technical success rate. Clinical outcomes at discharge were reassuringly good (albeit on the crude WFNS scale), and there is evidence suggesting a lower mortality rate in the SAH patient cohort than would be anticipated from ISAT results. The hydrogel coil system can be safely used in a wide spectrum of aneurysms with a risk profile equivalent to that of bare platinum coils. On average, a reduced length of coil was deployed in aneurysms in the hydrogel coil arm. A trend toward increased complications with all assist devices is demonstrated but is particularly associated with the use of stents in acutely ruptured aneurysms.

Acknowledgments

A list of HELPS Trial participating centers and principal investigators is included in the version of this article posted on www.ajnr.org.

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