

GREAT—a randomized aneurysm trial. Design of a randomized controlled multicenter study comparing HydroSoft/HydroFrame and bare platinum coils for endovascular aneurysm treatment

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Abstract The effectiveness of a hybrid hydrogel platinum detachable coil (HydroCoil; MicroVention Inc., Tustin, CA) for endovascular aneurysm treatment has been proven in a recently published RCT. Due to technical restrictions (coil stiffness, time restriction for placement), the HydroSoft coil as well as a corresponding 3D framing coil, the HydroFrame coil (MicroVention Inc., Tustin, CA), a class of new softer coils containing less hydrogel and swelling more slowly than

the HydroCoil, have been developed and brought to clinical practice. The present study aims to compare the effectiveness of endovascular aneurysm treatment with coil embolization between patients allocated HydroSoft/HydroFrame versus bare platinum coiling. GREAT is a randomized, controlled, multicentre trial in patients bearing cerebral aneurysms to be treated by coil embolization. Eligible patients were randomized to either coil embolization with HydroSoft/HydroFrame

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coils (>50 % of administered coil length), or bare platinum coils. Inclusion criteria were as follows: age 18–75, ruptured aneurysm (WFNS 1–3) and unruptured aneurysm with a diameter between 4 and 12 mm. Anatomy such that endovascular coil occlusion deemed possible and willingness of the neurointerventionalist to use either HydroSoft/HydroFrame or bare platinum coils. Exclusion criteria were as follows: aneurysms previously treated by coiling or clipping. Primary endpoint is a composite of major aneurysm recurrence on follow-up angiography and poor clinical outcome (modified Rankin scale 3 or higher), both assessed at 18 months post treatment. Risk differences for poor outcomes will be estimated in a modified intention-to-treat analysis stratified by rupture status (DRKS-ID: DRKS00003132).

Keywords Randomized controlled trial · Aneurysm · Coil embolization

Introduction

Endovascular coil embolization for treatment of intracranial aneurysms is now the preferred treatment option for many aneurysms [1]. A major limitation of the technique lies in the considerably high rate of reopening of coiled aneurysms. The recanalization rate reported in the literature varies between 4.7 and 28 % with a re-haemorrhage rate between 0 and 2.8 % in various patient series ranging between 141 and 960 patients [2]. Modifications to platinum coils have been proposed in order to reduce the tendency of coils to compact in large and wide-necked aneurysms. The effectiveness of a hybrid hydrogel platinum detachable coil (HydroCoil, MicroVention Inc., Tustin, CA) for endovascular aneurysm treatment has been proven in a recently published randomized controlled trial [3]. Due to technical restrictions (coil stiffness, time restriction for placement), the HydroSoft coil as well as a corresponding 3D framing coil, the HydroFrame coil (MicroVention Inc., Tustin, CA), a class of new softer coils containing less hydrogel and swelling more slowly than the HydroCoil, have been developed and brought to clinical practice [4–8]. A recently published multicentre study retrospectively compared 401 patients harbouring 430 intracranial aneurysms treated with endovascular coil embolization with HydroSoft coils with a control group of 221 patients harbouring 253 aneurysms that underwent coil embolization with bare platinum coils [9]. The authors did not find any differences regarding initial angiographic outcomes and procedure-related complications between the two arms of the study. In addition, the packing density obtained with HydroSoft was significantly higher when compared to treatment with bare platinum coils (36.0 ± 8.50 vs 32.1 ± 8.22 %, $p < 0.001$). The mid-term retreatment rates at 12 months

clearly favoured HydroSoft with 4 of 225 patients needing retreatment compared to 20 of 227 patients from the bare platinum arm of the study ($p = 0.004$). The authors acknowledge the following limitations to their study: (1) the study is retrospective with historical controls; (2) different percentage of patients with subarachnoid haemorrhage in the two arms of the study; and (3) differences in the use of stent-assisted coiling in the two arms of the study [9].

A prospective randomized controlled multicentre trial was designed to assess the effectiveness of endovascular aneurysm treatment with HydroSoft/HydroFrame coils compared to bare platinum coils. The present article summarizes the protocol of the corresponding study.

Study protocol: randomized controlled multicentre study comparing HydroSoft/HydroFrame and bare platinum coils for endovascular aneurysm treatment GREAT—a randomized aneurysm trial

The study is funded by MicroVention Inc. The study received appropriate ethics committee approval from the leading ethics committee (Faculty of Medicine, Freiburg University, 077/09) and the local ethics committees and was authorized by the competent French and German authorities. The study is registered in the German Clinical Trials Register (DRKS-ID: DRKS00003132). Funding bodies of the study have no role in study design, data analysis, data interpretation or writing of the report.

Study question

The principle research question is whether endovascular aneurysm treatment with HydroSoft/HydroFrame coils results in a decreased recanalization rate and retreatment rate when compared to bare platinum coils? Other questions to be addressed are whether any differences of clinical outcome may be observed between the patients treated with HydroSoft/HydroFrame coils and patients that received treatment with bare platinum coils. In addition, we want to find out how the administered coil lengths as well as the packing densities compare between the two arms of the study.

Study design

In order to answer the central questions on angiographic and clinical effectiveness, we designed a prospective randomized controlled multicentre trial. A total of 500 patients (amended sample size after publication of the results of the HELPS trial) were to be randomly assigned to two treatment arms:

1. Coil embolization with HydroSoft/HydroFrame coils (>50 % of the administered coil length)
2. Coil embolization with any bare platinum coil

Patients were predominantly recruited out of the clinical sample of patients that either presented with ruptured intracranial aneurysms or patients with incidental aneurysms diagnosed at or referred to the units of Neuroradiology and Neurosurgery of the study centres.

Inclusion criteria

Patients aged between 18 and 75 years presenting with a cerebral aneurysm deemed to require endovascular treatment by the neurovascular team, and presenting with a World Federation of Neurological Surgeons (WFNS) grade 0–3 could be included into the trial. In patients WFNS grade 0 + 1, fully informed consent was obtained for participation in the study. For patients WFNS grade 2 + 3, the attending senior neuroradiologist and senior neurosurgeon had to sign for inclusion in the study. At a second stage, consent was obtained from the patient or the legal guardian. Patients were randomized bearing aneurysms between 4 and 12 mm in diameter with an anatomy such that endovascular occlusion was deemed possible. To raise awareness that the physician had to accept the randomisation result, the neurointerventionalist's willingness to treat the patient with either bare platinum or HydroSoft/HydroFrame coils was explicitly mentioned as an inclusion criterion.

Exclusion criteria

Patients previously randomized in this trial or requiring treatment of more than one aneurysm in the same treatment episode as well as aneurysms pre-treated by coiling or clipping were ineligible.

Randomization

A blocked randomization with blocks of variable size, stratified by rupture status, was employed to ensure balance concerning the rupture status (recently ruptured [within 30 days] vs unruptured aneurysms) between the two arms of the study. Randomization was performed via a web-based randomization application (Randoulette, Institute for data management, Biometry, and Epidemiology, LMU, Munich, Germany). In total, 513 patients were randomized. Data collection and follow-up are ongoing.

Treatment

Standard local procedures for the coiling of aneurysms were followed. The use of coil assist devices such as stents or remodelling balloons was allowed. Within the HydroSoft/

HydroFrame arm of the study, HydroSoft/HydroFrame coils should constitute >50 % of the total coil length deployed.

Primary endpoint

Primary endpoint of the study is a composite outcome including major aneurysm recurrence on follow-up angiography judged by a blinded core lab and poor clinical outcome. The composite primary endpoint will be evaluated as poor outcome if a major recurrence is diagnosed within 18 months or if images are unavailable at 18 months due to adverse clinical outcome (modified Rankin scale [mRS] 3–6) and as good outcome if the status up to 18 months is determined as no major recurrence.

Secondary endpoints and follow-up procedures

Secondary endpoints include angiographic outcome at baseline and at 6 months after coiling and clinical outcome at 6 months measured by mRS. In addition, total coil length deployed as well as packing density obtained will be assessed.

Angiographic outcome An angiographic control will be performed at 18 months post-coiling using digital subtraction angiography (DSA) or MRA. In addition, it is common practice in the participating centres to perform angiographic controls at 6 months post coiling. The 6 months angiographic exams will be collected when available, as they will be used for assessing the primary outcome in case the 18 months images are missing. Incidental follow-up exams showing early recanalization will also be collected if they lead to a retreatment.

A core lab composed of two independent investigators (H.D., J.F.) blinded to treatment will confirm the degree of occlusion at end of treatment and on check angiograms using standard criteria [10]. DSA is preferred over MRA, but MRA is acceptable for centres where the 18 months control is routinely performed with MRA. Recurrences will be divided into minor and major [11].

Clinical outcome Clinical status at 6- and 18-months follow-up will be recorded as a secondary endpoint. This will be done by mRs assessment done in the centre by the team treating the patient [12].

Original and amended sample size estimate and power of the study

Recent research has shown that major recurrence rates at 18 months can be considerably higher than anticipated. In the HELPS trial [3], major recurrence rates of 10 % (coated coils) versus 20 % (bare platinum) were expected at the planning stage, 27 versus 36 % were observed, and the composite

angiographic and clinical endpoint at 18 months follow-up had 31 versus 38 % adverse outcomes. To detect these differences with adequate power required a higher sample size than the scenario which was originally planned for in the GREAT trial (initially, 5 vs 15 % were expected for coated vs bare platinum coils). Assuming, as in HELPS, that poor outcomes at 18 months occur at a rate of 10 % (HydroSoft/HydroFrame coils) versus 20 % (bare platinum), 218 patients per group were needed to detect a difference between HydroSoft/HydroFrame and bare platinum with a power of 80 % using Fisher's exact test at two-sided significance level of 5 % (STPLAN 4.3). When non-compliance and/or drop-out of patients after randomization was assumed to be in the order of 10 %, 486 patients had to be randomized to observe the desired amount of compliant patients. If the rates of recurrence, poor outcomes or drop-out were higher, even higher sample sizes were needed to obtain 80 % power. Although other scenarios requiring higher sample sizes would also be scientifically relevant, the trial steering committee decided to increase the target sample size from initially 306 to 500 patients, the maximum number assessed to be feasible in a reasonable time window.

Study sites

A multicentre study design was chosen to account for patient recruitment within a reasonable time frame, for inclusion of a wider range of patients increasing the generalizability of the results and for the dissemination of findings when they become available. All participating centres are broadly experienced in endovascular aneurysm treatment with coils. The research units are used to plan and carry out multicentre studies and research programmes. Clinical and research facilities with an experienced staff exist. Participating centres are located in France: Montpellier, Caen, Bordeaux, Reims, Clermont-Ferrand, Paris (3), Marseille, Besançon, Tours, Dijon, Rennes, Rouen, Limoges, and Germany: Freiburg (co-ordinating centre), Essen (2), Augsburg, Frankfurt, Mannheim, Gießen.

Statistical analysis

The primary analysis will present the absolute risk difference for the proportion of patients who have a poor outcome on the composite 18 months primary endpoint with a two-sided 95 % confidence interval, stratified by rupture status. Patients will be evaluated in the arm to which they were randomized irrespective of treatment received, however, excluding patients in whom the primary outcome is missing and those who received additional flow diverting stents, intravascular flow disrupters or aneurysm clipping instead of the randomized coiling procedure (modified intention-to-treat analysis). The lead investigator [C.A.T.] will determine treatment-based patient exclusions after final data cleaning of the data base with respect to

procedural data. Sensitivity analyses will explore the worst-case scenario where all missing outcomes for patients randomized to the HydroSoft arm are evaluated as poor and all those in the bare platinum arm are evaluated as favourable. Explorative secondary analyses of the primary outcome will be performed separately by rupture status.

Data safety monitoring board

The independent data safety monitoring board (DSMB) was supplied, in strict confidentiality, with an interim analysis of trial data on post-operative mortality/complication rates after the first 100 patients had been randomized. They also considered relevant information from other sources (e.g. any other relevant trials). In the light of these analyses, the DSMB advised the lead investigator [C.A.T.] to carry on with the trial and to perform a second interim analysis with respect to post-operative outcomes as soon as feasible, which was done when 300 patients had been randomized. Again, the DSMB advised to carry on with the trial. The primary endpoint was not evaluated in the interim analyses.

Discussion

Endovascular coil embolization has become a well-established therapy for intracranial aneurysm. A growing industry has established around this quickly evolving field. This evolution may advance endovascular therapy thanks to improvements of the material used. Yet the growing number of available devices and techniques make medical decision making harder for the treating physician. The vast majority of publications in the field derive from uncontrolled mostly self-assessed case series and are, at best, exploratory [13]. The present study is one of a relatively small number of randomized controlled multicentre trials dealing with coils used for aneurysm treatment [3, 14–16]. Our study protocol is well in line with essential standards of modern outcome research: (1) random allocation of the patients to the treatment (HydroSoft/HydroFrame) and control condition (bare platinum), (2) treatments implemented by trained specialists, (3) use of standardized diagnostic instruments for the assessment of clinical outcome (mRs), (4) assessment of angiographic data by an independent core lab, (5) modified intention-to-treat and worst-case analyses allowing for a clinically useful and a conservative strategy of data analysis, (6) source data verification and data cleaning by clinical monitors and a specialised clinical trials unit and (7) independent advice with respect to security of patients (data monitoring and safety board).

However, limitations of the study protocol need to be discussed. Inclusion into the study was limited to patients bearing aneurysms between 4 and 12 mm. We decided to limit

the aneurysm size for two reasons: (1) when the study started, only the HydroSoft Coil was introduced on the market. The largest available coil diameter of the HydroSoft coil in Germany and France at that time was 12 mm. For aneurysms >12 mm, the study physicians would have been obliged to use bare platinum coils for the initial framing. Especially in very large or giant aneurysms, it would have been difficult to obtain a HydroSoft coiling >50 % of the administered coil length. (2) When the HydroFrame 10/18 with larger coil diameters were made available, we refrained from a study protocol amendment which could have allowed including larger aneurysms because this patient population (aneurysm >10 mm) was addressed to by the Patients Prone to Recurrence after Endovascular Treatment (PRET) trial [16]. At that point in time, we wanted to avoid direct competition between the two trials.

Another difficulty was the determination of the sample size. Recanalization rates after aneurysm treatment with coils reported in the literature vary substantially. Although comparable to the size of other recent trials and compatible with scenarios found in the literature, our target sample size of 500 was chosen because higher numbers were deemed unattainable. The power achieved may be lower than 80 % for other realistic scenarios.

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Ethical standards and patient consent We declare that all human and animal studies have been approved by the leading Ethics Committee (Faculty of Medicine, Freiburg University, 077/09) and the local Ethics Committees and was authorized by the competent French and German authorities. The study is registered in the German Clinical Trials Register (DRKS-ID: DRKS00003132) and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. We declare that all patients gave informed consent according to the requirements of the study protocol approved by the Ethics Committees in France and Germany.

Conflict of interest CAT has consulted for MicroVention Inc., Stryker Neurovascular and Acandis GmbH.

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