Emergent aneurysm treatment compared with treatment on neurological improvement in patients with ruptured poor-grade aneurysmal subarachnoid haemorrhage: the TOPSAT2 RCT

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Scientific summary

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Background

Aneurysmal subarachnoid haemorrhage is a form of stroke that is associated with a high mortality rate, is characterised by a bleed in the brain, and is mostly caused by a ruptured aneurysm on one of the cranial arteries. During the latter part of the twentieth century it was recommended that the aneurysm be secured to prevent rebleed, deterioration and a poor outcome in cases of aneurysmal subarachnoid haemorrhage. In 2002, the randomised, controlled international subarachnoid aneurysm trial (ISAT) was published comparing two different methods of securing the aneurysm. The international subarachnoid aneurysm trial compared the usual neurosurgical technique of open surgery (placing a clip on the aneurysm neck) with a new endovascular technique of inserting detachable metal coils through a microcatheter placed (from the femoral artery in the groin) into the aneurysm itself to provide a dense scaffold to establish a clot that combined would occlude the aneurysm. This trial established that the endovascular procedure was more beneficial among the patients enrolled; however, it was mainly good-grade [World Federation of Neurosurgical Societies (WFNS) grades 1–3] aneurysmal subarachnoid haemorrhage patients who were recruited with a subset of aneurysm sizes and locations.

The WFNS grade relies primarily on the Glasgow Coma Scale score, with a score above 12 representing WFNS grades 1–3, a score of 3–6 (in profound coma) representing WFNS grade 5, and a score of 7–12 representing WFNS grade 4 [encompassing a range of impaired alertness from obtunded (Glasgow Coma Scale score 12) to markedly obtunded (Glasgow Coma Scale score 10) to moderate coma (Glasgow Coma Scale score 7 or 8)].

Since the 1980s, expert opinion has recommended expeditious treatment of a ruptured aneurysm in good-grade patients. For poor-grade patients (WFNS grades 4 or 5), because of the invasive nature of the operation and frequently unstable clinical status of these very ill patients, it was generally recommended that securing the aneurysm should be undertaken once the patient had improved neurologically. Although the international subarachnoid aneurysm trial demonstrated that the endovascular treatment (coiling) was preferable to clipping in good-grade patients (WFNS grades 1–3), there was no evidence as to whether or not this less invasive procedure should be preferentially undertaken in poor-grade patients, let alone on the optimum timing of such treatment. Seventy-two hours is very relevant because an important delayed complication of aneurysmal subarachnoid haemorrhage called delayed cerebral ischaemia (sometimes called symptomatic vasospasm) rarely develops before 72 hours, and it is widely recommended to avoid treatment within the 'vasospasm period' when possible. This applies more so for clipping than coiling but has applicability to both techniques, as the procedural risks are increased with both techniques if delayed cerebral ischaemia is present.

Objectives

To establish the efficacy of a strategy of early aneurysm treatment in a population of WFNS grade 4–5 (poor-grade) aneurysmal subarachnoid haemorrhage patients in comparison with the conventional strategy (developed when only clipping treatment was available) of treatment of the aneurysm after neurological improvement (to WFNS grades 1–3), whenever that occurred. Early treatment (or emergent treatment) meant securing the ruptured aneurysm by either coiling or clipping (as per local centre preference based on an individual case-by-case assessment) within 24 hours of randomisation at a neuroscience centre and within, at most, 72 hours of ictus. In the emergent arm, aneurysm treatment was to be undertaken regardless of any neurological response, provided that the patient met all the trial inclusion criteria (not including Glasgow Coma Scale score 3, as that is essentially an unresponsive patient with fixed, dilated pupils).

Methods

A prospective, randomised, open, parallel-group study with blinded outcome assessment (pragmatic, randomised, open-blinded, end-point design) was undertaken. The aim was to randomise 346 patients with aneurysmal subarachnoid haemorrhage and WFNS grades 4 or 5 to receive early treatment (within 72 hours of ictus) or to receive treatment for their aneurysm when they had improved neurologically (defined as improvement to WFNS grades 1–3). The treatment modality would be at the discretion of the local neurovascular team. Patients were to be recruited from 20 neuroscience centres in the UK that were able to undertake both management approaches, and 10 such centres in Europe. Web-based randomisation was used, randomising in the ratio 1 : 1 with minimisation criteria of WFNS grades 4 or 5, UK or non-UK centre, age band (18–50 years, 51–65 years and 66–80 years), and presence (or not) of clinically significant hydrocephalus requiring cerebrospinal fluid drainage. The primary outcome was measured at 12 months by a postal questionnaire sent to surviving patients (UK) or a similar follow-up by a local trial team (non-UK). Outcome was originally intended to be assessed using an ordinal analysis of the modified Rankin Scale (values 0 to 6), including death coded as a value of 6. Secondary outcomes included mortality, rebleed rate and dichotomisation cuts (at 0–2 vs. 3–6, and 0–3 vs. 4–6) of the modified Rankin Scale at 6 and 12 months.

Results

The trial was halted because of difficulties resulting in slow patient recruitment. Recruitment opened in December 2016 and the recruitment period was due to last for 44 months; however, by December 2018 only 23 patients had been recruited. Difficulties included an unexpectedly high rate of lack of clinical equipoise to enrol otherwise eligible patients [compared with findings in the treatment of poor-grade subarachnoid haemorrhage trial 1 (TOPSAT 1)]; competing studies in the most research-active centres; a slightly lower medical eligibility rate than predicted; and a change in approach by the UK trial sponsor (Newcastle upon Tyne Hospitals NHS Foundation Trust). The original sponsor changed policy mid-trial to no longer act as a sponsor for European Union-based sites. This resulted in substantial delays in agreeing new sponsorship arrangements for overseas sites, to contract finalisation between them and Newcastle University and to their eventual site set-up and initiation. This involved a change from direct sponsorship to a data-sharing agreement.

By the time the trial was halted, 15 sites had been initiated and 14 were screening (11 in the UK and three in Europe). A total of 1269 patients had been screened, of whom 305 were poor-grade patients. Of those, 111 were medically eligible and 23 had been randomised [11 to the emergent treatment arm and 12 to the treatment on neurological improvement (control) (whenever that occurred) arm]. Seventy-four out of 111 patients were not randomised because of a lack of equipoise. The baseline characteristics were similar in both groups with patients aged between 44 and 75 years (median age 63 years); 65% were female and 70% were from the UK. A total of 74% of patients were WFNS grade 5, and 26% were WFNS grade 4; 74% required drainage for hydrocephalus (or it was planned at time of enrolment). All patients were randomised within 48 hours of ictus with a median of 21 hours. Aneurysms tended to be located in the anterior communicating artery (43%) or posterior communicating artery (30%). The planned treatment as indicated at time of enrolment was endovascular (30%), neurosurgical (52%) or not stated (17%, applied to four patients in the treatment on neurological improvement arm). All patients in the emergent treatment arm had their aneurysm secured within 71 hours of ictus (median 26 hours), whereas for the four patients who went on to receive treatment on neurological improvement, the median time to treatment was 163 hours.

Primary outcome showed no difference between the two treatments ($p = 0.11$) but the mortality rate was, as expected with a population of mainly WFNS grade 5 subarachnoid haemorrhage patients, high, at 70% overall, with 55% of patients having died in the emergent treatment arm and 83% having died in the treatment on neurological improvement arm at 12 months ($p = 0.4$). Two patients did achieve a

modified Rankin Scale score of 0–2 at 12 months in the emergent treatment arm (18%) but none did in the treatment on neurological improvement arm ($p = 0.22$). A rebleed was reported for two patients in the treatment on neurological improvement arm (17%) but for none in the emergent treatment arm ($p = 0.48$).

Conclusions (implications for health care and recommendations for research)

The low recruitment limits the ability to draw firm conclusions from the data and make any recommendations in terms of treatment for poor-grade aneurysmal subarachnoid haemorrhage patients. The treatment of poor-grade subarachnoid haemorrhage trial 2 (TOPSAT 2) data indicate no evidence of a marked difference in outcome for the strategies of emergent treatment and treatment on neurological improvement, and is not able to provide evidence to indicate that the current heterogeneous approach to poor-grade management should change in one direction or another. Therefore, based on TOPSAT2, no service reconfiguration would be necessary.

The randomised controlled trial approach to investigating whether poor-grade aneurysmal subarachnoid haemorrhage patients should receive emergent treatment or be treated on neurological improvement proved unfeasible. The length of time between the feasibility study and the Phase III trial possibly resulted in a shift in practice by care staff at individual sites, which mitigated against the clinical equipoise required for a successful level of recruitment to TOPSAT2. A prospective observational study proposed to the funder, at their request, as an alternative method to collect systematic data during the final 2 years of the study about actual treatment received was not judged as providing adequate value for money.

Magnetic resonance imaging remains very challenging in aneurysmal subarachnoid haemorrhage patients, particularly in poor-grade patients, and therefore the use of magnetic resonance imaging-based biomarkers to stratify an approach to their treatment does not seem to provide a promising area for investigation at present.

Trial registration

This trial is registered as ISRCTN15960635.

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