EDITORIAL

CURES and the Dilemma of Unruptured Intracranial Aneurysms

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"The management of unruptured intracranial aneurysms remains one of the most controversial topics in neurosurgery"[1]

Although the natural history of unruptured intracranial aneurysms (UIAs) is controversial, and good evidence to support their treatment is scarce, we actually do know quite a lot about them. We know that they occur in anywhere from 0.4 -6% of the population in autopsy and imaging studies[2,3]. The annual risk of rupture from a UIA was thought to be around 1.9%[4,5] until the International Study of Unruptured Intracranial Aneurysms (ISUIA) dramatically lowered this rate to 0.1% for UIAs less than 7mm in diameter[6]. We know that the following may factor into annual rupture risk: diameter > 7mm; posterior circulation or posterior communicating artery location; high aspect ratio (dome/neck); presence of irregular surfaces or daughter sacs; a small parent artery; presence of symptoms other than hemorrhage; age and gender; history of smoking or hypertension; nationality; genetic factors, and medical co-morbidities[7-10]. Surgical treatment of UIAs carries morbidity rates of 10.1% to 13.6 % and mortality rates of 2.6% to 15.7%[1,3,6,11-13], and a low regrowth rate of less than 1%[1]. Endovascular therapy (EVT) of UIAs has morbidity rates of 1.7% to 7.4% and mortality rates of 0.5% to 1.4% (or up to 4.6% when stent-assistance is required), with incomplete aneurysm occlusion in up to 40%, and aneurysm recurrence in up to 33.6% of patients[1,3,6,14-17] necessitating re-treatment in 9%[14]. Retrospective comparisons between surgery and EVT of UIAs suggest that coiling is safer and more cost-effective than surgery, but less durable[18-20]. Many authors have called for a definitive randomized controlled trial (RCT) to determine which UIAs should be treated and how best to treat them[3,21-24].

Dr. Jean Raymond and his colleagues have relentlessly sought valid answers to the dilemma of UIAs. He has eloquently argued that our knowledge of the natural history and treatment of UIAs is either inadequate or deeply flawed[21,22,24]. He designed and led the Trial of Endovascular Aneurysm Management (TEAM), the first large, multicentre, prospective RCT of EVT vs. observation of UIAs, which was prematurely terminated due to insufficient recruitment and funding withdrawal. Undaunted, he has has now produced The Canadian Unruptured Endovascular versus Surgery trial (CURES) with Dr. Max Findlay and colleagues, a feasibility study to determine the best intervention to treat UIAs.[25]

The Canadian Unruptured Endovascular versus Surgery trial has risen from the ashes of TEAM, and the investigators have made the *a priori* decision that UIAs between 3mm to 25mm in diameter deserve to be treated. It is a Canadian feasibility RCT between EVT and surgery in 260 patients with UIAs. Outcome measures are: failure to accomplish aneurysm obliteration with initial treatment; major intracranial hemorrhage at one year, and treatment related morbidity/mortality within 31 days. The authors hope that this trial will lead to a definitive, international study of EVT vs. surgery. The Canadian Unruptured Endovascular versus Surgery trial will not address the question of whether UIAs should be treated or not. Will Canadian neurologists and neurosurgeons buy into Dr. Raymond's vision and randomize their patients to his study? Should they do so?

Ideally, the complication rate of any treatment for UIAs should be close to 0%. One must be sure that the results of treatment are better than the long- term risk of the underlying disorder. The data may be flawed, but ISUIA accumulated over 12,000 patient years of clinical follow-up[6] and we already know the results in over 11,000 patients who underwent surgery[12] and over 5,000 patients who underwent EVT[14] of their UIAs. Can randomization to surgery or EVT of a small (< 5mm diameter) anterior circulation UIA in an asymptomatic patient ever be justified? The CURES investigators believe it can and should be for the sake of scientific inquiry.

Others are not so sure. Following the first ISUIA report in 2000, Wardlaw and White concluded that "neither coiling nor surgery seems sufficiently safe to address this issue in most patients with unruptured aneurysms. A randomized trial of best medical therapy versus intervention with long-term follow-up is required"[3]. A consensus group in 2008, analyzing all relevant data to date, recommended the following: small, incidental aneurysms < 5 mm should be managed conservatively in nearly all cases; patients < 60 years-of-age with aneurysms > 5mm should be offered treatment unless there are major contraindications (the 5mm rather than 7mm diameter was chosen due to the limitations of ISUIA data); incidental aneurysms > 10 mm should be treated in all patients < 70 years-of-age; surgery should be the treatment of choice rather than coiling in low-risk cases, but coiling is a reasonable alternative if the surgical risk is high due to aneurysm location or medical co-morbidities[1].

The investigators of CURES have kept their goals modest and have designed a flexible, pragmatic pilot trial, which may partially answer the problem of UIA management. We already know, however that surgical repair of aneurysms has higher short-term risks than EVT, and that surgery usually offers more complete initial occlusion rates and fewer recurrences[26]. We know that EVT of UIAs can be performed safely and effectively[15,18]. It is quite likely that CURES will show more aneurysm neck remnants and possibly re-treatments with EVT compared to surgery at one year. This trial will not give us long-term anatomic or clinical results. Other concerns include the possibility of local bias influencing which aneurysms are randomized, and the unknown fate of those UIAs which are not entered into the study. Despite stratification of aneurysms by size and location, the heterogeneous but small aneurysm cohort with widely variant treatment techniques will make valid conclusions

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difficult to generalize. Finally, can randomization of a small (<5 mm diameter) UIA to a study lacking an observational arm ever be justified?

Dr. Raymond has argued that a "supreme" RCT with randomization into three groups (observation, EVT or surgery) would be impractical and likely unhelpful for a variety of reasons[24]. In reality, can any other trial provide definitive answers about which UIAs need treatment, and which treatment is best? Our centre would certainly be more enthusiastic about randomizing patients to such a study. Would the energies devoted to this and any follow-up trials be better utilized in a collaborative, multicentre, international "supreme" study to provide the information we need? Until investigators and funding agencies realize the merits of such a complex, costly and lengthy trial, we will be left with incomplete knowledge and unanswered questions. The CURES trial may shed some light on pieces of the UIA puzzle, but this study will not solve it. Time will tell if Dr. Raymond's current initiative will lead to answers that we can use.

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