

# Ultra-early aneurysm treatment for patients with poor neurological status after intracranial aneurysm rupture: abridged secondary publication

GKC Wong \*, COA Tsang, KY Yam, YC Po, KY Chan, KYV Pang, HKC Mak

## KEY MESSAGES

1. Ultra-early aneurysm treatment is not associated with favourable modified Rankin Scale score at 6 months and is not a valid surrogate for outcomes.
2. The ultra-early and non-ultra-early aneurysm treatment groups are comparable at 1, 3, and 6 months in terms of Montreal Cognitive Assessment score, Stroke-Specific Quality of Life score, Short-Form 36 score, return to work status.

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<sup>1</sup> GKC Wong, <sup>2</sup> COA Tsang, <sup>3</sup> KY Yam, <sup>4</sup> YC Po, <sup>5</sup> KY Chan, <sup>6</sup> KYV Pang, <sup>7</sup> HKC Mak

<sup>1</sup> Prince of Wales Hospital and The Chinese University of Hong Kong, Hong Kong SAR, China

<sup>2</sup> Queen Mary Hospital, Hong Kong SAR, China

<sup>3</sup> Tuen Mun Hospital, Hong Kong SAR, China

<sup>4</sup> Princess Margaret Hospital, Hong Kong SAR, China

<sup>5</sup> Kwong Wah Hospital, Hong Kong SAR, China

<sup>6</sup> Pamela Youde Nethersole Eastern Hospital, Hong Kong SAR, China

<sup>7</sup> Queen Elizabeth Hospital, Hong Kong SAR, China

\* Principal applicant and corresponding author: wongkwokchu@gmail.com

## Introduction

Intracranial aneurysm rupture resulting in aneurysmal subarachnoid haemorrhage (SAH) is a devastating form of cerebrovascular accident (CVA). In 2010, the overall incidence of SAH in Hong Kong was approximately 7.5 per 100 000 person-years. Most patients are unaware that they are at risk, despite reports of specific factors associated with SAH.

Although SAH only accounts for 5% of CVA cases, many of the affected patients are young (aged <65 years), leading to a loss of functional years comparable with that from ischaemic CVA. Worldwide, case fatality rates range from 8.3% to 66.7%. Recent studies suggest that SAH mortality has substantially declined over the past few decades. This improvement in SAH mortality reflects the use of more aggressive aneurysm treatment protocols and the implementation of modern critical care strategies. Thus, patients with SAH frequently require admission to intensive care units and high dependency units for close clinical monitoring and treatment. Ultra-early aneurysm treatment is defined as definitive aneurysm microsurgery, endovascular embolisation, or stenting to prevent rebleeding, all performed within 24 hours of ictus in aneurysmal SAH. In poor-grade aneurysmal SAH, ictus is defined as the time at which the patient developed reduced consciousness. Similarly, treatment beyond 24 hours is defined as definitive aneurysm microsurgery, endovascular embolisation, or stenting to prevent rebleeding, all performed

>24 hours after ictus in aneurysmal SAH. Ultra-early aneurysm treatment for patients with SAH admitted with poor neurological status could serve as a surrogate for favourable functional outcomes at 6 months. We prospectively assessed patients with poor-grade SAH in Hong Kong to determine whether ultra-early treatment was a valid surrogate for clinical outcomes. Specifically, we evaluated whether ultra-early aneurysm treatment was associated with improved clinical outcomes in hospitalised patients with poor neurological status after intracranial aneurysm rupture.

## Methods

This study was conducted between 1 August 2019 and 31 July 2022. Patients with aneurysmal SAH were recruited from seven hospitals in Hong Kong: Prince of Wales Hospital, Queen Mary Hospital, Princess Margaret Hospital, Kwong Wah Hospital, Tuen Mun Hospital, Queen Elizabeth Hospital, and Pamela Youde Nethersole Eastern Hospital. Ultra-early aneurysm treatment was defined as definitive cerebral aneurysm treatment (eg, coiling or clipping) within the first 24 hours after SAH. Non-ultra-early aneurysm treatment was defined as definitive cerebral aneurysm treatment >24 hours after SAH. Patients were followed up until 6 months post-SAH. Assessments were independently conducted at baseline, 30 days, 3 months, and 6 months by research assistants who were blinded to clinical management plans.

The primary outcome was modified Rankin

Scale (mRS) score at 6 months post-SAH. Secondary outcomes were Montreal Cognitive Assessment score, Stroke-Specific Quality of Life score, Short-Form 36 score, return to work status, and hospital resource utilisation at 30 days, 3 months, and 6 months. The mRS is validated for assessing recovery in patients with SAH. The mRS identifies activity limitations, which range from 0 (no symptoms) to 6 (death). Scores on the mRS were dichotomised as favourable (0-2) and unfavourable (3-6) for analysis. The Montreal Cognitive Assessment evaluates seven cognitive domains: visuospatial/executive function, naming, verbal memory registration and learning, attention, abstraction, 5-minute delayed verbal recall, and orientation. It is validated for assessing cognitive dysfunction and deficits in patients with SAH. The Stroke-Specific Quality of Life scale is validated for assessing disease-specific quality of life in patients with SAH. The Short-Form 36 is validated for assessing health-related quality of life in patients with SAH.

Sample size was calculated using Prince of Wales Hospital 2017 data, which showed that 49% of patients with SAH had ultra-early definitive aneurysm treatment. Post hoc analysis suggested that ultra-early aneurysm treatment increased the percentage of favourable outcomes at 6 months from 19% to 37%. With  $\alpha=0.05$  and  $\beta=0.2$ , the minimum sample size for each arm was 107. Logistic regression analyses were performed with adjustments for age, admission neurological grade, hypertension, and modality of aneurysm treatment. If quality of life outcomes showed improvement, incremental cost-effective ratios were calculated. A P value of  $<0.05$  was considered statistically significant; all tests were two-tailed.

## Results

Of the 659 patients with SAH screened, 235 had good-grade aneurysmal SAH, two had no SAH, 14 had traumatic SAH, and the remaining 408 had poor-grade aneurysmal SAH. Of the latter, 293 (72%) patients underwent ultra-early (n=163) or non-ultra-early (n=130) aneurysm treatment.

In univariable analysis, the proportion of patients with favourable mRS score ( $\leq 2$ ) at 6 months was lower in the ultra-early treatment group (35% vs 22%,  $P=0.011$ ). The significant difference remained after multivariable analysis (odds ratio=0.51, 95% confidence interval=0.28-0.93,  $P=0.027$ ). Therefore, the results did not support our hypothesis that ultra-early aneurysm treatment would result in a higher proportion of patients with SAH to achieve mRS score  $\leq 2$  at 6 months. The ultra-early and non-ultra-early aneurysm treatment groups were comparable in terms of secondary outcomes at 1, 3, and 6 months. Because the quality of life outcomes did not suggest a benefit, we did not perform a cost-

effectiveness analysis regarding hospital resource utilisation.

## Discussion

Ultra-early aneurysm treatment was not a valid surrogate for outcomes in patients with poor-grade SAH. However, studies (mostly single-centre observational case series) have reported that ultra-early aneurysm treatment (especially endovascular treatment) for patients with poor-grade aneurysmal SAH is associated with better outcomes. Other management parameters (eg, blood pressure control) may play important roles.<sup>1</sup>

The median transfer time has been reported to be 4 days.<sup>2,3</sup> Patients with secondary events and deterioration are more likely to receive desperate measures during earlier aneurysm treatment, leading to poor outcomes. Five themes are identified as facilitators and barriers to timely treatment of aneurysmal SAH: 'early recognition' leads to urgent response; 'accessibility to health care' depends on patient's location, transport, and environmental conditions; good 'coordination' between and within health services is a key facilitator; 'complexity' of patient's condition affects time to treatment in multiple time periods; and 'availability of resources' is identified most frequently during the diagnostic and treatment phases as both barrier and facilitator.<sup>4</sup>

The present study has limitations. It is a pragmatic trial (without a unified experimental protocol for patient management), which is less robust than a randomised controlled clinical trial. Because of prior agreements that the results of various centres would not be analysed or disclosed, no subgroup analyses were performed. A total of 115 (28%) of patients did not consent to participate; reasons for lack of consent were not recorded for analysis.

## Conclusions

Ultra-early aneurysm treatment is not associated with favourable mRS score at 6 months and is not a valid surrogate for outcomes.

## Funding

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