ORIGINAL ARTICLE

Indonesian Journal of Neurosurgery (*IJN*) 2024, Volume 7, Number 1: 42-45
P-ISSN.2089-1180, E-ISSN.2302-2914

Indonesian Journal of Neurosurgery

Association of onset-to-treatment time with mortality from aneurysmal subarachnoid hemorrhage

Annisa Amalina[1*], Abrar Arham[1,2], Beny Rilianto[2], Bambang Tri Prasetyo[2], Ricky G Kurniawan[2], Muhammad Kusdiansah[1]

[1]Neurosurgery Division, National Brain Center Hospital, Prof. Dr. dr. Mahar Mardjono, East Jakarta, Indonesia; [2]Neurointervention Division, National Brain Center Hospital, Prof. Dr. dr. Mahar Mardjono, East Jakarta, Indonesia.

*Corresponding author:
Annisa Amalina;
Neurosurgery Division, National Brain Center Hospital, Prof. Dr. dr. Mahar Mardjono, East Jakarta, Indonesia;
amalinaannisa21@gmail.com

Received: 2024-02-01
Accepted: 2024-03-22
Published: 2024-04-09

ABSTRACT

Background: The timing of neurosurgical and/or endovascular intervention for aneurysmal subarachnoid hemorrhage (aSAH) has been associated with the improvement of patient outcomes. However, there is still lack of evidence, also with a significant risk of bias from subjective stratifications such as timing, limited to one center, or treatment modality. This study aimed to examine the association between the onset-to-treatment time and in-hospital mortality in patients with aSAH.

Methods: We retrospectively reviewed the in-hospital records of aSAH patients admitted between January 2019 to December 2022 from the Stroke Registry in the National Brain Center Hospital, East Jakarta, Indonesia. Patients with aSAH derived from digital subtraction angiography (DSA) / computed tomography angiography (CTA) examination were analyzed for onset-to-treatment time to patient mortality. Statistical analyses were carried out with STATA 17.0. The p-value of < 0.25 was considered significant between groups.

Results: A total of 100 subjects who received endovascular coiling or neurosurgical clipping were studied and divided into two groups (dead and alive). The average age was 55.7 ± 11.3 and was dominated by females (64 subjects). In bivariate analysis, onset-to-treatment had significant differences between groups (OR 0.43 [95% CI 0.07-1.73]; $p = 0.20$) along with gender, SAH grading, location, hypertension, and dyslipidemia. However, in multivariate analysis, there was no association found between onset-to-treatment with in-hospital mortality ($p = 0.41$), while the grade of SAH had the greatest influence on hospital mortality (aOR 3.90 (95% CI 1.14-13.28); $p = 0.029$).

Conclusion: This study found no association between onset-to-treatment over three days with in-hospital mortality. Instead, the grade of SAH had the greatest influence on hospital mortality.

Keywords: aneurysmal subarachnoid hemorrhage, clipping, coiling, onset-to-treatment.
Cite This Article: Amalina, A., Arham, A., Rilianto, B., Prasetyo, B.T., Kurniawan, R.G., Kusdiansah, M. 2024. Association of onset-to-treatment time with mortality from aneurysmal subarachnoid hemorrhage. *Indonesian Journal of Neurosurgery* 7(1): 42-45. DOI: 10.15562/ijn.v7i1.280

INTRODUCTION

Intracranial aneurysms are abnormal vascular dilations that occur in 3-5% of the general population, with approximately 500,000 individuals being affected annually worldwide. Aneurysmal subarachnoid hemorrhage (aSAH) survival rates range from 15-35% of patients with some form of lifelong impairment, cognitive deficit, or personality change, with mortality rates of around 35-45%. Clinical guidelines from the American Heart Association and American Stroke Association in 2015 recommended treatment as early as feasible, whereas the 2013 European Stroke Organization recommended intervention within 72 hours after onset of symptoms. Management of ruptured intracranial aneurysm within either 48 or 72 hours after the aSAH is mainly for the prevention of rebleeding. Several studies found that early surgery which was defined as those performed within three days after the ictus significantly decreases the incidence of unfavorable outcomes.[1,2]

The timing of neurosurgical and/or endovascular intervention for aSAH has been associated with improvements in patient outcomes. Robust evidence to support this remains inadequate, taking into account data heterogeneity with a significant risk of bias from subjective stratifications such as timing and restriction to one treatment center or modality. This study aimed to examine the association between the onset-to-treatment time and in-hospital mortality among patients with aSAH. In addition, this study also determines another factor associated with hospital mortality among patients with aSAH.

METHODS

This retrospective study reviewed the in-hospital records of 100 patients with aSAH admitted between January 2019 to December 2022 from the stroke registry of the National Brain Center Hospital, East Jakarta, Indonesia. The subjects were aSAH patients who was admitted to National Brain Center Hospital in January 2019 until December 2022. The inclusion criteria were aSAH patients who underwent digital subtraction angiography (DSA) or computed tomography angiography (CTA)

examinations and received endovascular coiling or neurosurgical clipping. The exclusion criteria were discharged against medical advice (DAMA) or underwent interventional procedures related to SAH before being transferred to the National Brain Center Hospital. The subject was divided into two groups based on the outcome which were dead and alive.

In this study, the primary result was the association between the onset-to-treatment time and in-hospital mortality among patients with aSAH. The secondary result was the association between demographics data (age and gender) and other clinical characteristics such as posterior circulation, clipping, high-grade SAH, hypertension, diabetes mellitus, and dyslipidemia with in-hospital mortality. All of the data were obtained from medical records.

The data were analyzed using statistical software for data science (STATA 17.0). The chi-square test was used to compare each variable between groups (dead and alive). Co-variables that had $p < 0.25$ in chi-square test were included in multivariate analysis using a logistic regression test. The p value of < 0.25 was considered significant between groups (dead or alive). The odd ratio was also determined with a 95% confidence interval. This study was approved by the Research Ethics Committee of National Brain Center Hospital Prof. Dr. dr. Mahar Mardjono, East Jakarta, Indonesia (Reference Number DP.04.03/KEP/040/2023).

RESULTS

A total of 100 subjects had an average age of 55.7 ± 11.3 with the majority of patients aged 40-60 years old (63%). Subjects were dominated by females consisting of 64 subjects who received endovascular coiling or neurosurgical clipping. Most of the subjects were treated > 3 days after onset (71%). There were only two subjects (2%) had posterior circulation. Forty-two (42%) subjects underwent clipping. Thirty-four subjects had high-grade SAH (34%). The most common comorbidity was hypertension (85%), followed by

Table 1. Demographical and clinical data of aneurysmal subarachnoid hemorrhage patients

Demographical and clinical data	N	f (%)
Gender		
Male	36	36
Female	64	64
Age (Mean ±SD)	55.7 ± 11.3	
< 40 years old	10	10
40-60 years old	63	63
> 60 years old	27	27
Onset-to-treatment time		
<3 days	29	29
> 3 days	71	71
Posterior circulation		
Yes	2	2
No	98	98
Clipping		
Yes	42	42
No	58	58
Grade of SAH		
High grade (modified WFNS 4-5)	34	34
Low grade (modified WFNS 1-3)	66	66
Hypertension		
Yes	85	85
No	15	15
Diabetes mellitus		
Yes	46	46
No	54	54
Dyslipidemia		
Yes	76	76
No	24	24

SAH = Subarachnoid hemorrhage; WFNS = World Federation of Neurosurgical Society

Table 2. The association of risk factors with mortality from aneurysmal subarachnoid hemorrhage

Predictors	Dead N (%)	Alive N (%)	Crude OR (95% CI)	P-value
Female gender	55 (85.9%)	9 (14.1%)	0.49 (0.15-1.58)	*0.17
Age	55.7 ± 11.3			
< 40 years old	7 (70%)	3 (30%)	Reference	
40-60 years old	54 (85.7%)	9 (14.3)	0.38 (0.08-1.78)	0.22
> 60 years old	21 (77.8%)	6 (22.2%)	0.66 (0.13-3.39)	0.62
Onset-to-treatment time > 3 days	56 (78.9%)	15 (21.1%)	0.43 (0.07-1.73)	*0.20
Posterior circulation	1 (50%)	1 (50%)	4.76 (0.05-378.46)	*0.23
Clipping	47 (81%)	11 (19%)	1.17 (0.36-3.93)	0.76
High grade SAH (modified WFNS 4-5)	25 (73.5%)	9 (26.5%)	2.28 (0.70-7.30)	*0.11
Hypertension	72 (84.7%)	13 (15.3%)	0.36 (0.09-1.58)	*0.09
Diabetes mellitus	23 (85.2%)	23 (85.2%)	0.73 (0.15-2.67)	0.61
Dyslipidemia	38 (92.7%)	38 (92.7%)	0.23 (0.04-0.91)	*0.02

* = Chi-square test (p <0.25); OR = Odds ratio; SAH = Subarachnoid hemorrhage; WFNS = World Federation of Neurosurgical Society

Table 3. Multivariate analysis between risk factor and in-hospital mortality from aneurysmal subarachnoid hemorrhage

Predictors	Adjusted OR (95% CI)	P-value
Female gender	0.35 (0.10-1.16)	[a]0.087
Onset-to-treatment time > 3 days	0.49 (0.09-2.62)	0.412
Posterior circulation	12.65 (0.14-1,096.93)	0.265
High grade SAH (modified WFNS 4-5)	3.90 (1.14-13.28)	[a]0.029
Hypertension	0.30 (0.07-1.20)	[a]0.091
Dyslipidemia	0.20 (0.04-0.84)	[a]0.029

[a] = Logistic regression (p < 0.25); OR = Odds ratio; SAH = Subarachnoid hemorrhage; WFNS = World Federation of Neurosurgical Society

dyslipidemia (76%) and diabetes mellitus (46%). The demographic and clinical data of subjects can be seen in Table 1.

In the bivariate analysis which analyzes the association of onset-to-treatment and other demographic and clinical data with in-hospital mortality, six co-variables had significant differences between the two groups (dead or alive). That includes gender (OR 0.49 [95% CI: 0.15-1.58]; p = 0.17), onset to treatment time (OR 0.43 [95% CI 0.07-1.73]; p = 0.20), posterior circulation (OR 4.76 [95% CI 0.05-378.46]; p = 0.23), grade of SAH (OR 2.28 [95% CI 0.70-7.30]; p = 0.11), hypertension (OR 0.36 [95% CI 0.09-1.58] p = 0.09), and dyslipidemia (OR 0.23 [95% CI 0.04-0.91]; p = 0.02). The bivariate analysis can be seen in Table 2.

In multivariate analysis, six co-variables were included. However, only female gender (aOR 0.35 [95% CI 0.10-1.16]; p = 0.087), high-grade SAH (aOR 3.90 (95% CI 1.14-13.28); p=0.029), hypertension (aOR 0.30 (95% CI 0.07-1.20]; p = 0.091) and dyslipidemia (aOR 0.20 [CI 95% 0.04-0.84]; p = 0.091) which statistically significant. Meanwhile, this study found no association between onset-to treatment with in-hospital mortality among aSAH patients (aOR 0.49 [95% CI 0.09-2.62]; p = 0.41). The multivariate analysis can be seen in Table 3.

DISCUSSION

This study consisted of aSAH patients treated with endovascular coiling or neurosurgical clipping. Mortazavi *et al.* found the most common management for aSAH was coiling (54.8%), followed by medical treatment (27.9%), and surgical interventions (17.4%).[3] In the study by Liu *et al.* which included 1,169 subjects, they found 134 subjects (11.5%) underwent microsurgical clipping.[4] In this study, there were 58 subjects (58%) who were treated with clipping and 42 subjects (42%) were treated by coiling.

Delays in the treatment of aSAH appear to be common and may contribute to poor outcomes. Nguyen *et al.* found that a factor associated with treatment delay was pre-hospital delay which consists of patient delay, late referral, late arrival of ambulance, being transferred between hospitals, or arriving at the hospital outside of office hours.[5] Ruptured aneurysms are commonly treated within 24-48 hours after hemorrhage to reduce the risk of rebleeding and therefore complications.[1] Vasospasm is the most common complication of SAH and is the main cause of morbidity and mortality. Cerebral vasospasm is a phenomenon characterized by vasoconstriction of the intracranial arteries, which commonly occurs in the acute period following aSAH.[6] It usually occurs 3 to 14 days after the initial accident, with a peak incidence at seven days. The inflammatory response after SAH rolls out in two main phases. At SAH onset, blood extravasation leads to the invasion of the central nervous system by unselected white cells. After this initial step, the activation of the immune system can induce the secretion of cytokines and other factors able to promote a targeted immune reaction. Microglia and dendritic cell activation, immune cell chemotaxis and cytokine storm develop, with direct consequences in terms of microvascular architecture, vasospasm, early brain injury, and eventually long-term prognosis.[7,8]

Historically, during the 1960s and 1970s, neurosurgeons waited for 2-3 weeks after hemorrhage to avoid performing surgery on aneurysms during peak vasospasm and brain swelling periods, which is known to increase the rates of perioperative complications and mortality.[8] Previous studies found that the outcome of the patient treated in the acute phase (< 3 days) was better than the longer period because the procedure was performed before the vasospasm occurred.[1,4] Mees *et al.* found that ORs for poor outcome were 1.16 (95% CI = 0.89-1.50) for treatment (clipping and coiling combined) at 3 to 4 days, 1.39 (95% CI = 1.08-1.80) for treatment at 5 to 10 days, and 1.84 (95% CI = 1.36-2.51) for treatment > 10 days which indicates that the longer the procedure was carried, the worse the prognosis.[9]

However, in this study, we found no association between onset-to-treatment time over three days with in-hospital mortality (dead or alive) of aSAH patients in multivariate analysis. Previous studies found various results with shorter time needed to treat aSAH patient. Buscot *et al.* stated that endovascular treatment for aSAH should ideally be provided within 12.5 hours after onset but not beyond 24 hours because these results were associated with improved 12-month survival and a greater likelihood of home discharge, independent of the severity of the aneurysmal SAH and other confounders.[1] Hostettler *et al.* found that treatment > 24 hours after rupture is associated with higher mortality and cerebral infarction rates in lower grades aSAH. The rebleeding rate in those cohort was lower because the patients were treated within a median of 7 hours from admission which reduced the mortality rate in patients treated before 24 hours.[7] This study used a cut-off point of three days which is longer than 24 hours. According to Buscot *et al.* and Hostettler *et al.*, it did not give significant results to the patients if treated after 24 hours, even if it was under three days (72 hours). On the contrary, Liu *et al.* found no association between time from onset to surgery with poor outcomes which similar with this study.[4] A single-center study by Linzey *et al.* also revealed that 24-hour aneurysm repair could only reduce the risk of rebleeding by ≤ 0.3% which had no significant impact on the patient's outcome.[6]

Multivariate analysis found that the grade of aSAH had the greatest influence on mortality. As revealed by Hostettler *et*

al, the mortality rate was higher in patients treated < 4 hours. They believed that it reflected the severity of the hemorrhage rather than a real association between treatment timing and adverse events.[7] In this study, the grade of aSAH also gives a greater effect on mortality with adjusted OR 3,90. Zhang *et al*. also reported that shorter intervals in onset-to-treatment-time was associated with poorer outcomes because commonly, the patients in this group tend to have high-risk aSAH (higher grade of aSAH) which usually takes priority to receive therapy as soon as possible.[10] Nguyen *et al*. also found that patients with larger bleeding areas were generally treated more quickly than patients with less extensive bleeding (low-grade aSAH).[5] However, in general, shorter onset-to-treatment time remains the best consideration to reduce the incidence of in-hospital mortality.[9,10]

This was a single-center study with a limited sample size, therefore further studies with a large amount of sample may be needed to confirm the findings. Additionally, because data were derived from a single center, these results may not generalize to other centers. In particular, the vast majority of patients with aSAH who were admitted to our institution are transferred from outside hospitals, and these patients may be more likely to experience rebleeding before admission.

CONCLUSIONS

Onset-to-treatment over three days is not significantly related to the in-hospital mortality of aneurysmal subarachnoid hemorrhage patients. Instead, the grade of aSAH had the greatest influence on in-hospital mortality among aSAH patients who received endovascular coiling or neurosurgical clipping.

ACKNOWLEDGMENT

The authors gratefully acknowledge National Brain Center Hospital Prof. Dr. dr. Mahar Mardjono Jakarta for supporting this study.

FUNDING

No funding was received for this study.

CONFLICT OF INTEREST

The authors gratefully acknowledge National Brain Center Hospital Prof. Dr. dr. Mahar Mardjono Jakarta for supporting this study.

ETHICAL APPROVAL

The Research Ethics Committee of National Brain Center Hospital Prof. Dr. dr. Mahar Mardjono, East Jakarta, Indonesia approved our retrospective study design and protocol (Reference Number DP.04.03/KEP/040/2023). The data we obtained for this study did not require written informed consent from the respective patients.

AUTHORS' CONTRIBUTIONS

AA, AR, and BR contributed to the study's conception, design, and acquisition. AA, AR, and BR conducted the data analysis and wrote the manuscript. RGK, BTP, and MK contributed to the manuscript revision. All authors contributed to reading and approved the submitted version of the manuscript.

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