Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Full length article

Appropriate treatment within 13 hours after onset may improve outcome in patients with high-grade aneurysmal subarachnoid hemorrhage

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ARTICLE INFO

Keywords:
High-grade aneurysmal SAH
Treatment timing
Early surgical treatment
Outcome
Complications

ABSTRACT

Objective: This retrospective study evaluated whether earlier timing of appropriate treatment of high-grade aneurysmal subarachnoid hemorrhage (aSAH), defined as management of ruptured intracranial aneurysm (RIA) combined with required additional surgical measures for control of increased intracranial pressure (ICP), is associated with more favorable outcomes.

Methods: The study cohort comprised 253 patients with high-grade aSAH. Modified Rankin Scale score of 0–3 at 3-month follow-up after the ictus was considered as favorable outcome.

Results: Appropriate treatment of aSAH was completed in 205 patients (81 %), and included clipping or coiling of RIA without (64 cases) and with (141 cases) additional surgical measures for control of increased ICP (evacuation of intracranial hematoma, decompressive craniotomy, and/or cerebrospinal fluid drainage). Favorable outcome was noted significantly more often if appropriate treatment was completed within 13 h after aSAH than between 13 and 72 h (37 % vs. 17 %; adjusted $P = 0.0475$), which was confirmed by evaluation in the multivariate model along with other prognostic factors. Subgroup analysis revealed that completion of the appropriate treatment within 13 h was associated with more favorable outcome in those patients, who underwent management of RIA in combination with additional surgical measures for control of increased ICP ($P = 0.0023$), and in those, who felt into poor outcome predicting group ($P = 0.0046$).

Conclusions: Appropriate treatment of high-grade aSAH with management of RIA in combination with required additional surgical measures for control of increased ICP, may be associated with more favorable outcomes if completed within 13 h after the ictus.

1. Introduction

High-grade aneurysmal subarachnoid hemorrhage (aSAH) is associated with prominent morbidity and mortality rates, particularly caused by the severe primary brain damage and several acute complications, including rebleeding from the ruptured intracranial aneurysm (RIA). Moreover, active bleeding from RIA may be observed within 2 h after the ictus, and result in intracranial hypertension, which may necessitate initiation of treatment as soon as possible [1]. Nevertheless, the optimal timing of either microsurgical clipping or endovascular coiling in such cases still represents a matter of debates. Existing guidelines recommend definitive management of RIA within either 48 or 72 h after the aSAH onset (mainly for prevention of rebleeding) [2,3]. In their meta-analysis, Yao et al. [4] evaluated 14 reported studies on management of aSAH and found that early surgery for RIA (defined as those performed within 3 days after the ictus) significantly decreases the incidence of unfavorable outcomes. However, it remains unclear whether earlier intervention within this time frame positively impacts prognosis. Although some studies demonstrated that ultra-early (i.e., within 24 h after the ictus) clipping or coiling of RIA is associated with improved clinical outcomes [5–9], others did not confirm such results [10–14].

On the other hand, aSAH is frequently accompanied by such complications as formation of subdural (SDH), intracerebral (ICH), and/or intraventricular (IVH) hematomas, and acute hydrocephalus resulting in intracranial hypertension and brain herniation [8,12,15–26]. Management of increased intracranial pressure (ICP) in such cases is attained by

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https://doi.org/10.1016/j.clineuro.2023.107776
Received 27 January 2023; Received in revised form 26 April 2023; Accepted 7 May 2023

several synergistic therapeutic and surgical means, including emergency craniotomy directed not only at clipping of RIA, but also at evacuation of large-size intracranial hematomas with or without external decompression, and/or installation of the external ventricular drainage (EVD). Recently, we retrospectively assessed the optimal timing of EVD in 102 patients with aSAH treated with coiling of RIA and noted that conducting of both procedures within 13 h after the ictus was associated with the best outcomes [26]. It was presumed that such hyper-early treatment might allow for timely management of both RIA and intracranial hypertension caused by severe IVH and acute hydrocephalus, with subsequent use of more aggressive therapeutic protocols directed at the preservation of cerebral perfusion and oxygenation, and the prevention of vasospasm and delayed cerebral ischemia (DCI) [26]. The present study was directed at testing this hypothesis in cases of high-grade aSAH with an objective to reveal whether earlier timing of appropriate treatment, comprising management of RIA combined with the application of required additional surgical measures for control ICP, is associated with more favorable outcomes.

2. Materials and methods

Patients with high-grade aSAH corresponding to World Federation of Neurosurgical Society (WFNS) grades 4 or 5 admitted to Tokyo Women's Medical University Medical Center East (220 consecutive cases between January 2010 and December 2020) or Nagareyama Central Hospital (66 consecutive cases between January 2016 and December 2020) were deemed eligible for the present retrospective analysis. However, 33 cases were excluded later, because of either unknown timing of aSAH (which did not allow defining an interval between its onset and surgical procedures; N = 6) or unavailable information on outcome at 3-month follow-up (which was defined as primary endpoint; N = 27). Thus, the analyzed cohort comprised 253 patients. Some of these cases were included in our previous investigations on the related topics [26,27]. The study protocol was approved by the Ethics Committees of both participating clinical centers considering an opt-out consent method.

2.1. Treatment strategy

Upon admission to the hospital and diagnosis of the aSAH with computed tomography (CT) and CT angiography (CTA), medical treatment directed at pain relief and sedation, as well as administration of the antihypertensive and antifibrinolytic agents were initiated immediately. Blood pressure (BP) was monitored. A rigorous therapeutic protocol was applied to keep the systolic BP at < 140 mm Hg until the definitive management of RIA. A 1 mg or 2 mg bolus dose of nicardipine was given intravenously if systolic BP at admission was > 140 mm Hg or > 160 mm Hg, respectively; if systolic BP after admission sustained at > 140 mm Hg, prolonged infusion of nicardipine (up to 20 mg per hour) was done. Patients with high-grade aSAH and respiratory instability underwent immediate intubation and respiratory management under sedation.

Treatment strategy and timing of surgical intervention(s) were generally determined by the attending vascular neurosurgeon according to his/her clinical judgement based on the integrated consideration of multiple factors, including patient age, presence of comorbidities, clinical signs (e.g., the Glasgow Coma Scale [GCS] score, the WFNS aSAH grade, signs of brain herniation), and findings on CT and CTA.

Acute hydrocephalus was diagnosed if the bicaudate index exceeded the upper limit of its age-dependent normal values. If severe IVH (the original Graeb score 9–12 [15,22]) or acute hydrocephalus were presented, particularly in unconscious patients, EVD was usually urgently inserted. Drip chamber was set at the level of 15 cm above the head and this height was further adjusted to avoid excessive draining of the cerebrospinal fluid (CSF) [26]. In cases without hydrocephalus, preoperative EVD was not applied.

As generally recommended [2], surgical management of RIA was performed as soon as possible for avoidance of its rebleeding. The choice between microsurgical clipping and endovascular coiling was mainly determined by the location of RIA, its angioarchitecture, and presence of space-occupying intracranial hematoma. The volume of ICH was assessed as was suggested by Kothari et al. [28] according to the following formula: Volume = (Width x Length x Height) / 2. Large intracranial hematoma (SDH and/or ICH) was defined as those causing a midline shift ≥ 5 mm or with a volume of ≥ 17 mL [16,17,23], and in such cases emergency craniotomy directed at its evacuation and clipping of RIA was performed. During craniotomy, intraoperative installation of EVD and intraparenchymal sensor for prolonged ICP monitoring were done routinely, whereas external decompression in presence of brain edema and postoperative insertion of the lumbar CSF drainage remained on discretion of the treating neurosurgeon.

Elderly patients and those with bilaterally dilated unreactive pupils at admission were generally treated according to the same strategy, unless they demonstrated profound instability of vital functions (e.g., low BP not responding to vasopressors); in such cases conservative treatment was usually initiated until stabilization of the general condition, while occasionally, specific surgical measures for control of increased ICP, including evacuation of large intracranial hematoma, decompressive craniotomy, and/or EVD, were also applied.

According to objectives of the present study, the appropriate treatment of a patient with high-grade aSAH was defined as clipping or coiling of RIA combined, if necessary, with required additional surgical measures for control of increased ICP, namely (1) evacuation of large intracranial hematoma in case of its presence; and/or (2) decompressive craniotomy in presence of prominent brain edema and mass effect; and/or (3) CSF drainage (EVD in cases of severe IVH or acute hydrocephalus, and/or lumbar drainage during postoperative period).

2.2. Diagnosis of rebleeding, vasospasm, and DCI

Rebleeding from RIA was considered if sudden clinical deterioration of a patient was associated with the evidence of acute intracranial hemorrhage on CT not visible on the previous scan.

Vasospasm was assessed by CTA, magnetic resonance angiography (MRA), and/or digital subtraction angiography (DSA) at 7–12 days after the onset of aSAH and was considered in presence of segmental or diffuse narrowing of the arterial diameter by > 50 % in comparison with the baseline investigation. No specific medical measures for prophylaxis of the cerebral vasospasm were applied, whereas in cases of its development, treatment included triple-H therapy with or without targeted intraarterial administration of fasudil hydrochloride.

The diagnosis of DCI was based on both CT/MRI findings indicating related cerebral infarction not seen on imaging within 48 h after surgery for RIA (i.e., not resulting from the brain injury owed to aSAH itself, ICH, EVD procedure, or any other cause) with or without associated clinical deterioration (i.e., appearance of new focal neurological deficit or decrease of, at least, 2 points of the GCS score lasting 1 h and attributable to the cerebral hypoperfusion upon exclusion of all other potential causes) [27,29,30]. If deemed necessary, the diagnosis of DCI was supplemented by the CT perfusion imaging.

2.3. Outcome assessment

Outcome was assessed according to the modified Rankin Scale (mRS) at 1-month and 3-month follow-up after the aSAH onset and defined as favorable (scores 0–3) and unfavorable (scores 4–6). Mortality (mRS score 6) within 3 months after the ictus was also noted.

2.4. Data analysis

All evaluated clinical, radiological, surgical, and outcome data were extracted from the prospectively maintained electronic medical records. For evaluation of outcome, direct contact of patients and/or their families was done if deemed necessary.

The following 30 factors with potential impact on the outcome were taken into consideration: age and gender of the patient; current smoking, alcohol abuse, presence of chronic arterial hypertension; location of RIA (anterior circulation vs. posterior circulation); the WFNS aSAH grade (4 vs. 5); presence of bilaterally dilated unreactive pupils at admission; the Fisher grade of the amount of subarachnoid blood (group 3 vs. other groups); outcome predicting group (good vs. poor; according to Liu et al. [31]); presence of IVH and its grade (the original Graeb score 1–8 vs. 9–12 [15,22]); presence of acute hydrocephalus, SDH, or ICH; presence of large intracranial hematoma; treatment modality for RIA (microsurgical clipping vs. endovascular coiling vs. no treatment); ultra-early management of RIA (within 24 h after the ictus); management of RIA within 72 h after the ictus; any additional surgical measures for control of increased ICP, including evacuation of intracranial hematoma, decompressive craniotomy, and/or CSF drainage; completion of appropriate treatment (as defined above); timing to completion of appropriate treatment; presence of rebleeding from RIA, vasospasm, and DCI.

Timing to management of RIA was calculated as an interval in hours between the aSAH onset and positioning of the clip during microsurgical procedure or insertion of the last coil during endovascular intervention. Timing to completion of appropriate treatment was calculated as an interval in hours between the aSAH onset and attainment of the last surgical measure for control of increased ICP (evacuation of intracranial hematoma, decompressive craniotomy, or CSF drainage) or management of RIA, whichever was the final action.

2.5. Statistics

In univariate analysis, comparisons of numerical variables between groups were done using Student's t-test, and of nominal and ordinal variables by chi-square test (with continuity correction, if appropriate) or Fisher's exact test; Pearson correlation coefficient was calculated if deemed necessary. Factors, which showed statistically significant associations with the primary endpoint (i.e., outcome at 3-month follow-up after the aSAH onset) in the univariate analysis, were included in the multivariate model, which was accomplished using logistic regression with backward elimination and determination of odds ratios (OR) and their 95 % confidence intervals (CI). Youden index was used to calculate the most effective cut-off value of timing to completion of appropriate

Table 1
Clinical characteristics of the study cohort.

Clinical characteristics	Total cohort (N = 253; 100%)	Completion of appropriate treatment of aSAH		
		Yes (N = 205; 100%)	No (N = 48; 100%)	Adjusted P-value*
Patient age in years (mean ± SD)	63.6 ± 14.6	63.1 ± 14.6	65.9 ± 14.6	NS**
Women (N)	161 (64%)	129 (63%)	32 (67%)	NS***
Current smoking (N)	85 (34%)	68 (33%)	17 (35%)	NS***
Alcohol abuse (N)	74 (29%)	60 (29%)	14 (29%)	NS***
Chronic arterial hypertension (N)	121 (48%)	100 (49%)	21 (44%)	NS***
Location of RIA in the anterior circulation (N)	200 (79%)	163 (80%)	37 (77%)	NS***
WFNS aSAH grade 4 (N)	94 (37%)	78 (38%)	16 (33%)	NS***
Bilaterally dilated unreactive pupils at admission (N)	110 (43%)	84 (41%)	26 (54%)	NS***
Fisher group 3 (N)	214 (85%)	174 (85%)	40 (83%)	NS***
Poor outcome predicting group[1] (N)	230 (91%)	184 (90%)	46 (96%)	NS****
Intraventricular hemorrhage (N)	232 (92%)	188 (92%)	44 (92%)	NS****
Severe intraventricular hemorrhage[2] (N)	49 (19%)	37 (18%)	12 (25%)	NS***
Acute hydrocephalus (N)	108 (43%)	78 (38%)	30 (63%)	0.0504***
Subdural hematoma (N)	19 (8%)	17 (8%)	2 (4%)	NS****
Intracerebral hematoma (N)	101 (40%)	77 (38%)	24 (50%)	NS***
Large intracranial hematoma[3] (N)	87 (34%)	65 (32%)	22 (46%)	NS***
Microsurgical clipping of RIA (N)	102 (40%)	99 (48%)	3 (6%)	**< 0.0003*****
Endovascular coiling of RIA (N)	126 (50%)	106 (52%)	20 (42%)	NS***
No surgical management of RIA (N)	25 (10%)	NR	25 (52%)	NR
Management of RIA within 24 hours after the aSAH onset[4] (N)	180 (71%)	160 (78%)	20 (42%)	NS****
Management of RIA within 72 hours after the aSAH onset[4] (N)	220 (87%)	198 (97%)	22 (46%)	NS*****
Any additional surgical measures for control of increased ICP (N)	161 (64%)	141 (69%)	20 (42%)	**0.0104*****
Evacuation of intracranial hematoma (N)	74 (29%)	72 (35%)	2 (4%)	**0.0006*****
Decompressive craniotomy (N)	63 (25%)	60 (29%)	3 (6%)	**0.0225*****
CSF drainage (N)	171 (68%)	154 (75%)	17 (35%)	**< 0.0003*****
Appropriate treatment of aSAH (N)	205 (81%)	205 (100%)	NR	NR
Timing to completion of appropriate treatment in hours (mean ± SD)	27.3 ± 89.6	27.3 ± 89.6	NR	NR
Rebleeding from RIA (N)	24 (9%)	19 (9%)	5 (10%)	NS****
Vasospasm (N)	98 (39%)	83 (40%)	15 (31%)	NS***
Delayed cerebral ischemia (N)	51 (20%)	42 (20%)	9 (19%)	NS***
Favorable outcome[5] at 1-month follow-up after aSAH (N)	39 (15%)	35 (17%)	4 (8%)	NS***
Favorable outcome[5] at 3-month follow-up after aSAH (N)	63 (25%)	55 (27%)	8 (17%)	NS***
Mortality within 3 months after aSAH (N)	96 (38%)	65 (32%)	31 (65%)	**0.0006*****

aSAH, aneurysmal subarachnoid hemorrhage; CSF, cerebrospinal fluid; ICP, intracranial pressure; N, number of cases; NR, not relevant; NS, non-significant; RIA, ruptured intracranial aneurysm; SD, standard deviation; WFNS, World Federation of Neurosurgical Societies.
*All original P-values were adjusted according to Holm-Bonferroni correction method for the statistical significance of multiple comparisons. Adjusted P-values > 0.99 are designated as non-significant. **Bold**, statistically significant adjusted P-values.
**Calculated according to Student's t-test.
***Calculated according to chi-square test.
****Calculated according to chi-square test with continuity correction.
*****Calculated according to Fisher`s exact test.
[1] According to Liu et al. [31].
[2] Original Graeb score 9-12 [15, 22].
[3] Intracerebral hematoma with a volume ≥ 17 mL or any intracranial hematoma causing midline shift ≥ 5 mm.
[4] Cases without surgical management of RIA were excluded from this statistical comparison.
[5] Modified Rankin Scale scores 0-3.

treatment of aSAH as predictor of outcome at 3-month follow-up. For evaluation of sensitivity, specificity, positive (PPV) and negative (NPV) predictive values, favorable and unfavorable outcomes in cases below or even to defined cut-off values for timing, were considered as "true positive" and "false positive," respectively, and in cases above defined cut-off values for timing, as "false negative" and "true negative," respectively. Accuracy was defined as an overall number of correct "true positive" and "true negative" cases. The level of statistical significance was set at $P < 0.05$. For each set of univariate analyses, the original P-values were adjusted according to Holm-Bonferroni correction method for the statistical significance of multiple comparisons. All considered P values were two-tailed.

3. Results

Detailed clinical characteristics of the study cohort are presented in Table 1. The age of patients varied from 31 to 90 years (mean, 63.6 $\pm$ 14.6 years; median, 65 years). aSAH corresponded to WFNS grades 4 and 5 in 94 (37 %) and 159 (63 %) cases, respectively. Surgical management of RIA was performed in 228 patients (90 %) between 3 and 1104 h after the aSAH onset (mean, 26.8 $\pm$ 85.3 h; median, 12.5 h); in 180 cases (71 %) it was attained within 24 h and in 220 cases (87 %) within 72 h. Microsurgical clipping of RIA was done in 102 cases (40 %) and endovascular coiling in 126 cases (50 %). In 25 patients (10 %) surgical management of RIA was not performed. Additional surgical measures for control of increased ICP were applied either separately or in various combinations in 161 patients (64 %).

Favorable outcome at 3-month follow-up after aSAH onset was noted in 63 (25 %) cases; its associated factors are presented in Supplementary Table 1. Of note, favorable outcome at 3-month follow-up was never observed in patients without surgical management of RIA (adjusted $P = 0.0624$) and with rebleeding from RIA (adjusted $P = 0.0720$), while due to small number of such cases the differences did not reach the level of statistical significance. Patients who underwent surgical management of RIA within 24 h after the aSAH onset did not demonstrate significantly better rate of favorable outcome at 3-month follow-up (53 of 180 cases; 29 %) in comparison to those, who underwent such treatment within 24–72 h after aSAH (9 of 40 cases; 23 %; $P = 0.3772$).

Favorable outcome at 1-month follow-up after the aSAH onset was noted in 39 (15 %) patients and was significantly associated (adjusted $P < 0.0003$) with the outcome at 3-month follow-up; in 38 of 39 patients who demonstrated favorable outcome at 1-month follow-up, it was also noted at 3-month follow-up. Within 3 months after the ictus, 96 patients (38 %) died.

3.1. Appropriate treatment

Overall, appropriate treatment of aSAH was completed in 205 patients (81 %; Fig. 1). It comprised either only management of RIA (64 cases) or its combination with additional surgical measures for control of increased ICP (141 cases). Completion of appropriate treatment of aSAH was associated with microsurgical clipping of RIA (adjusted $P < 0.0003$) and application of additional surgical measures for control of increased ICP (adjusted $P = 0.0104$), including evacuation of intracranial hematoma (adjusted $P = 0.0006$), decompressive craniotomy (adjusted $P = 0.0225$), and CSF drainage (adjusted $P < 0.0003$), but with no other evaluated patient- or aSAH-related factor (Table 1).

In comparison to their counterparts, patients who underwent appropriate treatment of aSAH did not demonstrate significantly higher rates of favorable outcome at 3-month (55 of 205 cases; 27 % vs. 8 of 48 cases; 17 %; adjusted $P > 0.99$) and 1-month (35 of 205 cases; 17 % vs. 4 of 48 cases; 8 %; adjusted $P > 0.99$) follow-up, but had significantly lower mortality within 3 months after the ictus (65 of 205 cases; 32 % vs. 31 of 48 cases; 65 %; adjusted $P = 0.0006$).

3.2. Timing of appropriate treatment

Appropriate treatment was completed between 4 and 1104 h after the aSAH onset (mean, 27.3 $\pm$ 89.6 h; median, 14 h); in 160 cases it was done within 24 h and in 198 cases within 72 h. For detailed analysis of timing to completion of appropriate treatment and its effects on the outcome, 7 patients in whom it was done at > 72 h after the ictus were truncated. Comparison of these truncated cases with others (Supplementary Table 2) revealed statistically significant difference only in timing to completion of appropriate treatment (341.4 $\pm$ 384.9 h vs. 16.2 $\pm$ 12.9 h; adjusted $P < 0.0003$).

After exclusion of truncated cases, the median timing to completion of appropriate treatment in 198 patients who underwent it within 72 h after aSAH onset was 13 h. As shown in Supplementary Table 3, in comparison to the opposite subgroup, timing to completion of appropriate treatment was significantly shorter in cases without acute hydrocephalus (13.7 $\pm$ 10.9 h vs. 20.6 $\pm$ 14.9 h; adjusted $P = 0.0054$) and if management of RIA was performed within 24 h after the ictus (11.1 $\pm$ 5.2 h vs. 37.5 $\pm$ 13.6 h; adjusted $P < 0.0003$).

In comparison to the opposite subgroup, timing to completion of appropriate treatment was not significantly different in patients who demonstrated favorable outcomes at 3-month (13.8 $\pm$ 11.6 h vs. 17.1 $\pm$ 13.2 h; adjusted $P > 0.99$) and 1-month (11.3 $\pm$ 6.9 h vs. 17.2 $\pm$ 13.6 h; adjusted $P = 0.3528$) follow-up, and were alive by 3 months after the

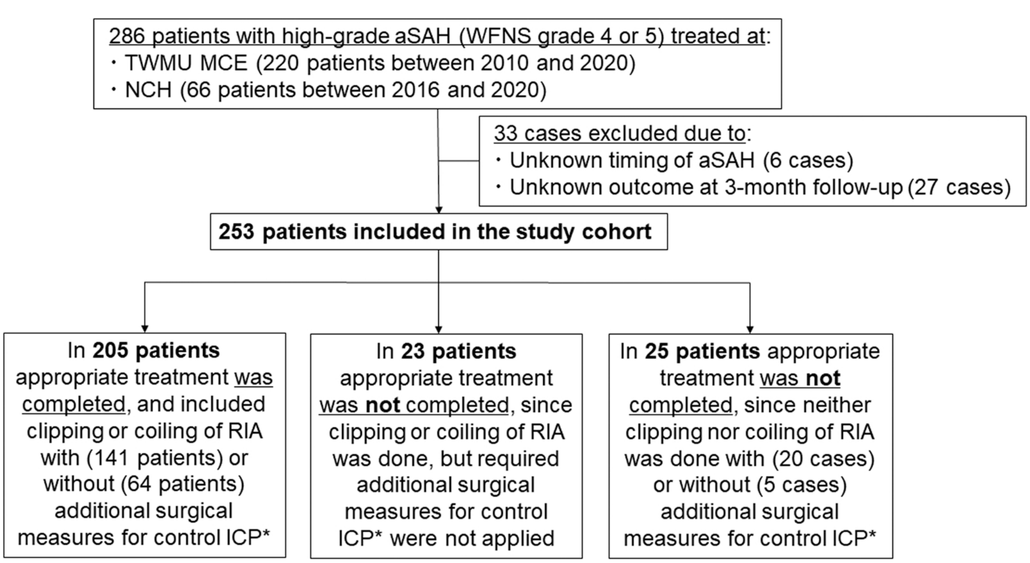

Fig. 1. Flowchart of cases selection for the present retrospective study. aSAH, aneurysmal subarachnoid hemorrhage; WFNS, World Federation of Neurosurgical Societies; TWMU MCE, Tokyo Women's Medical University Medical Center East; NCH, Nagareyama Central Hospital; RIA, ruptured intracranial aneurysm; ICP, intracranial pressure. *Surgical measures for control of increased ICP included evacuation of large subdural or intracerebral hematoma causing mass effect, decompressive craniotomy in presence of prominent brain edema, insertion of the external ventricular drainage in cases of severe intraventricular hemorrhage or acute hydrocephalus, and/or lumbar drainage during postoperative period.

Table 2
Outcome at 3-month follow-up after high-grade aneurysmal subarachnoid hemorrhage in different subgroups of 198 patients stratified according timing to completion of appropriate treatment within 72 h after the ictus.

Timing to completion of appropriate treatment after aSAH onset			Number of cases		
Quartile	Percentile interval	Hours interval	Total	Favorable outcome[1] at 3-month follow-up	Unfavorable outcome[2] at 3-month follow-up
Fourth	76th – 100th	21–72	46 (100 %)	9 (20 %)	37 (80 %)
Third	51st – 75th	13.5–20	52 (100 %)	8 (15 %)	44 (85 %)
Second	26th – 50th	7.5–13	47 (100 %)	22 (47 %)	25 (53 %)
First	1st – 25th	4–7	53 (100 %)	15 (28 %)	38 (72 %)

aSAH, aneurysmal subarachnoid hemorrhage.
The difference in outcome at 3-month follow-up was statistically significant between the second and third quartile (chi-square = 11.54; P = 0.0007), but not between the first and second quartile (chi-square = 3.66; P = 0.0557) of the timing to appropriate treatment. Among 7 truncated patients, in whom appropriate treatment was completed at > 72 h after the ictus, favorable and unfavorable outcomes were noted in 1 (14 %) and 6 (86 %) cases, respectively
[1] Modified Rankin Scale scores 0–3.
[2] Modified Rankin Scale scores 4–6.

ictus (16.0 ± 13.2 h vs. 16.3 ± 12.8 h; adjusted P > 0.99).

According to the maximal Youden index corresponding to greatest sum of sensitivity and specificity for prediction of the favorable outcome at 3-month follow-up, the most effective cut-off value for timing to completion of appropriate treatment was determined at 13 h (Supplementary Table 4). Favorable outcome at 3-month follow-up was noted in 37 of 100 patients (37 %) for whom appropriate treatment was completed within 13 h after aSAH, and in 17 of 98 patients (17 %) if it was done between 13 and 72 h (adjusted P = 0.0475). Cut-off value for timing to completion of appropriate treatment at ≤ 13 h after the ictus predicted favorable outcome at 3-month follow-up with 0.69 sensitivity, 0.56 specificity, 0.37 PPV, 0.83 NPV, and 0.60 accuracy. Additionally, there was statistically significant difference in outcome at 3-month follow-up between the second and third quartile (P = 0.0007), but not between the first and second quartile (P = 0.0557) of the timing to completion of appropriate treatment (Table 2).

Evaluation in the multivariate model along with other factors with potential impact on the outcome as derived from results of the univariate analysis (Supplementary Table 5), namely younger patient age, the WFNS aSAH grade 4, and good outcome predicting group, revealed independent statistically significant association of the completion of appropriate treatment within 13 h after the aSAH onset with the favorable outcome at 3-month follow-up (OR, 2.74; 95 % CI, 1.30 – 5.74; P = 0.0064; Table 3).

Among 7 truncated patients, in whom appropriate treatment was completed at >72 h after the aSAH onset, favorable and unfavorable outcomes at 3-month follow-up were noted in 1 (14 %) and 6 (86 %) cases, respectively.

3.3. Subgroup analysis

To attenuate impact of the retrospective nature of the study with heterogeneous clinical characteristics and subjective clinical decision-making on the obtained results, the effects of completion of appropriate treatment within 13 h after the aSAH onset on the clinical outcome were evaluated in different subgroups of 198 patients for whom such treatment was attained within 72 h after the ictus.

First, evaluations were done separately in those patients, who received appropriate treatment without (64 cases) and with (134 cases) additional surgical measures for control of increased ICP. In the former subgroup, i.e., in patients for whom additional surgical measures for control of increased ICP were deemed unnecessary and treatment was limited to management of RIA, favorable outcome at 3-month follow-up was noted in 15 of 37 cases (41 %) if appropriate treatment was completed within 13 h after the ictus, and in 8 of 27 cases (30 %) if it was done between 13 and 72 h (P = 0.3690). In contrast, in patients who underwent repairment of RIA in combination with additional surgical measures for control of increased ICP, favorable outcome at 3-month follow-up was noted in 22 of 63 cases (35 %) if appropriate treatment was completed within 13 h after the ictus, and in 9 of 71 cases (13 %) if it was done between 13 and 72 h (P = 0.0023).

Second, evaluations were done separately in patients within good (20 cases) and poor (178 cases) outcome predicting groups (as defined by Liu et al. [31]). In the good outcome predicting group, favorable outcome at 3-month follow-up was noted in 9 of 13 patients (69 %) if appropriate treatment was completed within 13 h after aSAH, and in 4 of 7 patients (57 %) if it was done between 13 and 72 h (P = 0.9608). In contrast, in the poor outcome predicting group, favorable outcome at 3-month follow-up was noted in 28 of 87 patients (32 %) if appropriate treatment was completed within 13 h after aSAH, and in 13 of 91 patients (14 %) if it was done between 13 and 72 h (P = 0.0046).

3.4. Rebleeding

In the entire study cohort, rebleeding from RIA was noted in 24 patients (9 %), and in all of them it happened before or during surgery for management of RIA. This complication was noted in 13 of 180 (7 %), 4 of 40 (10 %), 3 of 8 (38 %), and 4 of 25 (16 %) cases if management of RIA was performed, respectively, within 24 h after the aSAH onset, between 24 and 72 h, at > 72 h, and never. Patients who underwent surgical management of RIA within 24 h after the aSAH onset did not demonstrate significantly lower rate of rebleeding in comparison to

Table 3
Independent factors significantly associated with the favorable outcome at 3-month follow-up after high-grade aneurysmal subarachnoid hemorrhage in 198 patients for whom appropriate treatment was completed within 72 h after the ictus.

Evaluated factors	Odds ratio	95% confidence interval	P-value
- WFNS grade 4	5.00	2.35 – 10.66	< 0.0001
- Younger patient age[1]	1.04	1.01 – 1.07	0.0011
- Completion of appropriate treatment within 13 hours after aSAH onset	2.74	1.30 – 5.74	0.0064
- Good outcome predicting group[2]	3.79	1.32 – 10.84	0.0112

aSAH, aneurysmal subarachnoid hemorrhage; WFNS, World Federation of Neurosurgical Societies.
[1] Per year within the age interval from 31 to 90 years.
[2] According to Liu et al. [31].

those, for whom it was done within 24–72 h after the aSAH (7 % vs. 10 %; P = 0.7889). However, the rate of rebleeding in patients who underwent surgical management of RIA within 72 h after aSAH onset was significantly lower in comparison of those who underwent it later or never (P = 0.0318).

Rebleeding from RIA was noted relatively less often if appropriate treatment was completed within 13 h after aSAH (5 of 100 cases; 5 %) than if it was done between 13 and 72 h (11 of 98 cases; 11 %), but the difference did not reach the level of statistical significance (P = 0.1081).

4. Discussion

Whether management of RIA by means of either microsurgical clipping or endovascular coiling within 24 h after the ictus, particularly in patients with high-grade aSAH, is associated with more favorable outcome still remains doubtful. Although several studies demonstrated benefits of such ultra-early treatment [5–9], others did not confirm these findings [10–14]. Specifically, Rawal et al. [11] evaluated 16 studies on endovascular treatment of patients with aSAH of all grades, and found that its attainment within 24 h after the ictus was associated with the similar odds of poor outcome and case fatality, when compared with treatment between 24 and 72 h. In concordance, in their meta-analysis of 14 articles reporting on 1111 patients with high-grade aSAH, Han et al. [12] failed to reveal improved outcomes or reduced mortality after management of RIA within 24 h. In our relatively small series presented herein, surgical management of RIA within 24 h and within 24–72 h after the aSAH onset did not demonstrate significant difference in outcome at 3-month follow-up.

It should be noted however, that patients who underwent early treatment are frequently admitted in more severe clinical condition, with high-grade aSAH, higher Fisher grade of the amount of subarachnoid blood, large ICH, midline shift, and brain herniation [3,5,12]. All these factors have significant negative impact on the outcome. Thus, consideration of only management of RIA as a criterion of aSAH treatment (as has been done in nearly all previous studies) seems suboptimal, since rather often additional surgical measures for control of increased ICP are required. Their application, especially in high-grade aSAH, may positively impact the patient prognosis [20,23,26], but remains not standardized and a bit controversial; for example, Brandecker et al. [32] did not find significant advantages of decompressive craniotomy in such cases. Therefore, herein we have attempted to introduce new concept of so-called “appropriate treatment,” which was defined as not only management of RIA, but its combination with required additional surgical measures for control ICP (i.e., evacuation of large intracranial hematoma, decompressive craniotomy in presence of brain edema, and/or CSF drainage), and to evaluate its possible benefits.

In our patients with high-grade aSAH, completion of appropriate treatment was not associated with better outcomes, but was accompanied by statistically significant decrease of mortality within 3 months after aSAH. Nevertheless, if appropriate treatment was completed within 13 h after the ictus, it resulted in significant positive impact on the rate of favorable outcomes at 3-month follow-up, which was confirmed in multivariate model with inclusion of several other prognostic factors. From one side, these results corroborate a similar finding in our previous study directed at evaluation of the optimal timing of EVD in 102 patients with aSAH, including 52 cases of high-grade aSAH, treated with coiling of RIA [26]. In that investigation, overall, 49 patients underwent insertion of EVD, and favorable and fair outcomes (mRS scores 0–3 at discharge) were noted more frequently after early (≤ 13 h; N = 30) than late (>13 h; N = 19) EVD (40 % vs. 11 %; P = 0.026). Moreover, the best outcomes were noted in the small subgroup (N = 8) of those patients, who underwent both EVD and coiling of RIA within 13 h after the ictus [26]. On the other hand, our present findings are in concert with those recently reported by Buscot et al. [11], who assessed 575 retrospectively identified cases of aSAH and found more favorable patient outcomes reflecting in more frequent discharge home (a surrogate marker of greater functional independence) and better survival at 12-month follow-up throughout all WFNS grades if treatment was performed within 12.5 h after the ictus. Overall, these studies suggest that if surgical management of RIA provided within 12–13 h after aSAH, it may maximize beneficial effects of early treatment. Whether it is really so, should be confirmed in further well-designed investigations, since existing data are limited, inconsistent, and, sometimes, controversial. For example, Kaneko et al. [33] performed even earlier (within 6 h) management of RIA in patients with high-grade aSAH, and observed good functional outcomes in approximately 40 % of them. In contrast, Consoli et al. [34] did not identify any association between coiling of RIA within 12 h after aSAH and good clinical outcomes, and did not recommend such hyper-early treatment.

Owed to the retrospective design of our study, the evaluated cohort demonstrated prominent heterogeneity in evaluated characteristics and was affected by subjective clinical decision-making with variable surgical strategies determined on the case-by-case fashion by the attending vascular neurosurgeon. With an attempt to eliminate effects of such heterogeneity on obtained results, subgroup analysis was performed. It revealed statistically significant impact of the completion of appropriate treatment within 13 h after the ictus only in patients for whom additional surgical measures for control of increased ICP were applied (i.e., were deemed necessary at the time of treatment), and in those who felt into poor outcome predicting group determined according to the decision tree model based on the modified Fisher grade, GCS score, pupillary reactivity, and patient age, as was suggested previously by Liu et al. [31]. These results indicate that more severely affected patients with high-grade aSAH may benefit the most from the earlier completion of appropriate treatment comprising not only management of RIA, but application of required surgical measures for control of increased ICP. At the same time, the advantages of hyper-early treatment in patients for whom only management of RIA is required and in whom good outcome is anticipated based on presence of favorable prognostic factors, may be of limited value. It somewhat corroborates the previous study of Wong et al. [6], who revealed that ultra-early treatment of RIA within 24 h after the ictus has positive effects on outcomes in cases of high-grade, but not of low-grade aSAH. It can be speculated, that improved outcomes after appropriate treatment of aSAH within 13 h observed in more severely affected patients in our series were related to timely control of increased ICP with corresponding improvement of the brain perfusion due to evacuation of large intracranial hematoma, decompressive craniotomy, and/or CSF drainage, and prevention of profound and irreversible secondary brain injury [27,35,36].

Reduction of the rebleeding risk is considered as one of the most beneficial effects of ultra-early management of RIA [6,12,37], which may be even greater if intervention is performed within 12 h after the ictus, since in 83 % of cases rebleeding develops within this time interval [38]. Of note, early management of acute hydrocephalus, ICH, and IVH, may also contribute for prevention of rebleeding, since all these factors have been associated with a higher probability of this complication [26,39,40]. Nevertheless, several studies did not demonstrate statistically significant positive impact of the RIA management within 24 h after the aSAH onset on rebleeding rates [6,12,14]. In the study of Buscot et al. [9], time to treatment for RIA also was not associated with greater risk of any aSAH-related complications, including rebleeding. Similarly, in the series of Consoli et al. [34] the incidence of rebleeding from RIA before treatment was similar in patients who underwent endovascular coiling at < 12 h and between 12 and 48 h. Although in our study presented herein, the rate of rebleeding was slightly lower in patients who underwent surgical management of RIA within 24 h in comparison to those who underwent it between 24 and 72 h after the aSAH onset (7 % vs. 10 %), and in patients for whom appropriate treatment was completed within 13 h after aSAH in comparison to those for whom it was done between 13 and 72 h (5 % vs. 11 %), neither difference reached the level of statistical significance.

4.1. Study limitations

The main limitations of the present study are related to its retrospective design and relatively small number of evaluated patients. Overall, 33 cases were excluded from the analyzed study cohort, which might cause some bias. Although the strategy of surgical management was generally rather uniform and corresponded to the current international and Japanese clinical guidelines, its detail were determined on the case-by-case fashion by the attending vascular neurosurgeon, which resulted in heterogeneity of the applied techniques in different subgroups of patients. To attenuate negative impact of the heterogeneous clinical characteristics and subjective clinical decision-making on the obtained results, subgroup analysis was performed, while it results were, in turn, influenced by the limited number of cases in each subgroup. Moreover, we did not consider the order of surgical procedures in individual patients, who underwent appropriate treatment (e.g., cases with placement of EVD before or after management of RIA were not differentiated). While all evaluated clinical characteristics were extracted from the prospectively maintained electronic medical records, which did not allow for missing parameters, the information on each individual case was primarily input by different doctors and might be somewhat flawed. Results of statistical analyses might be affected by confounding variables and multiple comparisons, while we have tried to decrease such negative impacts by adjustment of P-values using Holm-Bonferroni correction method, application of two-stage statistical analysis, and use of multivariate modeling by means of logistic regression. Only early functional outcomes after the aSAH onset were assessed. For the evaluation of outcome, direct contact of patients and/or their families was occasionally done, while not all patients were evaluated in our center during follow-up. Finally, some cases of the presented series were included in our previous investigations on related topics, but seemingly it did not affect the results of the present study.

5. Conclusion

According to results of the present retrospective study, appropriate treatment of high-grade aSAH comprising management of RIA combined with required additional surgical measures for control of increased ICP (i.e., evacuation of large intracranial hematoma, decompressive craniotomy in presence of brain edema, and CSF drainage) may be associated with more favorable outcomes if completed within 13 h after the ictus. Moreover, such hyper-early treatment strategy may be particularly beneficial for more severely affected patients with poor prognosis for whom surgical measures for control of increased ICP are deemed necessary. Nevertheless, while suggested time window for intervention in such cases may indeed maximize effects of early treatment, it should be emphasized that the level of evidence of the present study is rather limited owed to its retrospective design, relatively small size of the study cohort, and its significant heterogeneity with regard to both clinical characteristics and surgical decision-making. Therefore, the results presented herein definitely require additional testing and confirmation, which should be preferably performed in well-designed multi-institutional studies. If its beneficial effects on the outcome are validated, the concept of hyper-early appropriate treatment may significantly change the paradigm of the high-grade aSAH management.

Informed consent

Retrospective study based on routine clinical practice without any identifiable personal information does not require consent for publication from individual patients.

Code availability

Not applicable.

Funding

None.

Ethical statement

Research protocol was approved by the Ethics Committee of Tokyo Women's Medical University (No. 5717).

CRediT authorship contribution statement

Hidenori Ohbuchi: Methodology, Conceptualization, Data collection, Data analysis, Investigation, Formal analysis, Statistical analysis, Writing – Original Draft, Writing – Review & Editing, Project administration. Hidetoshi Kasuya: Methodology, Conceptualization, Formal analysis, Writing – Review & Editing, Project administration, Study supervision. Shinji Hagiwara: Formal analysis, Project administration. Ryuzaburo Kanazawa: Formal analysis, Project administration. Suguru Yokosako: Formal analysis, Project administration. Naoyuki Arai: Formal analysis, Project administration. Yuichi Takahashi: Formal analysis, Project administration. Mikhail Chernov: Conceptualization, Formal analysis, Statistical analysis, Writing – Review & Editing. Yuichi Kubota: Study supervision.

Conflict of Interest

None.

Data Availability

May be considered upon appropriate request.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.clineuro.2023.107776.

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