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ORIGINAL WORK

Clinical Outcome of Patients with Poor-Grade Aneurysmal Subarachnoid Hemorrhage with Bundled Treatments: A Propensity Score-Matched Analysis

Young Hoon Choi[1], Eun Jin Ha[2,3*], Youngbo Shim[2], Jungook Kim[2], Yoon-Hee Choo[4], Hye Seon Kim[5], Sung Ho Lee[3,6], Kang Min Kim[3,6], Won-Sang Cho[3,6], Hyun-Seung Kang[3,6] and Jeoug Eun Kim[3,6]

Abstract

Background: Poor-grade aneurysmal subarachnoid hemorrhage (aSAH), defined as Hunt and Hess (HH) grades IV and V, is a challenging disease because of its high mortality and poor functional outcomes. The effectiveness of bundled treatments has been demonstrated in critical diseases. Therefore, poor-grade aSAH bundled treatments have been established. This study aims to evaluate whether bundled treatments can improve long-term outcomes and mortality in patients with poor-grade aSAH.

Methods: This is a comparative study using historical control from 2008 to 2022. Bundled treatments were introduced in 2017. We compared the rate of favorable outcomes (modified Rankin Scale score 0–2) at 6 months and mortality before and after the introduction of the bundled treatments. To eliminate confounding bias, the propensity score matching method was used.

Results: A total of 90 consecutive patients were evaluated. Forty-three patients received bundled treatments, and 47 patients received conventional care. The proportion of patients with HH grade V was higher in the bundle treatment group (41.9% vs. 27.7%). Conversely, the proportion of patients with fixed pupils on the initial examination was higher in the conventional group (30.2% vs. 38.3%). After 1:1 propensity score matching, 31 pairs were allocated to each group. The proportion of patients with 6-month favorable functional outcomes was significantly higher in the bundled treatments group (46.4% vs. 20.7%, $p = 0.04$). The 6-month mortality rate was 14.3% in the bundled treatments group and 27.3% in the conventional group ($p = 0.01$). Bundled treatments (odd ratio 14.6 [95% confidence interval 2.1–100.0], $p < 0.01$) and the presence of an initial pupil reflex (odd ratio 12.0 [95% confidence interval 1.4–104.6], $p = 0.02$) were significantly associated with a 6-month favorable functional outcome.

Conclusions: The bundled treatments improve 6-month functional outcome and mortality in patients with poor-grade aSAH.

*Correspondence: 65932@snuh.org
[2] Department of Critical Care Medicine, Seoul National University Hospital, Seoul National University College of Medicine, 101, Daehak-ro Jongno-gu, Seoul 03080, Republic of Korea
Full list of author information is available at the end of the article

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Introduction

Poor-grade aneurysmal subarachnoid hemorrhage (aSAH), defined as Hunt and Hess (HH) grades IV and V, accounts for about 18–30% of all aSAH cases [1–3]. Previous studies have demonstrated that more than 60% of these patients die or are left with disabilities [3, 4]. Unfavorable clinical outcomes of poor-grade aSAH are caused by early brain injury due to increased intracranial pressure (IICP) and frequent delayed cerebral ischemia (DCI) in the late phase [5].

Treatment modality and aggressive neurocritical care have improved for several decades since the 1980s. The mortality rate has decreased from about 70–58% [6], and good functional recovery has increased up to about 30% of patients [6–9], yet the result is still unsatisfactory.

In the Neurocritical Care Society guidelines [5], three essential treatments are emphasized in poor-grade aSAH care as follows:

1. Initial treatment, including medical stabilization, prevention of early rebleeding, and aggressive IICP control
2. Multimodal neuromonitoring for early detection and active treatment of DCI
3. Identification and treatment of medical complications

However, specific manuals on how to apply these treatments are lacking, and clinical applications in practice are heterogeneous.

Bundle, a concept developed for clinicians to deliver more reliable and effective bedside care, is a method of treatment established by the US Institute for Healthcare Improvement. There have been concerns about inconsistent practice of the five evidence-based components of a bundle at the bedside. It is particularly suitable in the intensive care unit (ICU), where multidisciplinary teams are involved in caring for patients with severe and variable disease courses in which the mortality rate increases when treatment application is heterogeneous.

Considering the characteristics of poor-grade aSAH, we established bundled treatments that integrate the five components. This study aims to identify if applying bundled treatments improves the 6-month functional outcome and mortality of poor-grade aSAH.

Methods

Patients and Data Collection

We retrospectively reviewed the electronic medical records of all patients with aSAH who received surgical clipping or endovascular treatment for aneurysm repair between January 2008 and June 2022. There were 382 patients with aSAH during this period, and patients described as having poor-grade aSAH, defined as HH grade IV or V, were selected. Ninety-seven patients were diagnosed with poor-grade aSAH. Among these patients, 43 were treated with bundled treatments. We collected data on the patients' baseline characteristics and findings of imaging such as computed tomography (CT) of the brain, distal subtraction angiography, and magnetic resonance images of the brain. Information on the initial treatment modality and procedural-related complications for aneurysm repair was recorded. Additional treatment was conducted at the ICU. To evaluate functional outcomes, the modified Rankin Scale (mRS) score at discharge and after 6 months was also collected. Patient consent was waived by the institutional review board (No. 2302–045-1402) of our institute.

The Conventional Treatment

Based on the Korean clinical practice guidelines for aSAH [10], the treatment approach can be summarized as follows:

1. *Aneurysm treatment*: The primary focus is to reduce the risk of rebleeding and associated mortality. Aneurysms are treated as quickly as possible, with the majority of cases treated within 24 h.
2. *External ventricular drainage (EVD)*: EVD is performed based on the presence of hydrocephalus (HCP) confirmed by CT scans or the likelihood of HCP progression due to intraventricular hemorrhage.
3. *Transcranial Doppler (TCD) monitoring and nimodipine administration*: regular TCD checks are conducted, and nimodipine is administered to prevent vasospasm and subsequent DCI.
4. *Management of vasospasm*: In cases in which vasospasm is suspected, various diagnostic criteria are used, including increased mean flow velocity (> 120 cm/second) in the middle cerebral artery on TCD, significant spasm (> 50%) confirmed through angiography, or confirmed delay in time to peak. Treatment

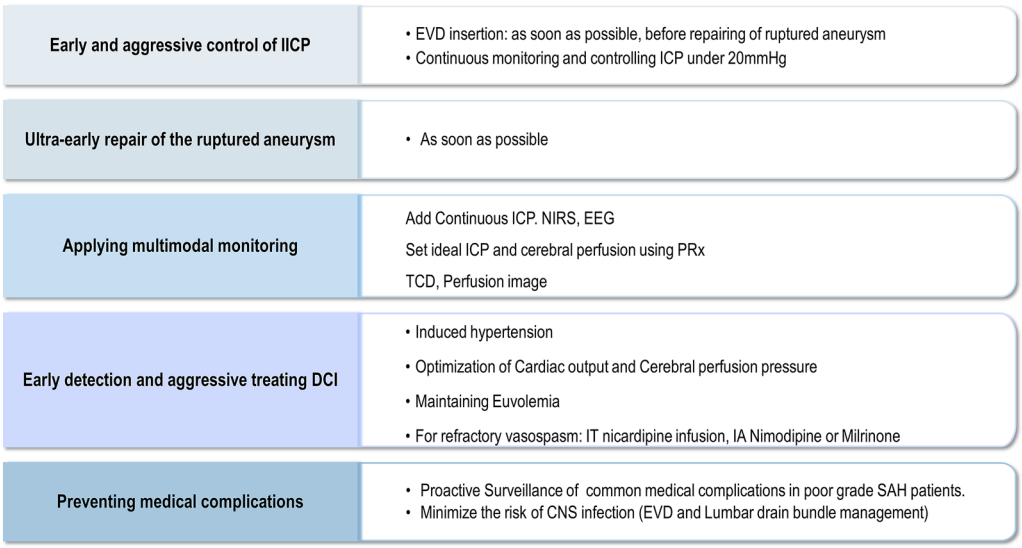

Fig. 1 Five components of bundled treatments. The five crucial components of managing patients with poor-grade aSAH are (1) early and aggressive control of IICP, (2) performing ultra-early repair of the ruptured aneurysm, (3) applying multimodal monitoring, (4) early detecting and aggressively treating DCI, and (5) preventing medical complications. *aSAH* aneurysmal subarachnoid hemorrhage, *CNS* central nervous system, *DCI* delayed cerebral ischemia, *EEG* electroencephalography, *EVD* external ventricular drainage, *IA* intra-arterial, *ICP* intracranial pressure, *IICP* increased intracranial pressure, *IT* intrathecal, *NIRS* near-infrared spectroscopy, *PRx* pressure reactivity index, *SAH* subarachnoid hemorrhage, *SICMP* stress-induced cardiomyopathy, *TCD* transcranial Doppler

options may include induced hypertension and intra-arterial administration of nimodipine.

5. *Intracranial pressure (ICP) control*: traditional step-ladder-type protocols are employed for managing intracranial hypertension (IICP).

Bundled Treatments

Early and Aggressive Control of IICP

EVD insertion is performed before the repair of a ruptured aneurysm. ICP is continuously monitored and adequately controlled within the target according to our algorithm (Fig. 1, Supplementary Fig. 1).

Ultra-Early Repair of the Ruptured Aneurysms

The ultra-early repair of an aneurysm is known to reduce early rebleeding risk and improve functional outcomes in patients with aSAH [11, 12]. We repair the ruptured aneurysm as soon as possible after EVD insertion. Continuous monitoring of ICP and interventions to maintain ICP below the target level were implemented during transfemoral cerebral angiography and aneurysm repair procedures.

Applying Multimodal Monitoring

In addition to traditional monitoring, such as TCD, we apply continuous ICP monitoring, Pressure reactivity index (PRx), near-infrared spectroscopy (NIRS), and electroencephalography (EEG) (Fig. 1).

The PRx is used to determine optimal cerebral perfusion pressure and maintain adequate cerebral blood flow (CBF). It is a secondary parameter derived from ICP and mean arterial blood pressure. The PRx is a marker of cerebral autoregulation, and cerebral perfusion pressure is optimized when the PRx is set to a range below 0.3. It is also known that the PRx increases as vasospasm progresses [13, 14]. We use it to predict vasospasm in patients with poor-grade aSAH who are sedated or unconscious.

NIRS is the surrogate monitor of cerebral oxygenation and blood flow. Vasospasm is suspected when the value decreases by more than 12% from baseline or the absolute value decreases to less than 50.

EEG is also monitored for changes in the alpha to delta ratio as a sensitive cerebral blood flow surrogate marker.

Early Detecting and Aggressively Treating DCI

Using multimodal monitoring, we attempt to augment the detection rate of DCI. We improve the outcome of DCI with various drugs and injection methods tailored to the patient. In patients with stress-induced cardiomyopathy with hypotension, milrinone is given via intravenous route instead of nimodipine to reduce vasospasm and maintain cardiac output. Intra-arterial nimodipine therapy is considered for refractory vasospasm, or intrathecal nicardipine infusion is applied to patients in whom

intra-arterial nimodipine therapy is impossible for various reasons (Fig. 1).

Preventing Medical Complications

Proactive surveillance for systemic complications is applied. In particular, the risk of central nervous system infection is minimized by applying an EVD and lumbar drainage bundle management. Medical problems that commonly occur in patients with poor-grade aSAH, such as cardiac dysfunction, renal dysfunction, and electrolyte imbalance, are thoroughly investigated (Fig. 1).

Primary Outcome and Secondary Outcome

The primary endpoint of this study was to ascertain the proportion of patients achieving favorable functional outcomes at six months post-treatment. Functional outcomes were quantitatively evaluated using the modified Rankin Scale (mRS). Favorable functional outcomes were characterized by an mRS score of 2 or less. Secondary endpoints encompassed the mortality rate at the six-month mark, as well as factors contributing to favorable functional outcomes.

Statistical Analysis

The normal distribution data analyzed by Student's *t*-test were expressed as mean and standard deviation (SD). χ^2 tests and Fisher's exact tests were used for comparing categorized variables. To correct for confounding bias in the long-term functional outcome of poor-grade aSAH, we used the propensity score matching (PSM) method. One-to-one PSM was performed using the R software MatchIt package (version 4.4.0). The caliper width was set to 0.1 SD. As a result, 31 matched pairs were assigned to each group. The variables used in performing PSM were age, HH grade, initial absence of a pupil reflex, acute HCP, intraparenchymal hemorrhage, and DCI.

To evaluate factors associated with a 6-month favorable functional outcome, univariate and multivariate binary logistic regression tests were performed. Following univariate analysis, we identified significant factors associated with favorable functional outcomes with a significance level of $p < 0.05$. And the factors with $p < 0.1$ from the univariate analysis subsequently included in a multivariate analysis. For statistical analysis, we utilized IBM SPSS version 27.0 and the MatchIt package from the R software.

Results

Baseline Characteristics and Treatments

A total of 90 patients were enrolled and divided into two groups: 47 patients in the conventional treatment group and 43 patients in the bundled treatment group (Table 1). The mean age of the patients in the bundled treatment group was 56.6 years, and 60.5% of patients were female. There was no difference in age (56.6 ± 12.5 vs. 56.6 ± 12.5; $p = 0.69$) or composition of sex (60.5% vs. 61.7%; $p = 0.904$). The aneurysm location and treatment modality for ruptured aneurysm repair in the two groups were not different. Although not statistically different, the proportion of patients with HH grade V was greater in the bundled treatment group (41.9% vs. 13%). Conversely, in the initial pupil reflex examination, the proportion of patients with fixed pupils was higher in the conventional group, at 38.3% compared to 30.2%. Several factors known to be associated with long-term functional outcomes—such as HH grade V, initial pupil reflex, acute HCP, and intraparenchymal hemorrhage observed on CT scans—differed slightly between the two groups [2, 3, 14–16]. However, after conducting 1:1 Propensity Score Matching, these factors were equalized across both groups [15–21].

The proportion of patients with EVD (88.4% vs. 74.5%; $p = 0.31$) was similar in the two groups. However, the proportions of the treatments that were performed in the ICU were fairly different between the two groups. Continuous ICP monitoring was conducted more in the bundled treatment group (60% vs. 23.4%; $p < 0.01$). Lumbar drainage for toileting subarachnoid hemorrhage or infusing intrathecal nicardipine was more often inserted in the bundled treatment group (60.5% vs. 23.4%; $p < 0.01$). More patients in the bundled treatment group received sedation, a treatment aimed at lowering brain metabolism and controlling ICP (64.4% vs. 42.6%; $p < 0.01$). Targeted temperature management was performed more often in the bundled treatment group (30.2% vs. 8.5%; $p = 0.01$). Osmotic agents, especially hypertonic saline, were administered frequently in the bundled group (53.5% vs. 42.6%; $p < 0.01$). DCI was detected more often in the bundled treatment group (27.9% vs. 6.4%; $p = 0.01$). Thus, rescue vasospasm therapy was applied frequently in the bundled treatment group (53.5% vs. 36.2%; $p < 0.01$).

Clinical Outcomes

The functional outcome at discharge was not different between the two groups (23.3% vs. 17.0%; $p = 0.46$). The proportion of patients with favorable outcomes in the bundled treatment group increased over time. The proportion of patients with 6-month favorable outcomes was approximately two times higher in the bundled treatment group (46.4% vs. 20.7%; $p = 0.039$) (Table 2). The 6-month mortality (mRS score = 6) rate of the bundled treatment group was 14.3%, and that of the conventional group was 27.3% ($p = 0.01$) (Fig. 2).

The infection rate during hospitalization was 44.7% in the conventional group and 48.8% in the bundle

Table 1 Baseline characteristics and treatments of before and after propensity score matching

Variable	Total population			Propensity score matching		
	Bundle (*n* = 43)	Control (*n* = 47)	*p* value	Bundle (*n* = 31)	Control (*n* = 31)	*p* value
Baseline characteristics and treatments before ICU						
Age (year), mean ± SD	56.6 ± 12.5	56.6 ± 12.5	0.69	56.19 ± 12.9	58.00 ± 15.1	0.61
Sex, *n* (%)			0.90			
Female	26 (60.5)	29 (61.7)		19 (61.3)	15 (48.4)	0.31
Underline disease, *n* (%)						
HTN	20 (46.5)	24 (51.1)	0.67	16 (51.6)	18 (58.1)	0.61
Diabetes	6 (14.0)	7 (14.9)	0.90	3 (9.7)	6 (19.4)	0.28
Coronary artery disease	2 (4.7)	6 (12.8)	0.16	2 (6.5)	5 (16.1)	0.23
Atrial fibrillation	4 (9.3)	2 (3.1)	0.30	5 (16.1)	2 (6.5)	0.23
Chronic kidney disease	3 (7.0)	1 (2.1)	0.35	1 (3.2)	1 (3.2)	1.00
Lung disease	0	0	1.00	0	0	1.00
Smoking, *n* (%)	9 (20.9)	8 (17.0)	0.64	6 (19.4)	5 (16.1)	0.74
Previous aSAH history, *n* (%)	1 (2.3)	2 (4.3)	0.60	0	2 (6.5)	0.15
Interval symptom to treatment (hour), mean ± SD	3.5 ± 2.3	5.3 ± 5.2	< 0.01			
Fixed pupils, *n* (%)	13 (30.2)	18 (38.3)	0.58			
Bilateral	13 (100)	17 (94.4)	0.51			
Aneurysm location, *n* (%)			0.46			0.49
Anterior circulation	33 (76.7)	39 (83.0)		25 (80.6)	27 (87.1)	
Posterior circulation	10 (23.3)	8 (17.0)		6 (19.4)	4 (12.9)	
Initial cardiopulmonary resuscitation, *n* (%)	6 (14.0)	5 (10.6)	0.63	2 (6.5)	3 (9.7)	0.64
Hunt and Hess grade, *n* (%)			0.16			1.00
IV	25 (58.1)	34 (72.3)		19 (61.3)	19 (61.3)	
V	18 (41.9)	13 (27.7)		12 (38.7)	12 (38.7)	
Modified Fisher Scale, *n* (%)			0.12			0.05
1	0 (0)	1 (2.1)		0 (0)	0 (0)	
2	0 (0)	2 (4.3)		0 (0)	1 (3.2)	
3	7 (16.3)	13 (27.7)		3 (9.7)	10 (32.3)	
4	36 (83.7)	31 (66.0)		28 (90.3)	20 (64.5)	
Acute hydrocephalus, *n* (%)	12 (27.9)	14 (28.9)	0.84	8 (25.8)	11 (35.5)	0.53
Intraparenchymal hemorrhage, *n* (%)	9 (20.9)	13 (27.7)		7 (22.5)	6 (19.4)	0.70
Aneurysm repair, *n* (%)			0.55			0.77
Coil embolization	36 (83.7)	37 (78.7)		24 (77.4)	23 (74.2)	
Surgical clipping	7 (16.3)	10 (21.3)		7 (22.6)	8 (25.8)	
Extraventricular drainage, *n* (%)	38 (88.4)	35 (74.5)	0.09	27 (87.1)	24 (77.4)	0.32
Treatments in the ICU, *n* (%)						
Lumbar drain	26 (60.5)	11 (23.4)	< 0.01	18 (58.1)	6 (19.4)	< 0.01
ICP control						
Sedation			< 0.01			0.05
None	11 (25.6)	27 (57.4)		11 (35.5)	16 (51.6)	
Light	8 (18.6)	1 (4.6)		7 (22.6)	1 (3.2)	
Deep	5 (11.6)	0 (0)		2 (6.5)	0 (0)	
Coma	20 (44.2)	19 (40.4)		11 (35.5)	14 (45.2)	
TTM	13 (30.2)	4 (8.5)	0.01	6 (19.4)	2 (6.5)	0.13
Osmotic therapy			< 0.01			< 0.01
None	20 (46.5)	27 (57.4)		15 (48.4)	17 (54.8)	
Mannitol only	5 (11.5)	19 (40.4)		6 (19.4)	13 (41.9)	
Hypertonic saline	18 (41.9)	1 (2.1)		10 (32.3)	1 (3.2)	
Delayed cerebral ischemia	12 (27.9)	3 (6.4)	0.01	3 (9.7)	3 (0.7)	1.00
Vasospasm therapy			< 0.01			0.23
None	20 (46.5)	27 (57.4)		16 (51.6)	22 (71.0)	
Intra-arterial	5 (11.5)	19 (40.4)		14 (45.2)	8 (25.8)	
Intrathecal	18 (41.9)	1 (2.1)		1 (3.2)	1 (3.2)	

aSAH aneurysmal subarachnoid hemorrhage, *HTN* hypertension, *ICP* intracranial pressure, *ICU* intensive care unit, *TTM* targeted temperature management

Table 2 Clinical outcomes after propensity score matching

Functional outcome	Conventional ($n=31$)	Bundled treatments ($n=31$)	p value
At discharge			
Favorable (mRS ≤ 2)	3 (9.7)	6 (19.4)	0.51
Unfavorable (mRS > 2)	28 (90.3)	25 (80.6)	
6-month follow-up			
Favorable (mRS ≤ 2)	6 (20.7)	13 (46.4)	0.04
Unfavorable (mRS > 2)	23 (79.3)	15 (53.6)	

mRS, modified Rankin Scale

treatment group, with no significant difference between the two groups ($p=0.69$).

The mean ICU length of stay was 14.3 days (SD 8.7) in the conventional group and 16.7 days (SD 8.7) in the bundle treatment group, with no significant difference between the two groups ($p=0.18$). There was no difference in the total hospital length of stay, with a mean of 29.6 days (SD 17.4) in the conventional group and 34.0 days (SD 17.5) in the bundle treatment group ($p=0.23$). However, both lengths of stay were longer in the bundle treatment group, which is thought to be due to the fact that there were 11 patients who died within 10 days of ICU admission in the conventional group, which created a difference in the length of stay.

Factors associated with favorable functional outcome

Before PSM, univariate analysis revealed two factors significantly associated with favorable functional outcomes: the presence of an initial pupil reflex (OR 6.4 [95% CI 1.7–23.7], $p < 0.01$) and the absence of acute hydrocephalus (HCP) (OR 3.3 [95% CI 1.0–11.1], $p = 0.05$). After PSM, the only variable significantly associated with a favorable functional outcome was the application of bundled treatments (OR 3.3 [95% CI 1.0–10.7], $p = 0.04$) (Table 3).

After conducting the univariate analysis, we performed a selection of significant factors associated with favorable functional outcomes ($p<0.05$), and from this set, we chose the factors with a significance level of ($p<0.1$) for further investigation using multivariate analysis. Multivariate logistic regression revealed three variables significantly linked to favorable functional outcomes prior to PSM: bundled treatments application (OR 32.3 [95% CI 3.1–334.9], $p < 0.01$), initial pupil reflex presence (OR 13.2 [95% CI 1.3–136.6], p = 0.03), and absence of acute HCP (OR 14.1 [95% CI 1.8–113.5], $p = 0.01$). Post-PSM, two variables remained significant: bundled treatments application (OR 14.6 [95% CI 2.1–100.0], $p < 0.01$) and initial pupil reflex presence (OR 12.0 [95% CI 1.4–104.6], $p = 0.02$).

Recovery of Pupil Reflex After Treatment

In the initial pupillary light reflex assessment, 18 patients (38.3%) from the conventional treatment group presented with an absence of the pupillary light reflex, of which 17 demonstrated a bilateral loss of this reflex. Conversely, within the bundled treatment group, 13 patients (30.2%) displayed an absence of the pupillary light reflex, with all exhibiting a bilateral loss in responsiveness. There was no significant difference between the two groups ($p=0.58$) (Table 4).

In the bundled treatment cohort, 61.5% of patients who initially exhibited fixed pupils regained their pupillary reactivity subsequent to initial interventions. Conversely,

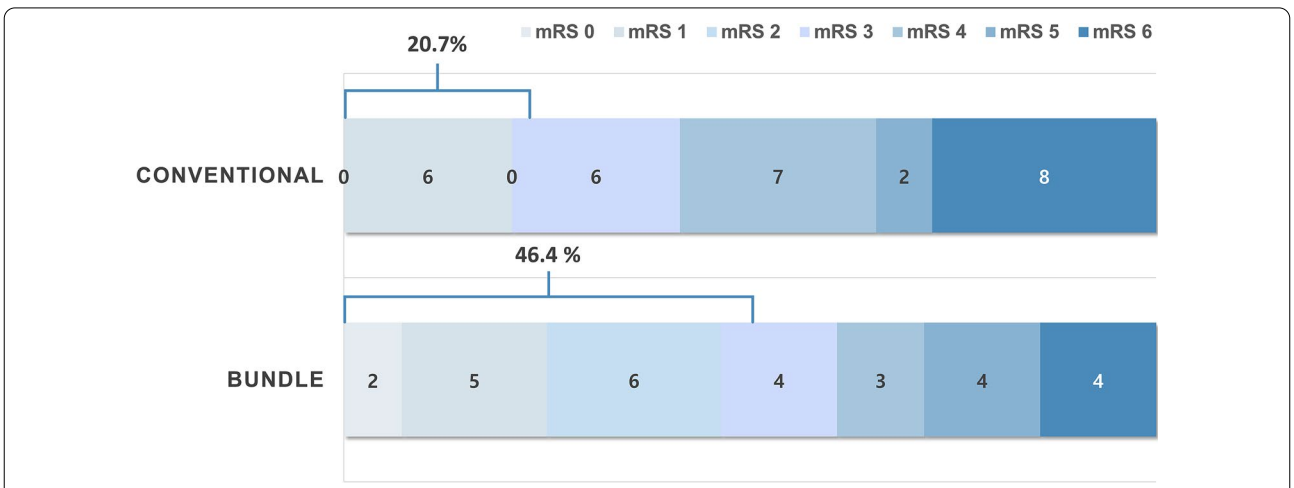

Fig. 2 Distribution of mRS scores at 6 months. The proportion of 6-month favorable outcomes was 46.4% in the bundled treatments group and 20.7% in the conventional group ($p=0.039$). The mortality (mRS score = 6) rate of the bundled treatments group was 14.3%, and that of the conventional group was 27.3% ($p=0.01$). *mRS* modified Rankin Scale

Table 3 Factor-associated favorable functional outcome before and after PSM

Variable	Before PSM						After PSM					
	Univariate			Multivariate			Univariate			Multivariate		
	OR	95% CI	*p* value	OR	95% CI	*p* value	OR	95% CI	*p* value	OR	95% CI	*p* value
Bundle treatment	**2.3**	**0.9–5.7**	0.08	**32.3**	**3.1–334.9**	**< 0.01**	**3.3**	**1.0–10.7**	**0.04**	**14.63**	**2.1–100.0**	**< 0.01**
Initial pupil reflex (+)	**6.4**	**1.7–23.7**	0.01	**13.2**	**1.3–136.6**	**0.03**	**3.5**	**0.9–14.0**	0.08	**12.01**	**1.4–104.6**	**0.02**
Hunt and Hess grade IV	2.2	0.7–5.9	0.14				0.4	0.1–1.3	0.13			
Acute hydrocephalus (−)	**3.3**	**1.0–11.1**	< 0.05	**14.1**	**1.8–113.5**	**0.01**	**5**	**1.0–24.7**	**0.05**			
Intraparenchymal hemorrhage (−)	0.84	0.3–2.5	0.83				0.7	0.2–2.3	0.53			
Extraventricular drainage	0.49	0.2–1.5	0.2				0.3	0.1–1.4	0.14			
ICP monitor insertion	0.6	0.2–1.5	0.29				0.8	0.2–2.6	0.7			
Lumbar drain	1	0.4–2.4	0.1				1.2	0.4–3.7	0.71			
Sedation												
None			ref						ref			
Light	4.1	1.2–11.8	0.01				0.7	0.1–3.6	0.67			
Deep	1.9	0.4–9.9	0.43				0	0	0.1			
Coma	2.6	0.4–18.5	0.35				0.3	0.1–2.3	0.06			
TTM	0.3	0.1–1.2	0.09				0.4	0.1–2.3	0.33			
Osmotic therapy												
None			ref						ref			
Mannitol	1.3	0.4–4.1	0.65				0.3	0.1–1.3	0.11			
Hypertonic saline	0.2	0.0–1.0	0.04				1.3	0.3–5.3	0.73			
Delayed cerebral ischemia (−)	1.3	0.4–4.6	0.66				2.2	0.2–12.4	0.52			

Bold values indicate statistical significance ($p < 0.05$)

CI confidence interval, *ICP* intracranial pressure, *OR* odds ratio, *PSM* propensity score matching, *TTM* targeted temperature management

Table 4 Recovery of pupil reflex

Results	Bundle ($n = 13$)	Control ($n = 18$)	*p* value
Pupil recovery, *n* (%)	8 (61.5)	5 (23.1)	0.70
Recovery time (hours), mean ± SD	9.6 ± 17.5	54.0 ± 30.0	0.07
6-month favorable outcome, *n* (%)	3 (23.1)	0 (0)	0.13

in the conventional group, only 27.5% of patients experienced a restoration of pupillary reactivity. Among those with recovered pupillary reflexes, 23.1% demonstrated favorable functional outcomes at the six-month follow-up.

Regarding patients with reflex recovery, the conventional group comprised four patients (22.2%), with an average time to recovery of 54 hours (SD 30.2). In the bundled treatment cohort, six patients (46.2%) experienced reflex recovery, with an average time until recovery of 9.2 hours (SD 6.7).

Discussion

Versus Recent Research

In a review article by de Oliveira Manoel et al. [6], it was reported that favorable outcomes in aSAH increased from 13% in the late 1970s to early 1980s to 35% in the late 1980s to early 1990s and remained relatively stable thereafter. Although some studies included in their analysis reported highly favorable outcomes, studies published since the 2010s generally show favorable outcomes around 30% [7–9], which is slightly lower than our group's outcome (46.4%).

In their 2016 publication in *Critical Care*, de Oliveira Manoel et al. [5] presented a very specific critical care management strategy, and their single-center outcome was outstanding. They reported a favorable functional outcome (mRS score ≤ 2) of 45% [6], which is similar to the results reported by our group. Their management protocol was highly detailed and shares similarities with our bundle approach. Particularly, the emphasis on aggressive ICP control and the use of an institutional protocol for SAH management align with our strategies.

Functional outcome after poor-grade aSAH and modifiable factor associated with poor outcomes.

Poor-grade aSAH has been reported to have a poor long-term prognosis [6, 7, 9, 22–24]. Suggested factors associated with poor outcomes were the absence of a pupil reflex [2, 24], HH or World Federation of Neurological Surgeons (WFNS) grade V [2, 3, 6, 25–29], Intracerebral hemorrhage [2, 24], acute HCP [15, 27, 28], DCI [3, 24, 26, 27], Modified Fisher grading scale [3, 25, 27, 29], advanced age [2, 3, 25–29], and conservative treatment.

It is noteworthy that early conservative care is associated with poor outcomes, as the rest of the factors are not correctable. Wostrack et al. [30] reported that patients with a WFNS grade V exhibited an initial mortality rate of 31% and a 27% rate of poor outcomes. However, the authors suggested that more favorable outcomes can be anticipated when aggressive treatment approaches are implemented. The mortality rate was reported as 16% at discharge, and the proportion of patients with a good outcome was 26% at discharge [30]. Konczalla et al. [31] reported that early and aggressive treatment resulted in a significant improvement in the survival rate (49%) and a favorable outcome rate of 29% for comatose patients with HH grade V subarachnoid hemorrhage. Therefore, the application of aggressive treatment is essential for these patients. However, there are a few guidelines on how to apply and monitor these therapies precisely. Thus, our team devised the bundled treatments based on essential treatments recommended by the Neurocritical Care Society and its guidelines.

Bundled Treatments Improved Outcomes of Poor-Grade aSAH

The application of the bundle treatment was found to be the most significant factor influencing the outcomes rather than individual interventions, such as EVD placement or specific treatments. Additionally, the bundle treatment demonstrated favorable outcomes and a strong association with rapid recovery in patients with absent pupil reflexes. This further supports the effectiveness of the bundle approach and its potential impact on improving patient outcomes. Indeed, even with early aggressive management, if appropriate aneurysm repair is not performed or medical management is inadequately applied and if DCI is not detected or appropriately treated, there will ultimately be limitations in improving overall patient outcomes. Therefore, it is crucial to thoroughly manage and apply all components to maximize the potential benefits and optimize patient outcomes.

Why are Bundled Treatments Effective?

Previous studies have shown that certain treatments, such as EVD insertion or early timing, can improve the prognosis of aSAH [5, 15]. Nevertheless, one specific treatment has limitations in improving the overall prognosis of severe disease. Moreover, if essential treatments are applied together, they would affect the clinical outcomes of the patients [17, 18, 20].

In our study, there was a remarkable improvement in clinical outcomes after the introduction of the bundled treatments. The efficacy of the bundled treatments was demonstrated in the outcomes of severe diseases, such as sepsis and intracerebral hemorrhage, after applying the bundle treatments. One-hour sepsis bundles reduced the mortality rate and improved clinical outcomes remarkably [32], and the acute bundle of care for intracerebral hemorrhage bundle of intracerebral hemorrhage reduced 30-day fatality by introducing protocoled initial care [33]. The reasons why the quality and outcome of treatment improved when bundled form was applied to severe diseases are as follows: First, bundled treatments enhance the delivery of evidence-based and guideline-recommended treatments to patients. In cases of severe illness, it is important not to skip core treatment. The bundled treatments ensure that all treatments are performed in a timely manner without omission. Second, the application of the bundle can improve treatment adherence and maintain quality of care by providing education and feedback to multidisciplinary teams. This is because implementing a successful bundle requires the use of four strategies: educational activities, notifications, audits, and feedback [34].

Key Elements of Bundled Treatments

Although all elements of bundled treatments were essential, the most important step contributing to favorable outcomes was the control of IICP. In the bundled treatment group, under algorithm-guided aggressive IICP control, pupil reactivity recovered in 61.5% of the patients with fixed pupils. Although nonreactive pupils were related to poor outcomes, one third of these patients had favorable clinical outcomes.

In addition, failure to control IICP in the early stages of vasospasm increases the risk of early brain damage, resulting in a vicious cycle [5]. Therefore, it is very

important to resolve IICP at an earlier stage to improve patient outcomes.

Another essential element of bundled treatments was applying multimodal monitoring to detect and guide DCI treatments. We applied a continuous ICP monitor, the PRx, which was a secondary parameter of ICP monitoring, NIRS, and EEG, as well as conventional monitoring, such as TCD and intermittent neuroimaging. By applying multimodal monitoring, we detected more cases of DCI in the bundled treatment group. Commonly, detecting DCI in poor-grade aSAH is considered challenging [10]. Moreover, it is also difficult to assess the adequacy of treatments for DCI. Inappropriate management of DCI leads to worse outcomes. Using multimodal devices for monitoring helps to overcome these blind spots in diagnosis and evaluation [35]. In our country, it is not feasible to continuously monitor brain tissue oxygenation and cerebral blood flow. As a result, we have chosen to use PRx and NIRS as surrogate methods for continuous monitoring. However, more research is needed on the usage of these devices, and there is also a need for the development of better monitoring methods. More research needs to be done on the application of these devices, and the development of better monitoring methods is also needed. Furthermore, it is crucial to understand that the choice of appropriate monitoring devices should be tailored to the specific needs and resources of each medical institution. This means that we should do our utmost to implement effective monitoring. The application of such monitoring is not only for the diagnosis of DCI but also to evaluate the effectiveness of treatments and guide the proper management of DCI.

Strong leadership is also important to sustain bundled treatments. A dedicated neurointensivist plays a key role in bundled treatments. Giving constant feedback and education regarding the treatment process is essential to sustaining qualified bundled treatments [36–40].

Limitations

This study had several limitations. This is a small retrospective study conducted at a single center. There may be some aspects in which the contribution of the bundle effect to the improvement of outcomes has been overlooked, as it was not conducted contemporaneously with the control group. The recent advancement in neurocritical care may have influenced the results, and the initiation of neurointensivist management could also have had an impact. The shorter time interval to initiate treatment in the bundle treatment group, which could be attributed to factors such as the development of the emergency medical system, may have had a positive impact on both mortality rates and functional outcomes. PSM was performed to increase comparability, but the number of patients for analysis was reduced. A large-scale multicenter study is needed to evaluate the generalizability and effectiveness of bundled treatments.

Conclusions

Bundled treatments significantly improved 6-month functional outcomes and mortality in patients with poor-grade aSAH. Bundled treatments are strongly associated with favorable outcomes in these patients.

Supplementary Information
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Author details
[1] Department of Radiology, Seoul National University Hospital, Seoul, Republic of Korea. [2] Department of Critical Care Medicine, Seoul National University Hospital, Seoul National University College of Medicine, 101, Daehak-ro Jongno-gu, Seoul 03080, Republic of Korea. [3] Department of Neurosurgery, College of Medicine, Seoul National University, Seoul, Republic of Korea. [4] Department of Neurosurgery, Seoul St. Mary's Hospital and College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea. [5] Department of Neurosurgery, Incheon St. Mary's Hospital and College of Medicine, The Catholic University of Korea, Incheon, Republic of Korea. [6] Department of Neurosurgery, Seoul National University Hospital, Seoul, Republic of Korea.

Author Contributions
Conceptualization: EJH. Formal analysis: YHC. Investigation: YS, JK, Y-HC, HSK, SHL, KmK, W-SC, H-SK, JEK. Writing (original draft): YHC. Writing (review and editing): EJH. All authors approved the final version of the manuscript before submission.

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Conflict of interest
The authors declare that they have no conflict of interest.

Ethical Approval/Informed Consent
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The institutional review board of our institute approved this study (No. 2302-045-1402). Informed consent was waived for the retrospectively studied participants because our study did not adversely affect their rights and welfare. Participants or the legal guardians of participants in the newly developed bundle protocol group provided written informed consent prior to study enrollment.

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