Original Article

Results of a Preventive Rebleeding Protocol in Patients with Ruptured Cerebral Aneurysm: A Retrospective Cohort Study

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Abstract

Objective: In 2015, a protocol to prevent rebleeding was implemented to improve the outcome of patients with ruptured intracranial aneurysm. We performed a single-center retrospective analysis to compare the outcomes of pre/post using protocol. **Methodology:** Over a 3-year period, 208 patients with ruptured cerebral aneurysm were treated at our institution. The protocol for preventing rebleeding was initiated in 2015. We compared the two cohorts between the group of patients before initiating the protocol (n = 104) and after initiating the protocol (n = 104). We analyzed the protocol for preventing rebleeding which consisted of absolute bed rest, adequate pain control, avoiding stimuli (R), keeping euvolemia (E), preoperative systolic blood pressure <160 mmHg and within 140–180 mmHg after definite treatment (S), a short course (<72 h) of intravenous transaminic acid, and aneurysm treatment as early as possible (T). Outcomes are presented as in-hospital rebleeding, delayed cerebral ischemia (DCI), and proportion of unfavorable outcomes (score of 4–6 on a modified Rankin scale at 6 and 12 months). **Results:** Postprotocol, there was a reduction in the incidence of in-hospital rebleeding from 6.7% to 2.8% (P = 0.20, odds ratio [OR] = 0.4, 95% confidence interval [CI] = 0.10–1.63) and in the proportion of patients who presented with good WFNS grades (1–3) with unfavorable clinical outcomes at 12 months from 27.0% to 12.8% (P = 0.03, OR = 0.40, 95% CI = 0.17–0.95). The DCI experienced a significant reduction from 44.2% to 7.7% (P < 0.001, OR = 0.10, 95% CI = 0.04–0.23), and their 180-day mortality rate in good WFNS grades patients decreased from 16.3% to 8.8% (hazard ratio 0.80, 95% CI = 0.28–2.28). **Conclusion:** Ruptured cerebral aneurysm patients benefit from this protocol due to its ability to reduce the incidence of DCI and reduce unfavorable outcome on good WFNS grade patients.

Keywords: *Delayed cerebral ischemia, outcome, subarachnoid hemorrhage*

Introduction

The worldwide incidence of subarachnoid hemorrhage (SAH) is 9.1/100,000 population with higher incidences in Finland and Japan.[1]

Initial hemorrhage, early rebleeding, and delayed cerebral ischemia (DCI) lead to high mortality and morbidity rates in patients with ruptured cerebral aneurysms. The 30-day mortality may be 40%–45%.[2] The timing to treatment remains controversial, but the general consensus is that early treatment (<3 days after SAH) is preferred.[3] Because aneurysm rebleeding significantly affects morbidity and mortality, most neurovascular surgeons aim to treat the aneurysm as early as possible. However, aneurysm treatment may be delayed due to reasons which are difficult to avoid. Symptomatic cerebral vasospasm before aneurysm treatment may also complicate treatment.[4] There is no standard guideline outlining patient management before definite treatment of the aneurysm. In-hospital management varies, but there is no established protocol for optimizing the patient's condition while waiting for definite treatment or for improving their long-term outcome.

Thus, we compared the incidences of in-hospital rebleeding and long-term outcomes before and after implementation of our protocol in preventing rebleeding.

Methodology

Patient populations

All patients were treated at a single center with a high case volume (more than 70 ruptured aneurysm cases per year) by experienced neurosurgeons and neuro-interventionists. The study period was from 2013 to 2015. Two hundred and

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eight patients presented during this period with definite SAH proven by computed tomography (CT) or lumbar puncture. The intracranial aneurysm was confirmed with cerebral angiography or CT angiography (CTA). Patients were excluded if they had aneurysms related to arteriovenous malformation, infectious aneurysm, or traumatic aneurysm.

Prior to July 1, 2014, treatment for aneurysmal SAH at our institution varied depending on the neurosurgeon overseeing the patient. These treatments included blood pressure control, antifibrinolytic agents, and ventriculostomy care. However, after July 2014, a protocol to prevent rebleeding was implemented. We named this the "REST protocol." R stands for absolute bed rest, adequate pain control, minimizing stimuli, and use of laxatives; E stands for euvolemic hydration status;[5] S stands for systolic blood pressure (SBP) control, <160 mmHg prior to definite treatment and within the range of 140–180 mmHg after treatment; and T stands for the earliest possible treatment[6] and intravenous tranxemic injection in patients with an expected delay in treatment of more than 72 h.[7] For patients with intracranial pressure >20 cmH_2O who required ventriculostomy, we avoided transmural pressure reduction.[8] In patients with intracranial hypertension for whom CTA did not provide sufficient information for definite treatment, ventriculostomy for hydrocephalus or blood clot removal for large intracerebral hematoma was performed, without treating the aneurysm.

We collected the following data from all participants: age, sex, history of smoking and hypertension, WFNS grade, Hunt and Hess grading, Fisher grading, preoperative hydrocephalus, aneurysm location, size, number, timing of clipping or coiling, in-hospital rebleeding, postoperative complications during hospitalization such as DCI, medical complications, and discharge outcomes. WFNS grading was divided into good grade WNFS 1–3 and poor grade WFNS 4–5.

Aneurysm rebleeding was defined as new bleeding, as shown in the CT scan. We defined DCI as the presence of focal neurological deficits or decrease on the Glasgow Coma Scale of at least two points. Those neurological deficits should be absent immediately after aneurysm occlusion and should not be due to other causes such as rebleeding, acute or worsening hydrocephalus, electrolyte disturbance, or seizure.[9] Hydrocephalus was defined as ventricular dilatation with enlarged temporal horns (>2 mm wide) on a CT scan. The surgical-related complications included ventriculostomy, ventriculoperitoneal shunt, decompressive craniectomy or lobectomy, and tracheostomy. Medical complications included pneumonia, pulmonary edema, myocardial complication, and meningitis.

The main outcome was assessed using the modified Rankin Scale (mRS) at 6 and 12 months. This outcome was classified as being either favorable (mRS 0–3) or unfavorable (mRS 4–6). Continuous data were presented as mean ± standard deviation and categorical data as number (percentage). An independent sample *t*-test was performed for continuous variables. A Chi-square test or Fisher's test was used for categorical variables. The odds ratio (OR) and 95% confidence interval (CI) were calculated. $P < 0.05$ was considered statistically significant. Survival in both cohorts was analyzed, and Kaplan–Meier survival estimates were used to evaluate the differential effect of the preventive rebleeding protocol. Subgroup analysis of WFNS good grade (1–3) and poor grade (4–5) at presentation survival for survival was also estimated. Wilcoxon testing was used to compare survival estimates to determine the equality of the survival curves. The protocol of the present study was approved by the Ethics Committee of Khon Kaen University, according to the standards laid out in the Helsinki Declaration.

Results

One hundred and four patients were treated before the implementation of the protocol and another 104 patients were treated thereafter.

Baseline characteristics

We identified 208 patients with ruptured cerebral aneurysm from 2013 to 2015. One hundred and four patients were treated before the protocol implementation, and 104 patients were treated thereafter. Baseline characteristics and coexisting conditions are shown in Table 1. In the preprotocol cohort, 56.73% of patients were women, 46.1% had elevated SBP prior to surgery, 28.8% had poor grade WFNS 4–5, 87.5% had Fisher's grade 3–4, and 85.6% had an anterior circulation aneurysm. The average age in this group was 55.48 ± 12.7, and average aneurysm size was 5.9 ± 3.5 mm. Nearly 85.6% of the patients in this group underwent surgical treatment, 8.6% underwent endovascular treatment, and 5.8% underwent conservative treatment. There were no significant differences in terms of baseline characteristics between the two cohorts, with two exceptions. Hydrocephalus was lower in the postprotocol group than in the preprotocol group (32.7% vs. 53.8%; $P = 0.002$), and a higher proportion of patients underwent conservative treatment in the postprotocol than in the preprotocol group (16.3% vs. 5.8%; $P = 0.015$).

Perioperative outcomes

Time to definite aneurysm treatment

During the preprotocol period, definite aneurysm treatment was initiated at a median interquartile range of 95.5 (55–154) h from the onset of symptoms of SAH; 66.3% of patients underwent delayed definite treatment after 72 h. In the postprotocol period, time to definite aneurysm was at a median interquartile range of 82.0 (53–226) h from the onset of symptoms. Nearly 57.9% had delayed definite treatment after 72 h, as shown in Table 2.

Table 1: General characteristics

Characteristic	Preprotocol (*n*=104)	Postprotocol (*n*=104)	*P*
Age mean	55.48±12.7	56.25±13.11	0.39
Female (%)	59 (56.73)	66 (63.4)	0.66
Preoperative hypertension (initial SBP >140)	48 (46.1)	43 (48.8)	0.42
WFNS Grade 4 or 5 (%)	30 (28.8)	34 (32.7)	0.54
H and H Grade 4 or 5 (%)	27 (25.9)	32 (30.7)	0.44
Fisher Grade 3 or 4	91 (87.5)	84 (87.5)	0.99
Hydrocephalus	56 (53.8)	34 (32.7)	0.002
Mean aneurysm size±SD (mm)	5.90±3.56	5.30±2.68	0.17
Multiple aneurysm (%)	8 (7.7)	17 (16.3)	0.055
Aneurysm in anterior circulation, 1–6 (%)	89 (85.6)	86 (82.7)	0.7
Saccular aneurysm (%)	96 (92.3)	89 (85.6)	0.12
Aneurysm site (%)			
ICA (paraclinoid, PCOM, Ach)	32 (30.7)	33 (31.7)	0.88
ACA (ACOM and distal ACA)	49 (47.1)	37 (35.6)	0.09
MCA	8 (7.7)	17 (16.35)	0.055
VBA (basilar tip and trunk, VA, PICA)	15 (14.42)	17 (16.35)	0.7
Aneurysm treatment			
Surgical (clipping or bypass)	89 (85.6)	76 (73.1)	0.03
Endovascular	9 (8.6)	11 (10.6)	0.015
Conservative	6 (5.8)	17 (16.3)	0.015

SBP – Systolic blood pressure; H and H – Hunt and Hess; SD – Standard deviation; ICA – Internal carotid artery; WFNS – World federation of neurosurgical societies; PCOM – Posterior communicating artery; Ach – Anterior choriodal artery; ACA – Anterior cerebral artery; MCA – Middle cerebral artery; VBA – Vertebrobasilar artery; VA – Vertebral Artery; PICA – Posterior inferior cerebellar artery; ACOM – anterior communicating artery

Comparison of in-hospital rebleeding and complications

The incidence of in-hospital rebleeding before definite treatment was 6.7% (7/104), as in Table 2, during the preprotocol period and 2.8% (3/104; OR 0.4, 95% CI = 0.10–1.63, $P = 0.20$) during the postprotocol period. In the postprotocol cohort, 7.7% had DCI versus 44.2% in the preprotocol cohort (OR = 0.10, 95% CI = 0.04–0.23, $P < 0.001$).

The postprotocol cohort had lower rates of perioperative medical and surgical complications (e.g., pneumonia; 26.9% vs. 36.5%; OR = 0.63, 95% CI = 0.35–1.15, $P = 0.13$) and had shorter hospital stays (median of 8 days vs. 11 days, $P = 0.09$).

Proportion of unfavorable outcomes and 180-day mortality

During the preprotocol period, 33 of 104 (32.7%) patients had unfavorable outcomes (mRS 4–6) at 1 year compared with 28 of 104 (26.9%) in the postprotocol period. The OR of unfavorable outcome postprotocol was 0.74 (95% CI = 0.41–1.35, $P = 0.33$). There was no significant difference in 180-day mortality between the two cohorts (14.4% preprotocol vs. 13.5% postprotocol).

Subgroup analysis was performed according to WFNS grading. The good grade was defined in WNFS grade 1–3 and poor WFNS grade 4–5. Good-grade patients treated using the new protocol had slightly lower in-hospital rebleeding rates (2.8% vs. 6.7%; OR = 0.4, 95% CI = 0.07–2.16, $P = 0.29$) experienced significantly lower rates of DCI (4.3% vs. 40.5%, OR = 0.06, 95% CI = 0.01–0.22, $P < 0.001$) and had a lower proportion of unfavorable outcomes at 1 year (mRS 4–6; 12.8% vs. 27.0%; OR = 0.40, 95% CI = 0.17–0.95, $P = 0.03$), as in Table 3. Poor-grade patients in the postprotocol group also had significantly lower rates of DCI (14.7% vs. 53.3%, OR = 0.15, 95% CI = 0.04–0.49, $P < 0.001$). However, the differences in rebleeding incidence and clinical outcomes did not reach statistical significance.

Mortality among patients' WFNS scores of 1–3 at 1 month after preventive implementation of the rebleeding protocol decreased from 10.8% to 5.7% ($P = 0.57$), and mortality at 6 months decreased from 16.3% to 8.8% ($P = 0.68$). After implementation of the preventive rebleeding protocol, mortality at 1 month in patients with WFNS scores of 4–6 increased from 13.8% to 17.8% ($P = 0.63$), but mortality at 6 months decreased from 27.6% to 23.5% ($P = 0.98$). The survival curves were shown in Figure 1.

Discussion

Rebleeding has been recognized as a leading preventable cause of death and disability after aneurysmal SAH and is associated with higher rates of complications. The mortality associated with rebleeding has been reported to be as high as 70%.[10] The optimal timing of ruptured intracranial aneurysm treatment remains controversial, but the general consensus tends to favor early treatment (<3 days after SAH). However, a previous study found that, despite early treatment, the rebleeding incidence is still 5.7%.[11] In this study, the incidence of rebleeding in the preprotocol period was 6.7% compared to 2.8% in the postprotocol period. Delayed patient referral is a common problem due to the difficulty of SAH diagnosis, lack of interhospital communication, delayed vascular study, and avoidance of suboptimal condition for aneurysm obliteration at night.[12] Aneurysm treatment was delayed more than 72 h in 66.3% and 57.9% of cases in the preprotocol period and postprotocol period, respectively. If early aneurysm obliteration is not possible, the patients' blood pressure should be strictly controlled (<160 mmHg), and they should undergo a short course of antifibrinolytic agents. These patients should also be given stool softeners, bed rest, and analgesia (e.g., morphine sulfate) to diminish hemodynamic fluctuations. There is controversy with regard to the optimal therapy for hypertension in SAH patients.[13] Although decreasing SBP to < 160 mmHg is reasonable,[7] the benefits gained from this may be offset by increased risk of infarction. In one report, control of diastolic blood pressure (<100

Table 2: Perioperative outcomes of patients pre/post implementation of the preventive rebleeding protocol

Perioperative outcome	Pre	Post	OR (95% CI)	*P*
Hospital rebleeding, *n* (%)	7 (6.7)	3 (2.8)	0.4 (0.10-1.63)	0.20
DCI, *n* (%)	46 (44.2)	8 (7.7)	0.10 (0.04-0.23)	<0.001
30 days mortality	10 (9.6)	10 (9.6)	HR 0.99 (0.39-2.51)	0.99
180 days mortality	15 (14.4)	14 (13.5)	HR 0.92 (0.43-1.98)	0.84
mRS score of 3-6 at 6 months, *n* (%)	44 (42.3)	33 (31.7)	0.63 (0.35-1.11)	0.11
mRS score of 3-6 at 12 months, *n* (%)	38 (37.6)	34 (32.7)	0.79 (0.45-1.41)	0.43
mRS score of 4-6 at 6 months, *n* (%)	36 (34.6)	28 (26.9)	0.69 (0.38-1.25)	0.23
mRS score of 4-6 at 12 months, *n* (%)	33 (32.7)	28 (26.9)	0.74 (0.41-1.35)	0.33
Medical complications, *n* (%)				
Neurogenic pulmonary edema	1 (0.9)	1 (0.9)	0.99 (0.06-16.20)	0.99
Pneumonia	38 (36.5)	28 (26.9)	0.63 (0.35-1.15)	0.13
Meningitis	12 (11.5)	9 (8.6)	0.72 (0.29-1.80)	0.49
Procedure-related complications				
Ventriculostomy	33 (31.7)	30 (28.9)	0.87 (0.48-1.57)	0.65
Ventriculoperitoneal shunt	10 (9.6)	11 (10.6)	1.11 (0.45-2.74)	0.81
Tracheostomy	20 (19.2)	13 (12.5)	0.60 (0.28-1.28)	0.18
Symptoms prior to definite treatment >72 h, *n* (%)	65 (66.3)	51 (57.9)	N/A	0.23
Symptoms prior to definite treatment, median (IQR 1-3)	95.5 (55-154)	82.0 (53-226)	N/A	0.65
Length of hospital stay				
Mean	14.6±8.9	10.36±8.7	N/A	0.19
Median	11 (9-19)	8 (6-11)	N/A	0.19

OR – Odds ratio; CI – Confidence interval; IQR – Interquartile range; N/A – Not available; mRS – Modified Rankin Score; HR – Hazard ratio; DCI – Delayed cerebral ischemia

Table 3: Comparison of clinical outcomes, according to subgroup analysis

Outcome	Good grade WFNS 1–3				Poor grade WFNS 4–5			
	Preprotocol	Postprotocol	OR (95% CI)	*P*	Preprotocol	Postprotocol	OR (95% CI)	*P*
Hospital rebleeding (%)	5 (6.7)	2 (2.8)	0.40 (0.07-2.16)	0.29	2 (6.6)	1 (2.9)	0.42 (0.03-4.92)	0.48
Delay cerebral ischemia (%)	30 (40.5)	3 (4.3)	0.06 (0.01-0.22)	<0.001	16 (53.3)	5 (14.7)	0.15 (0.04-0.49)	<0.001
30 days mortality	8 (10.8)	4 (5.7)	HR 0.68 (0.18-2.54)	0.57	4 (13.8)	6 (17.8)	HR 1.39 (0.35-5.49)	0.63
180 days mortality	12 (16.3)	6 (8.8)	HR 0.80 (0.28-2.28)	0.68	8 (27.6)	8 (23.5)	HR 1.01 (0.31-3.22)	0.98
mRS score of 3-6 at 6 months	24 (32.4)	10 (14.3)	0.34 (0.15-0.79)	0.01	20 (19.4)	23 (22.1)	1.04 (0.36-2.97)	0.93
mRS score of 3-6 at 12 months	22 (29.7)	11 (15.7)	0.44 (0.19-0.99)	0.049	17 (58.6)	23 (67.7)	1.41 (0.52-4.13)	0.45
mRS score of 4-6 at 6 months	22 (29.7)	8 (11.4)	0.30 (0.12-0.74)	0.009	14 (46.7)	20 (58.8)	1.61 (0.60-4.39)	0.33
mRS score of 4-6 at 12 months	20 (27.0)	9 (12.8)	0.40 (0.17-0.95)	0.03	14 (48.3)	19 (55.9)	1.35 (0.50-3.66)	0.54

OR – Odds ratio; CI – Confidence interval; mRS – Modified Rankin Score; HR – Hazard ratio; WFNS – World federation of neurosurgical societies

mmHg) led to a lower incidence of rebleeding but a higher incidence of infarction.[14]

DCI is one of the leading causes of morbidity and mortality in patients with SAH. Up to one-third of these patients with developing DCI, but aggressive vasospasm treatment, can only be pursued after the aneurysm has been secured. Previous systematic reviews examining triple-H therapy for vasospasm prophylaxis have found no strong evidence to support this.[15] More recently, the focus has shifted toward maintenance of euvolemia with the crystalloid or colloid solution and induced hypertension with vasopressor agents such as phenylephrine, norepinephrine, or dopamine.[16]

However, during the postprotocol period in this study, this present strictly in euvolemic, nimodipine oral form and SBP <160 mmHg for in-hospital rebleeding prevention but immediate postoperative period, this protocol tries to drive SBP with hypervolemia first and stepwise with vasopressor keep SBP 140–180 mmHg due to more than half of the patients in this study were secured aneurysm in vasospasm

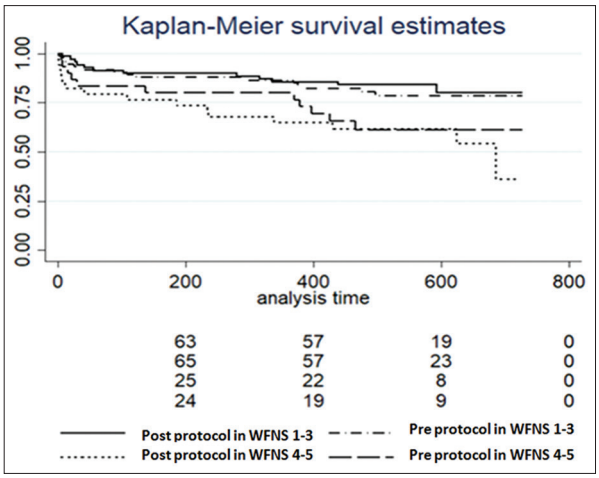

Figure 1: Survival after implementation of the preventive rebleeding protocol in patients with WFNS scores of 1–3 and 4–5

period and transcranial doppler was not available. Our study found a DCI reduction from 44.2% to 7.7% ($P < 0.001$). The effect size is important and relatively large (OR 0.10, 95% CI = 0.04–0.23, $P < 0.001$) compared with that in a previous study.[17]

To reduce the occurrence of unfavorable outcomes (mRS 4–6) in patients with ruptured cerebral aneurysm, some neurovascular surgeons implemented urgent treatment within 24 h[18] including direct referral on acute presentation, early vascular study, aneurysm treatment, and emergency protocol. These steps were able to significantly reduce the incidence of in-hospital rebleeding to 2.1% and lower the proportion of patients with unfavorable clinical outcomes at 1 month (mRS4-6) from 20.3% to 12.1% ($P = 0.008$). For several reasons effect to delayed aneurysm obliteration then protocol was implemented. This study showed a significant reduction in unfavorable outcomes at 12 months (OR 0.4, 95% CI = 0.17–0.95, $P = 0.03$) in patients with WFNS grades of 1–3 in terms of a reduction in hospital rebleeding, DCI, and 30- and 180-day mortality rates. However, changes in terms of clinical outcome did not reach statistical significance in patients with poor WFNS because of higher proportions of whom had poor WFNS grades and underwent conservative treatment during the postprotocol period.

This study has several limitations. First, it was a retrospective analysis from a single institute and compared data from different time periods, making it difficult to avoid selection bias. Second, almost all patients were transferred from another hospital after 24 h, which might affect the incidence of rebleeding. Third, patients with poor WFNS grades often present with coma, making it difficult to identify DCI which may have led to an underestimated incidence of DCI.[19] Finally, some factors that may have impacted outcomes may not have been identified such as surgeon experience, aneurysm complexity, perioperative blood testing, and complication.

Conclusion

The preventive rebleeding protocol significantly reduced unfavorable outcomes in patients with ruptured aneurysm by reducing in-hospital rebleeding, DCI, and medical complications, especially in patients with good WFNS grades.

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Conflicts of interest

There are no conflicts of interest.

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