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Clinical Study

Early rebleeding in patients with subarachnoid haemorrhage under intensive blood pressure management

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ABSTRACT

The objective of this study was to report the frequency and clinical characteristics of early rebleeding in subarachnoid haemorrhage (SAH) patients who underwent intensive blood pressure (BP) management. Patients with aneurysmal SAH frequently present to the emergency department (ED) with elevated BP. Intensive BP management has been recommended to lower the risk of early rebleeding. However, few studies have reported the frequency of early rebleeding in SAH patients undergoing BP management. In our institution, SAH patients with systolic BP (SBP) > 140 mmHg received continuous intravenous nicardipine to maintain their SBP within 120 ± 20 mmHg after diagnosis. An attempt to implement intensive BP management was made on 309 consecutive SAH patients who presented to our ED within 48 hours of SAH onset. Overall, 24 (7.8%) of the 309 patients sustained early rebleeding. Fifteen patients sustained early rebleeding before the implementation of BP management, and the other nine sustained early rebleeding after the implementation of BP management. Therefore, the frequency of early rebleeding under BP management was 3.1% (9/294). When the 309 patients were dichotomised using ED SBP of 140 mmHg as a cut off (SBP > 140 mmHg; n = 239 *versus* SBP ⩽ 140 mmHg; n = 70), the latter counter-intuitively exhibited a significantly higher frequency of early rebleeding (5.9% *versus* 14.2%; $p = 0.04$). This relatively low frequency of early rebleeding under BP management may be acceptable. However, early rebleeding is not eradicated even with strict BP control as factors other than elevated BP are involved. ED SBP within the target range (SBP ⩽ 140 mmHg) does not negate the risk of early rebleeding. Other treatment options that reduce the risk should also be explored.

1. Introduction

It is common for patients with aneurysmal subarachnoid haemorrhages (SAH) to present to the emergency department (ED) with elevated blood pressure (BP). A recent study reported that more than 40% of SAH patients had a systolic blood pressure (SBP) ⩾ 185 mmHg in the ED [1]. Untreated elevated BP appears to increase the probability of early rebleeding from a ruptured aneurysm or dissection, and recent Stroke Guidelines recommend prompt BP reduction to lower this risk [2,3]. However, the efficacy and safety of BP management has rarely been demonstrated in an evidence-based manner in SAH patients and only a few retrospective studies have evaluated the relationship between SBP measured in the ED (ED-SBP) and the frequency of early rebleeding [4–7]. Since 2008, aneurysmal SAH patients who present with elevated BP have been vigorously treated with intravenous (IV) nicardipine in our institution to maintain their SBP 120 ± 20 mmHg. The objective of this study was to report the frequency and clinical characteristics of early rebleeding in SAH patients who underwent this intensive BP management.

2. Materials and methods

2.1. Patients

This was a retrospective analysis of a prospectively instituted protocol. Data for aneurysmal SAH patients treated between January 2008 and December 2013 were retrospectively collected. The study was approved by our internal Institutional Review Board and informed consent was obtained from patients and/or their surrogates. The SAH grades were described using the Hunt–Hess grading system [8]. Patients suspected of having aneurysmal SAH had their BP measured repeatedly using automated

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sphygmomanometers (Nihon Koden, Tokyo, Japan) at 10–15 minute intervals. Immediately after the diagnosis of SAH was established by CT scan, CT angiography (CTA) was performed to identify the location of the ruptured aneurysm or dissection. Diagnostic transarterial angiography was not routinely performed, except in patients in whom the ruptured aneurysm was unidentifiable by CTA. Subsequently, SAH patients were transferred from the CT scan room to the Neurological Intensive Care Unit (NICU) and underwent intensive BP management until surgical/endovascular obliteration of the ruptured aneurysm was performed. Our institutional protocol for the management of aneurysmal SAH patients mandates that SBP be strictly maintained within 120 ± 20 mmHg and that the ruptured aneurysm be obliterated either surgically or endovascularly within 24 hours of symptom onset. Early rebleeding was defined as bleeding that occurred between ED arrival and aneurysmal obliteration. We made every effort to perform follow-up brain CT scans in patients who exhibited either neurological deterioration or a rapid change in vital signs (particularly a rapid change in SBP), and only those patients who showed radiographic evidence of rebleeding (an increase in SAH volume) were included in the rebleeding group. The frequency and clinical characteristics of those who sustained early rebleeding were evaluated. In addition, SAH patients were dichotomised on the basis of their ED-SBP with a cut off value of 140 mmHg, and patients with levels over this immediately received IV nicardipine. The differences in the frequency of early rebleeding between the two groups were investigated. SAH patients who presented after 48 hours of symptom onset, showed deterioration in the pre-hospital setting, or who had Grade V SAH and were not candidates for aneurysmal obliteration because of their poor condition, were excluded from analysis.

2.2. BP management

Maintenance of SBP within 120 ± 20 mmHg was undertaken with the following steps. First, after the establishment of the diagnosis by brain CT scan, continuous intravenous (CIV) nicardipine administration was implemented as soon as the patient's SBP exceeded 140 mmHg. CIV nicardipine was initiated with a dosage of 5 mg/hour and was increased up to 20 mg/hour. When SBP was lowered to <100 mmHg, CIV nicardipine was discontinued. Patients with ED-SBP <100 mmHg were given inotropes to maintain SBP $\geqslant$100 mmHg. Although analgesics/sedatives were frequently used before aneurysmal obliteration procedures in our institution to reduce the risk of early rebleeding, their use was not standardised and was therefore not evaluated in this study. Similarly, the use of IV anti-fibrinolytics had not been standardised and was not evaluated.

2.3. Statistical analyses

The Fisher's exact test was used for the comparison of categorical variables, and student t-test was used for the comparison of numerical variables. JMP software (SAS Institute, Cary, NC, USA) was used for statistical analysis. Numerical data were expressed as the mean ± standard deviation, and p values of <0.05 were considered statistically significant.

3. Results

3.1. Background data

Between January 2008 and December 2013, 309 consecutive SAH patients presenting to our ED within 48 hours of symptom onset underwent prospective BP management and subsequent emergency surgical/endovascular procedures within 24 hours of ED arrival to obliterate a ruptured aneurysm/dissection. The 309 patients consisted of 94 men and 215 women with a mean age of 62.2 ± 14.2 years. The mean interval between symptom onset and ED arrival was 2.83 ± 3.47 hours, and the mean ED arrival to surgery (open/endovascular) interval was 11.10 ± 8.65 hours. According to the Hunt–Hess grading system, 114 patients had Grade I/II SAH, 75 had Grade III SAH, 51 had Grade IV SAH, and 69 had Grade V SAH at the time of ED arrival. The anatomical distribution of ruptured aneurysms in the order of frequency was as follows: internal carotid artery (ICA) in 92, anterior communicating artery in 74, middle cerebral artery in 71, anterior cerebral artery in 31, vertebral artery (VA) in 25 and basilar artery in 16 patients. Among the 309 patients, 20 (6.5%) had a ruptured arterial dissection (7 ICA/13VA).

3.2. Early rebleeding

Among the 309 SAH patients, early rebleeding occurred in 24 (7.8%; Table 1). For the 24 patients with early rebleeding and the 285 patients without early rebleeding, the interval between onset to ED arrival was not significantly different (2.20 ± 2.22 hours *versus* 2.93 ± 4.17 hours; $p = 0.41$). Similarly, there was no significant difference in the interval between ED arrival and surgery between the two groups (8.96 ± 6.42 hours *versus* 11.41 ± 8.90 hours; $p = 0.20$).

In 15 of the 24 patients (62.5%), early rebleeding occurred in the ED before the implementation of BP management (Fig. 1; Table 2). Among the 294 patients who were admitted to NICU without rebleeding in the ED and who underwent BP management, nine exhibited acute neurologic deterioration because of early rebleeding (Fig. 1). Hence, the frequency of early rebleeding in patients under BP management was 3.1% (9/294). In all nine patients, SBP had been maintained within the target range when the rebleeding occurred. Failure to achieve the target SBP range within 2 hours of admission to NICU despite the maximal dose of IV nicardipine (20 mg/hour) was observed in 11 of the 294 patients (4%). None of these 11 patients subsequently developed early rebleeding. One patient developed a transient right-sided hemiparesis during BP reduction, which rapidly improved after discontinuation of IV nicardipine. In total, 27 patients (9%) did not require CIV nicardipine because their SBP never exceeded 140 mmHg. Among these, 12 patients required the use of inotropic agents because of persistent hypotension.

Subsequently, a comparison was made between the 15 patients who sustained rebleeding in the ED and nine patients who sustained rebleeding in the NICU. The compared variables included age, male to female ratio, ratio of Grade IV/V SAH, presence of arterial dissection, mean ED-SBP value, onset to ED arrival interval, ED arrival to surgery interval, and in-hospital mortality. No significant differences in any of the variables were observed between the two groups except that the mean ED-SBP tended to be higher in the former group (170.9 ± 44.3 mmHg *versus* 139.0 ± 28.1 mmHg; $p = 0.07$). Although the frequency of arterial dissection was higher in the former group, the difference was not statistically significant (46.7% *versus* 11.1%; $p = 0.18$).

3.3. Relationship between SBP in ED and early rebleeding

The frequencies of early rebleeding were compared between the two groups dichotomised by their ED-SBP value (>140 mmHg [n = 239] *versus* $\leqslant$140 mmHg [n = 70]). Fourteen in the ED-SBP > 140 mmHg group and 10 in the ED-SBP $\leqslant$ 140 mmHg group sustained early rebleeding. The latter group exhibited a significantly higher frequency of early rebleeding (5.9% *versus* 14.2%; $p = 0.04$). Subsequently, relevant clinical variables were compared

Table 1
Summary of 24 patients with aneurysmal subarachnoid haemorrhage who sustained early in-hospital rebleeding

Patient	Age, sex	H–H Grade/aneurysm location	ED arrival to rebleed interval (hours)	BP management	Admission SBP (mmHg)	Timing/location of rebleeding	Analgesics/ sedatives
1	68, M	II, MCA	⩽1	No	254	ED, waiting for CT	No
2	52, F	II, ICAD	⩽1	No	234	ED, waiting for CT	No
3	66, F	III, ICA	⩽1	No	230	ED, waiting for CT	No
4	49, M	V, VAD	⩽1	No	202	During CT scan	No
5	78, F	V, ICAD	⩽1	No	190	Shortly after CT	No
6	70, M	II, VAD	⩽1	No	179	ED, waiting for CT	No
7	47, M	V, VAD	⩽1	No	172	Shortly after CT	No
8	54, M	IV, ICA	⩽1	No	164	ED, waiting for CT	No
9	82, F	III, ICA	⩽1	No	163	During CT scan	No
10	48, M	V, ICA	⩽1	No	144	Shortly after CT	No
11	38, M	III, Acom	⩽1	No	140	Shortly after CT	No
12	47, M	V, VAD	⩽1	No	136	Shortly after CT	No
13	31, M	III, MCA	⩽1	No	134	ED, waiting for CT	No
14	28, F	III, VAD	⩽1	No	119	During CT scan	No
15	44, F	IV, Acom	⩽1	No	103	ED, waiting for CT	No
16	49, M	IV, VAD	2	Yes	200	NICU	No
17	53, F	III, Acom	2	Yes	112	NICU	No
18	70, F	V, ACA	2	Yes	107	NICU	Propofol
19	66, F	III, ICA	3	Yes	140	NICU	Propofol
20	69, F	IV, Acom	3	Yes	133	NICU	Propofol
21	48, F	III, ACA	3	Yes	116	NICU	No
22	45, F	III, ICA	4	Yes	146	NICU	Buprenorphine
23	59, M	V, Acom	4	Yes	144	NICU	Propofol
24	59, F	II, Acom	6	Yes	153	NICU	Propofol

ACA = anterior cerebral artery, Acom = anterior communicating artery, BP = blood pressure, ED = emergency department, H–H = Hunt and Hess, ICA = internal carotid artery, ICAD = internal carotid artery dissection, MCA = middle cerebral artery, NICU = neurological intensive care unit, SBP = systolic blood pressure, VAD = vertebral artery dissection.

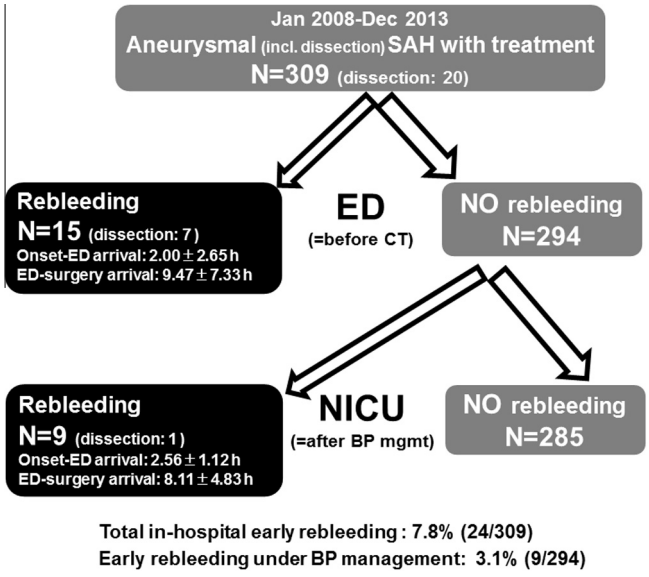

Fig. 1. The number of subarachnoid haemorrhage (SAH) patients who sustained early rebleeding illustrated at each treatment stage (emergency department [ED] and neurological intensive care unit [NICU]). The total in-hospital early rebleeding rate was 7.8% (24/309), whereas in those patients undergoing intensive blood pressure (BP) management (mgmt) it was 3.1% (9/294).

between the two groups. The variables included age, male to female ratio, ratio of Grade IV/V SAH, ratio of anterior *versus* posterior circulation aneurysms, ratio of open surgery *versus* endovascular surgery and presence of chronic hypertension, diabetes and hyperlipidaemia. The ED-SBP > 140 mmHg group was significantly older (63.3 ± 13.9 years *versus* 58.5 ± 14.4 years; $p = 0.01$) and tended to harbour chronic hypertension as an underlying condition more frequently (51.5% *versus* 40.0%; $p = 0.10$) than the ED-SBP ⩽ 140 mmHg group. Apart from that, no significant intergroup differences were present in the evaluated variables. The results are summarised in Table 3.

4. Discussion

Several randomised controlled trials (RCT) to evaluate the efficacy of intensive BP management for the prevention of haematoma expansion have been conducted in patients with hypertensive intracerebral haemorrhage and most have shown the efficacy of therapeutic intervention in an evidence-based manner [9,10]. According to these studies, the optimal target SBP appears to be 140–150 mmHg [9,10]. In contrast, no such RCT have been conducted in SAH patients, therefore, the efficacy of intensive BP management as well as the optimal target SBP range remains unclear. Only a few retrospective studies have investigated the relationship between ED-SBP and early rebleeding [4–7]. A recent meta-analysis found that patients with ED-SBP > 160 mmHg were significantly more likely to sustain early rebleeding than those with ED-SBP > 140 mmHg [7]. However, the influence of BP management on the frequency of early rebleeding was not evaluated in any of them.

Table 2
Comparison of demographic variables in 24 patients on the basis of timing of aneurysmal rebleeding (before *versus* after blood pressure management)

	Before BP management (n = 15)	After BP management (n = 9)	*p* value
Age (years), mean ± SD	53.5 ± 16.2	57.6 ± 9.4	0.50
Male : Female	9:6	2:7	0.10
H–H Grade IV/V SAH, n (%)	7 (46.7)	4 (44.4)	1.00
Arterial dissection, n (%)	7 (46.7)	1 (11.1)	0.18
ED-SBP (mmHg), mean ± SD	170.9 ± 44.3	139.0 ± 28.1	0.07
Onset to ED arrival interval (hours), mean ± SD	2.00 ± 2.65	2.56 ± 1.12	0.57
ED arrival-surgery interval (hours), mean ± SD	9.47 ± 7.33	8.11 ± 4.83	0.63
In-hospital mortality, n (%)	2 (13.3)	3 (33.3)	0.33

ED = emergency department, H–H = Hunt and Hess, SAH = subarachnoid haemorrhage, SBP = systolic blood pressure, SD = standard deviation.

Table 3
Comparison of demographic variables in 309 patients with subarachnoid haemorrhage dichotomised by systolic blood pressure of 140 mmHg in the emergency department

	ED-SBP > 140 mmHg (n = 239)	ED-SBP ⩽ 140 mmHg (n = 70)	*p* value
Age (years), mean ± SD	63.3 ± 13.9	58.5 ± 14.4	0.01*
Male: Female	76:163	18:52	0.38
Early rebleeding, n (%)	14 (5.9)	10 (14.2)	0.04**
H–H Grade IV/V SAH, n (%)	90 (37.7)	34 (48.6)	0.13
Aneurysm location (anterior : posterior)	210: 29	60: 10	0.68
Open : endovascular surgery	157: 82	40:30	0.21
Chronic hypertension, n (%)	123 (51.5)	28 (40.0)	0.10
Diabetes, n (%)	22 (9.2)	3 (4.3)	0.22
Hyperlipidemia, n (%)	32 (13.3)	7 (10.0)	0.54

*,** Statistically significant.
ED-SBP = emergency department systolic blood pressure, H–H = Hunt and Hess, SAH = subarachnoid haemorrhage, SD = standard deviation.

Of the 309 SAH patients in our cohort, 24 (7.8%) sustained early in-hospital rebleeding. The frequency appeared to be comparable to that reported in the literature (3.2–8.6%) [4–7]. It should be noted that some previous studies included patients with early rebleeding in pre-hospital settings, for example, during ambulance transport [11–13]. Such patients were not included in this study because physicians can do little to reduce the frequency of early pre-hospital rebleeding. Early in-hospital rebleeding may be dichotomised on the basis of the timing of any intervention for elevated BP; either before or after the implementation of BP management. We were particularly interested in the latter, and this is the first clinical study, to our knowledge, to report the frequency of early rebleeding under BP management (3.1%) in SAH patients. The majority of patients in our cohort sustained early rebleeding before the implementation of BP management (Table 1; Fig. 1). There were no significant demographic or prognostic factor differences between those who had rebleeding before, and those who had rebleeding after, BP management (Table 2), although the frequency of arterial dissection was higher in the former, but did not reach significance. It is widely known that rebleeding frequently occurs during transport to the CT scan room or during diagnostic transarterial angiography [14,15]. One of the reasons why the frequency of early rebleeding was relatively low in our institution may have been that transarterial angiography has been replaced by CTA. CTA seems to have substantially lower complication rates (including early rebleeding) than transarterial angiography [16].

In our institution, the treatment algorithm for aneurysmal SAH patients includes the implementation of CIV nicardipine in those patients with ED-SBP > 140 mmHg, only after the diagnosis of SAH has been established by a brain CT scan (Fig. 1). Although there has been little evidence to support the pre-emptive (before CT scan acquisition) use of IV anti-hypertensives for patients who present with elevated BP and symptoms suggestive of SAH [17], such clinical practice may reduce the frequency of early rebleeding in the ED and be justified in selected patients. Nevertheless, it should be noted that those who sustained early rebleeding before the acquisition of a CT scan may not always be hypertensive. In our cohort, four of the 15 patients who sustained early rebleeding in the ED (before intensive BP management) presented with ED-SBP ⩽ 140 mmHg. Patients with arterial dissection (ICA/VA) seem to be particularly vulnerable to early rebleeding in the ED (Table 1), and even pre-emptive intervention for BP reduction may have limited efficacy [18].

Adverse events associated with BP management occurred in only one patient (0.3%) in our study, suggesting that setting a target SBP range of 120 ± 20 mmHg is safe and acceptable in SAH patients. A SBP of 140 mmHg as a cut off value to start CIV nicardipine is lower than that recommended in the recent Guidelines by the American Heart Association [2]. Nevertheless, several neurosurgical institutions have adopted a SBP of 140 mmHg as a cut off [19]. The relatively low frequency of early rebleeding under BP management reported here (3.1%) appears to be acceptable and may be used in future studies as a reference. At the same time, this figure may represent the limitations of intensive BP management as all nine patients who sustained rebleeding in the NICU had their SBP maintained within the target range. It remains to be determined whether the frequency would be further reduced by setting the cut off value at a lower level, for example, 120 mmHg. Despite all efforts, early rebleeding may not be reducible to zero because factors other than elevated BP, including platelet aggregability and thrombin–antithrombin complex levels, may also be involved in early rebleeding [20,21]. The use of anti-fibrinolytics or sedatives/analgesics was not evaluated in this study because their use was at the discretion of the attending neurosurgeon and had not been standardized. In addition to BP management, other treatment options that may reduce the risk of early rebleeding should be explored in a more prospective and controlled manner [20,21].

The significantly higher frequency of early rebleeding in the ED-SBP ⩽ 140 mmHg group than in the ED-SBP > 140 mmHg group is counter-intuitive (Table 3). The higher frequency of poor grade (Hunt–Hess Grade IV/V) SAH patients in the former may partly explain this finding because poor grade SAH is a documented risk factor for early rebleeding [4–7,11–13,22]. The present finding also indicates that admission ED-SBP ⩽ 140 mmHg alone may never be used as an indicator of safety for early rebleeding. The ED-SBP ⩽ 140 mmHg group was significantly younger than the ED-SBP > 140 mmHg group (Table 3), which may explain why the frequency of chronic hypertension tended to be lower in the former.

This study had several limitations. First, this was a retrospective study, although the patients were treated under the same prospectively instituted protocols and selection criteria. The study had no control group for the target SBP value, so its efficacy in reducing early rebleeding was not evaluable in a comparative manner, although it was intuitively probable that a substantial amount of early rebleeding may have been prevented by the implementation of BP management. Because it is no longer acceptable from an ethical standpoint to leave elevated BP untreated in SAH patients, future RCT will have to be designed to evaluate the efficacy of two different target SBP, similar to RCT on hypertensive intracerebral haemorrhage patients. Second, the frequency of early rebleeding under BP management (3.1%) may have been low simply because a substantial number of patients with arterial dissection had already sustained early rebleeding in the ED and were excluded from the final analysis. Among the 20 patients with ruptured arterial dissection in this study, as many as eight (40%) sustained early rebleeding, and seven of the eight early rebleedings had occurred in the ED. Prevention of early rebleeding in patients with ruptured arterial dissection remains an unsolved issue [23]. Third, despite a low complication rate related to over-reduction of BP in our cohort (one in 294 patients; 0.3%), our target SBP range (120 ± 20 mmHg) may have been too low in elderly patients with the subsequent risk of reduced cerebral blood flow which had already been compromised by the initial aneurysmal bleeding. Finally, it was apparent that the frequency of early rebleeding was dependent on the interval between the initial aneurysmal bleeding and timing of intervention to obliterate the aneurysm, therefore, the frequency may vary from institution to institution. Naturally, a shorter ED arrival to surgery interval may lower the frequency of early rebleeding. The frequency may have been low

in our institution because of the relatively short ED arrival to surgery interval (11.10 ± 8.65 hours).

5. Conclusion

Twenty-four of 309 consecutive SAH patients (7.8%) who presented to our ED within 48 hours of onset sustained early rebleeding. Fifteen patients sustained early rebleeding before, and the other nine patients sustained early rebleeding after, the implementation of BP management to maintain SBP within 120 ± 20 mmHg. Therefore, the frequency of early in-hospital rebleeding under BP management was 3.1%. Although the relatively low frequency appears to be acceptable, the figure also represents the limitations of BP management. Other treatment options that may reduce the risk of early rebleeding should also be explored.

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

References

[1] Qureshi AI, Ezzeddine MA, Nasar A, et al. Prevalence of elevated blood pressure in 563,704 adult patients with stroke presenting to the ED in the United States. Am J Emerg Med 2007;25:32–8.
[2] Connolly Jr ES, Rabinstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2012;43:1711–37.
[3] Shinohara Y, Yanagihara T, Abe K, et al. IV. Subarachnoid hemorrhage. J Stroke Cerebrovasc Dis 2011;20:S100–15.
[4] De Marchis GM, Lantigua H, Schmidt JM, et al. Impact of premorbid hypertension on haemorrhage severity and aneurysm rebleeding risk after subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry 2014;85:56–9.
[5] Tanno Y, Homma M, Oinuma M, et al. Rebleeding from ruptured intracranial aneurysms in North Eastern Province of Japan. A cooperative study. J Neurol Sci 2007;258:11–6.
[6] Naidech AM, Janjua N, Kreiter KT, et al. Predictors and impact of aneurysm rebleeding after subarachnoid hemorrhage. Arch Neurol 2005;62:410–6.
[7] Tang C, Zhang TS, Zhou LF. Risk factors for rebleeding of aneurysmal subarachnoid hemorrhage: a meta-analysis. PLoS ONE 2014;9:e99536.
[8] Lindsay KW, Teasdale G, Knill-Jones RP, et al. Observer variability in grading patients with subarachnoid hemorrhage. J Neurosurg 1982;56:628–33.
[9] Anderson CS, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med 2013;368:2355–65.
[10] Butcher KS, Jeerakathil T, Hill M, et al. The intracerebral hemorrhage acutely decreasing arterial pressure trial. Stroke 2013;44:620–6.
[11] Ohkuma H, Tsurutani H, Suzuki S. Incidence and significance of early aneurysmal rebleeding before neurosurgical or neurological management. Stroke 2001;32:1176–80.
[12] Fujii Y, Takeuchi S, Sasaki O, et al. Ultra-early rebleeding in spontaneous subarachnoid hemorrhage. J Neurosurg 1996;84:35–42.
[13] Guo LM, Zhou HY, Xu JW, et al. Risk factors related to aneurysmal rebleeding. World Neurosurg 2011;76:292–8 [discussion 253–4].
[14] Yasui T, Kishi H, Komiyama M, et al. Very poor prognosis in cases with extravasation of the contrast medium during angiography. Surg Neurol 1996;45:560–4 [discussion 564-5].
[15] Kusumi M, Yamada M, Kitahara T, et al. Rerupture of cerebral aneurysms during angiography–a retrospective study of 13 patients with subarachnoid hemorrhage. Acta Neurochir (Wien) 2005;147:831–7.
[16] Hashiguchi A, Mimata C, Ichimura H, et al. Rebleeding of ruptured cerebral aneurysms during three-dimensional computed tomographic angiography: report of two cases and literature review. Neurosurg Rev 2007;30:151–4.
[17] Culyer V, McDonough E, Lindsell CJ, et al. Antihypertensives are administered selectively in emergency department patients with subarachnoid hemorrhage. J Stroke Cerebrovasc Dis 2013;22:1225–8.
[18] Inamasu J, Nakamura Y, Saito R, et al. Endovascular treatment of ruptured vertebral artery dissection in the acute stage. Cerebrovasc Dis 2003;16:306–8.
[19] Shirani P, Fukuda K, Tieu L, et al. Strict blood pressure control with intravenous nicardipine is associated with lower risk of acute re-bleeding after aneurysmal subarachnoid hemorrhage. Stroke 2013;44:A51.
[20] Germans MR, Post R, Coert BA, et al. Ultra-early tranexamic acid after subarachnoid hemorrhage (ULTRA): study protocol for a randomized controlled trial. Trials 2013;14:143.
[21] Parkhutik V, Lago A, Tembl JI, et al. Influence of COX-inhibiting analgesics on the platelet function of patients with subarachnoid hemorrhage. J Stroke Cerebrovasc Dis 2012;21:755–9.
[22] Inamasu J, Miyatake S, Tomioka H, et al. Subarachnoid haemorrhage as a cause of out-of-hospital cardiac arrest: a prospective computed tomography study. Resuscitation 2009;80:977–80.
[23] Li S, Yan B, Kaye A, et al. Prognosis of intracranial dissection relates to site and presenting features. J Clin Neurosci 2011;18:789–93.