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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