Safety of heparin loading during endovascular embolization in patients with aneurysmal subarachnoid hemorrhage

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ABSTRACT

Objective: Of the complications that can occur during endovascular surgery in aneurysmal subarachnoid hemorrhage (aSAH) patients, thromboembolism remains a particular challenge for many surgeons. Heparin has been widely used for its prevention, but it has not been able to eliminate concerns about bleeding. Therefore, in this study, we tried to determine the risk of rebleeding associated with heparin use.

Methods: We retrospectively analyzed the medical and surgical records of 109 patients that underwent endovascular embolization for a ruptured cerebral aneurysm at a single institution from 2010 to 2014. These patients were divided into two groups according to whether heparin was loaded or not, to determine the effect of heparin on rebleeding and to identify other risk factors of rebleeding.

Results: This series included 40 men (36.7 %) and 69 women (63.3 %) of mean age 57.9 ± 14.8 years. In 80 patients (73.4 %), endovascular embolization was conducted using an intraoperative bolus of 5000 units of heparin, whereas in the other 29 (26.6 %) endovascular embolization was performed without an intraoperative heparin bolus. After procedures, 16 patients (14.7 %) experienced rebleeding and 2 (1.8 %) a thromboembolic event. Intraoperative heparin loading (OR 0.683 [95 % CI 0.199–2.338]) was not found to be related to postoperative rebleeding. Rather, logistic regression analysis showed preoperative modified Fisher grade (OR 2.037 [95 % CI 1.077–3.853]) and external ventricular drainage (OR 5.389 [95 % CI 1.171–24.801]) independently predicted rebleeding.

Conclusions: Heparin loading during endovascular treatment of ruptured cerebral aneurysms did not affect rebleeding. We conclude heparin loading to prevent thromboembolism during endovascular treatment may be considered a good option in aSAH patients.

1. Introduction

Endovascular embolization using detachable coils is a widely accepted alternative to clipping for the treatment for aneurysmal subarachnoid hemorrhage (aSAH) [1–3], but aneurysm rebleeding during or after surgery and thromboembolic events during surgery remain major concerns. However, these complications are difficult to prevent because their mechanisms are diametrically opposed. Anticoagulant and antiplatelet agents are essential to prevent thromboembolic events during the endovascular embolization of unruptured cerebral aneurysms, but the use of these agents in patients with a ruptured aneurysm is limited by rebleeding concerns [1,4].

The aim of this study was to investigate the relationship between the use of heparin to prevent thromboembolic events and rebleeding risk in patients with aSAH from a ruptured aneurysm treated by endovascular embolization.

2. Material and methods

2.1. Patient selection and data collection

We retrospectively studied patients that underwent endovascular embolization for a ruptured cerebral aneurysm at a single institution from 2010 to 2014. Patients that underwent endovascular treatment more than 72 h after aneurysmal rupture, those scheduled for parent artery occlusion at primary planning, and patients without contrast...
filling by angiography due to severe brain swelling before surgery were excluded. A total of 109 patients were included, and gender, age, Hunt and Hess grade at presentation, aneurysmal size and location, preoperative Fisher and modified Fisher grades, intraoperative heparin loading, immediate postoperative external ventricular or lumbar drainage, and the endovascular treatment techniques used were investigated and analyzed.

This retrospective analysis was approved by the institutional review board of Yonsei University Wonju College of Medicine (CR319003).

2.2. Endovascular procedure

Treatment modalities were chosen based on the results of the International Subarachnoid Aneurysm Trial (ISAT) [2]; clipping was preferred in patients with a small or wide-necked aneurysm or large intracranial hemorrhage. Diagnostic digital subtraction angiography and embolization were performed using an angiography unit (Allura Xper FD20, Philips). Three-dimensional rotational angiography was performed in all 109 patients to confirm aneurysm shapes. Heparin and embolization were performed using an angiography unit (Allura Xper FD20, Philips). Three-dimensional rotational angiography was performed in all 109 patients to confirm aneurysm shapes. Heparin (5000 IU (international units)) was loaded through a femoral sheath at the beginning of the procedures at surgeon’s discretion. During all 109 endovascular procedures, catheter flushing was maintained using a heparin/saline mixture (5000 IU in 1 L of normal saline). Although partial thromboplastin time (PTT) and activated clotting time (ACT) monitoring were not performed during procedures, PTT prolongation was confirmed by immediate postoperative examination in all patients that underwent heparin loading. The two surgeons that performed the procedures were both neuro-interventionists with at least five years of experience. All aneurysms were coiled to a packing density of at least 30%. Patients were admitted to an intensive care unit (ICU) immediately after procedures and arterial blood pressure and electrocardiography were continuously monitored for at least a week. All patients underwent a computed tomography (CT) perfusion scan immediately after procedures and 3 days later to check for rebleeding and the presence of an ischemic lesion. Rebleeding was defined as an increase in SAH size or the occurrence of new intracerebral hemorrhage (ICH), excluding contrast on follow-up CT scans.

2.3. Statistical analysis

The two-sample t-test, the Chi-square test, or Fisher’s exact test were initially used to identify associations with postoperative rebleeding, and logistic regression analysis was used to identify factors that independently predicted rebleeding. Results are expressed as odds ratios (ORs) and 95% confidence intervals (CIs). Quantitative variable results are expressed as means ± SDs, and qualitative variable results as properties of variables. Statistical significance was accepted for p values < 0.05, and the analysis was conducted using SPSS (version 24.0. Armonk, NY: IBM Corp.)

3. Results

Forty (36.7%) of the 109 patients were men and overall mean patient age was 57.9 ± 14.8 years (range 27–90 years). Eighty (73.4%) of the study subjects underwent heparin loading during endovascular embolization and 29 did not. Rebleeding immediately after surgery occurred in 16 (14.7%) patients, and 2 (1.8%) patients experienced a thromboembolic event. Intraoperative aneurysmal rebleeding was confirmed in one patient with rebleeding (0.92%), whereas the remaining 15 patients showed hematoma expansion on CT scans immediately after the procedure. On the other hand, both patients that experienced a thromboembolic event developed parent artery occlusion due to thrombus during embolization. In one of these patients, right vertebral artery occlusion occurred during the procedure, but left vertebral artery flow was intact and the procedure was completed with total occlusion of the right vertebral artery. In the other patient, ipsilateral A2 occlusion occurred during anterior communicating artery aneurysm coil embolization, the procedure was completed by stent deployment after recanalization had been achieved by intra-arterial abciximab injection. Neither patient showed any special symptoms after the procedure. Patient characteristics are provided in Table 1.

No significant difference was observed except age the preoperative characteristics of patients that underwent endovascular embolization between the with heparin and without heparin groups. During endovascular treatment, thromboembolic events occurred in one patient in each group, which was not significantly different (1.3% and 3.4%, respectively). However, the stent-assisted technique was used more frequently in the with heparin group (p = 0.016), whereas the double catheter technique was used more frequently in the without heparin group (p = 0.039), indicating surgeon’s choice was less restricted by heparin loading (Table 2). No difference intergroup difference was observed with respect to rebleeding (p = 0.760). However, modified Fisher grades, which reflect hemorrhage amounts, were significantly higher for patients that experienced rebleeding (p = 0.014) (Table 3).

| Table 1 Patient characteristics. |
|----------------------------------|
| Gender (male)                    | 40 (36.7) |
| Age                              | 57.9 ± 14.8 |
| History                          |           |
| Hypertension                     | 38 (34.9) |
| Diabetes mellitus                | 6 (5.5)   |
| Antithrombotic medication        | 6 (5.5)   |
| Hunt and Hess grade              |           |
| I                                | 22 (20.2) |
| II                               | 25 (22.9) |
| III                              | 23 (21.1) |
| IV                               | 19 (17.4) |
| V                                | 20 (18.3) |
| Fisher grade                     |           |
| 0                                | 2 (1.8)   |
| 1                                | 26 (23.9) |
| 2                                | 26 (23.9) |
| 3                                | 8 (7.3)   |
| 4                                | 74 (67.9) |
| Modified Fisher grade            |           |
| 0                                | 2 (1.8)   |
| 1                                | 26 (23.9) |
| 2                                | 26 (23.9) |
| 3                                | 8 (7.3)   |
| 4                                | 47 (43.1) |
| Aneurysm location                |           |
| Anterior cerebral artery         | 6 (5.5)   |
| Anterior communicating artery    | 35 (32.1) |
| Basilar artery tip               | 8 (7.3)   |
| Superior cerebellar artery       | 1 (0.9)   |
| Anterior choroidal artery        | 5 (4.6)   |
| Posterior communicating artery   | 35 (32.1) |
| Middle cerebral artery           | 14 (12.8) |
| Posterior inferior cerebellar artery | 1 (0.9) |
| Others                           | 4 (3.7)   |
| Aneurysm size                    | 6.0 ± 2.8 |
| Intraoperative heparin loading   | 80 (73.4) |
| Techniques                      |           |
| Single catheter                  | 70 (64.2) |
| Double catheter                  | 13 (11.9) |
| Stent-assisted                   | 25 (22.9) |
| Parent vessel occlusion          | 1 (0.9)   |
| Complication                     |           |
| Rebleeding                       | 16 (14.7) |
| Thromboembolic event             | 2 (1.8)   |

Forty (36.7%) of the 109 patients were men and overall mean patient age was 57.9 ± 14.8 years (range 27–90 years). Eighty (73.4%) of the study subjects underwent heparin loading during endovascular embolization and 29 did not. Rebleeding immediately after surgery occurred in 16 (14.7%) patients, and 2 (1.8%) patients experienced a thromboembolic event. Intraoperative aneurysmal rebleeding was confirmed in one patient with rebleeding (0.92%), whereas the remaining 15 patients showed hematoma expansion on CT scans immediately after the procedure. On the other hand, both patients that experienced a thromboembolic event developed parent artery occlusion due to thrombus during embolization. In one of these patients, right vertebral artery occlusion occurred during the procedure, but left vertebral artery flow was intact and the procedure was completed with total occlusion of the right vertebral artery. In the other patient,
Table 2
Comparison of two groups according to intraoperative heparin loading.

|                  | Heparin loading | No heparin loading | P Value |
|------------------|-----------------|--------------------|---------|
| Age              | 56.2 ± 14.7     | 62.6 ± 14.4        | 0.044   |
| Gender (male)    | 33 (41.3)       | 7 (24.1)           | 0.101   |
| Preoperative GCS | 11.3 ± 4.0      | 12.0 ± 3.5         | 0.430   |
| Hunt and Hess grade | 2.9 ± 1.5       | 2.8 ± 1.2          | 0.719   |
| Fisher grade     | 3.4 ± 1.0       | 3.0 ± 1.2          | 0.113   |
| Modified Fisher grade | 2.7 ± 1.3       | 2.7 ± 1.3          | 0.889   |

Table 3
Univariate analysis of baseline variables associated with rebleeding.

| Rebleeding       | No rebleeding   | P Value |
|------------------|-----------------|---------|
| Age              | 57.1 ± 15.8     | 58.0 ± 14.7 | 0.829   |
| Gender (male)    | 6 (37.5)        | 34 (36.6)  | 0.943   |
| History          |                 |           |         |
| Hypertension     | 4 (25.0)        | 34 (36.6)  | 0.370   |
| Diabetes mellitus| 0 (0)           | 6 (6.5)    | 0.589*  |
| Antithrombotics medication | 0 (0)  | 6 (6.5)    | 0.589*  |
| Preoperative GCS | 10.3 ± 4.3      | 11.7 ± 3.8  | 0.178   |
| Hunt and Hess grade | 3.3 ± 1.4       | 2.9 ± 1.4   | 0.292   |
| Fisher grade     | 3.6 ± 0.9       | 3.3 ± 1.1   | 0.286   |
| Modified Fisher grade | 3.3 ± 1.0       | 2.6 ± 1.3   | 0.014   |
| Aneurysm size    | 6.1 ± 2.5       | 5.9 ± 2.9   | 0.852   |
| Intraoperative heparin loading | 11 (66.8) | 69 (74.2) | 0.760*  |

| Techniques       |                 |           |         |
| Single catheter  | 10 (62.5)       | 60 (64.5) | 0.877   |
| Double catheter  | 3 (18.8)        | 10 (10.8) | 0.402*  |
| Stent-assisted   | 3 (18.8)        | 22 (23.7) | 0.666   |
| External ventricular drainage | 8 (50.0) | 19 (20.4) | 0.024*  |
| Lumbar drainage  | 1 (6.3)         | 6 (6.5)   | 1.000*  |

- *Adjusted for age, gender.
- †Adjusted for age, gender, hypertension, aneurysm size, Hunt and Hess grade, procedure techniques.

4. Discussion

Despite technological developments and increased surgical experience, thromboembolism remains one of the most common causes of endovascular embolization-associated morbidity and mortality [3]. Thromboembolism occurs during or immediately after cerebral aneurysm endovascular embolization at rates of between 3 and 28% [5–7], and delayed postoperative thromboembolic complications have been reported to occur at rates of 2%–61% [3,5,8]. Peri-operative thromboembolism can cause temporary or permanent neurological deficits [3], and thus, it is important measures be taken to prevent thrombus formation during endovascular treatment [5]. Thromboembolic events are caused by inadequate antithrombotic therapy [9], but the use of anti-platelet or antiocoagulation has always been limited by bleeding concerns, although it has been reported that most cases of rebleeding during endovascular treatment are attributable to the procedure [10]. However, few studies have been conducted to determine whether heparin use influence rebleeding.

4.1. Roles of heparin

The main clinical roles of heparin during endovascular embolization for the treatment of aSAH are systemic heparinization and the prevention of venous thromboembolism (VTE). Interestingly, heparin has effects in addition to those on the coagulation cascade, and these other effects broaden its utility for the treatment of aSAH. In particular, several studies have shown that heparin and its low molecular weight derivative (enoxaparin) reduce the incidence of clinical vasospasm and delayed cerebral infarction after aSAH [11–14]. Despite inconsistencies in the literature, previous reviews accede to the notion that heparin acts to prevent delayed cerebral ischemia by aSAH [11,15,16]. In addition to vasospasm, heparin can improve the outcomes of aSAH by preventing inflammation and promoting restoration of blood-brain barrier integrity. Given the adverse side effects of aSAH, which include inflammation, edema, and increased blood-brain barrier dysfunction, these extravascular effects of heparin are more important therapeutic considerations than the prevention of vasospasm [11].

4.2. Heparinization amount

Studies on the use of heparin in patients with aneurysmal SAH have been reported for low- and high-dose heparin after endovascular treatment. Simard et al. [12] showed heparin antagonizes many pathophysiological mechanisms associated with secondary brain injury following aSAH, and suggested postoperative low-dose intravenous heparin infusion may be relatively safe and beneficial. In contrast, Post et al. [17] reported that the incidences of delayed cerebral ischemia (DCI) in patients with aSAH administered low molecular weight heparin (LMWH) at high or low doses were similar, but noted patients given a high dose were more likely to be discharged to home and had a lower mortality rate [17]. However, these studies on dosage focused mainly on delayed cerebral ischemic improvements after surgery in patients with aSAH, and comparatively little is known of the relation between intraoperative heparin and thromboembolic complications encountered during or immediately after endovascular treatment.

Although the effects of heparin loading before endovascular embolization for aSAH have not been well-studied, several case reports have been issued on intraoperative heparin loading at various doses (3000–10000 IU) [5,9,18]. In the present study, heparin was administered at a relatively high dose of 5000 IU through a femoral sheath and...
maintained by flushing with a 5000 IU/1 L normal saline mixture through a guiding catheter and microcatheters during procedures.

4.3. Heparinization timing and method

Several studies have been conducted on systemic heparinization after surgery or heparin injection during endovascular treatments to investigate the effects of administration methods and timings on thromboembolic complications. Vance et al. [3] performed continuous systemic heparinization for 24 h after surgery to prevent thromboembolic complications occurring immediately after surgery, and concluded systemic heparinization after the endovascular treatment of ruptured intracranial aneurysms was safe. In this previous study, only 2 of 140 patients (1.4 %) that underwent postoperative systemic heparinization experienced a hemorrhagic complication requiring additional surgery. Nonetheless, though postoperative heparinization was considered stable, a thromboembolic complication occurred in 7.8 % of patients during endovascular treatment [3]. In contrast, in our study, a thromboembolic complication occurred in only 1.8 % of patients.

Antiplatelet therapy has also been attempted to reduce thromboembolic events during the endovascular treatment of ruptured cerebral aneurysms. Shimamura et al. [19] reported preoperative dual-antiplatelet therapy reduced thromboembolic events and did not increase bleeding complication rates. Ries et al. [20] reported that the intravenous administration of acetylsalicylic acid after first coil deployment reduced thromboembolic events during the endovascular embolization of ruptured or unruptured intracranial aneurysms.

Regarding the timing of heparinization, Cronqvist et al. [21] and Hilditch et al. [18] reported heparinization was best performed immediately after sheath insertion, whereas Pelz et al. [22] concluded that bolus heparin injection was best performed prior to commencing the endovascular treatment of acute aSAH (as was performed in the present study). Nomura et al. [5] in a delayed heparinization study, reported thromboembolism occurred during placement of the first coil, and suggested the optimal timing of systemic heparinization might be immediately after guiding catheter placement.

4.4. Postoperative bleeding risk

The risk factors of bleeding complications immediately after the endovascular treatment of ruptured aneurysms in patients with aSAH have not been clearly elucidated. The rate of rebleeding during surgery has been reported to range from 6% to 15 % [23], whereas in the present study it was 14.7 %. Several authors have reported remote bleeding during/after endovascular coiling in aSAH. Hilditch et al. [18] claimed hematoma-induced Sylvian expansion can damage small pial branches and increase the risk of bleeding in the subpial space, and proposed anticoagulant doses be reduced during the endovascular treatment of aSAH patients with Sylvian hematoma [18]. In the present study, intraoperative heparinization use to prevent thromboembolic events associated with endovascular treatment, was found to be relatively safe. However, preoperative modified Fisher grade was identified as a risk factor of immediate postoperative rebleeding, which suggests preoperative hemorrhage amount is an important indicator of remote hemorrhage in aSAH.

Our analysis also identified EVD as a risk factor of rebleeding. Lord et al. [24] reported medical complications such as respiratory failure, hyponatremia, fever, and hydrocephalus were associated with rebleeding during hospitalization. In the present study, EVD was performed in cases of acute hydrocephalus attributed to intraventricular hemorrhage (IVH), and lumbar drainage was performed when hemorrhage amounts were relatively small.

4.5. Clinical implications

In our cohort, catheter flushing was maintained using a heparin/saline mix (5000 IU in 1 L of normal saline) in all patients. In addition, in the heparin-loaded group, 5000 IUs of heparin were loaded through a femoral sheath at the beginning of procedures, and the results obtained showed that rebleeding rates did not increase in the heparin-loaded group. Therefore, we recommend an appropriate dose of heparin be administered to prevent thromboembolic events even during the endovascular treatment of ruptured aneurysms.

4.6. Limitations

This study is inherently limited by its non-randomized, retrospective, single-center design, and the relatively small number of cases included, which limit the generalizabilities of our findings. Furthermore, heparin loading and procedural specifics were determined by surgeons, In addition, prothrombin times were not routinely measured in the heparin-loaded group, and a heparin loading dose of 5000 IU was used throughout.

Therefore, we suggest a large-scale, multicenter, prospective study be conducted to determine appropriate heparin loading for thromboembolic event prevention during the endovascular treatment of ruptured aneurysms.

5. Conclusion

The results of our study favor heparin loading to prevent possible thromboembolic complications during the endovascular treatment of intracranial aneurysms. Heparin loading during endovascular embolization for even ruptured aneurysms can be used relatively reliably...
because it does not increase the risks of hemorrhagic complications such as rebleeding. However, the present study shows the risk of rebleeding after aSAH is greater in patients with large hemorrhage amounts and a high pre-operative modified Fisher grade, and thus, cautions the use of heparin be carefully considered in such cases. A large-scale prospective study is needed to optimize the procedure with respect to heparin bolus dosage and timing.

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CRediT authorship contribution statement

Jongwook Choi: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft. Youn moo Koo: Investigation, Data curation. Kum Whang: Validation. Sungmin Cho: Visualization. Jongyeon Kim: Conceptualization, Writing - review & editing, Supervision, Project administration.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

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