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The effects of timing of aneurysm surgery on vasospasm and mortality in patients with Subarachnoid Hemorrhage

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Abstract

Objective: The purpose of the present study was to compare the effects of early and late surgery on post-operative vasospasm and mortality in patients with subarachnoid hemorrhage (SAH).

Methods: The data of patients with SAH who underwent aneurysmal clipping at the Kartal Training and Research Hospital between 1999 and 2005 were retrospectively analyzed. The patients who underwent early (0-3 days) and late surgery (≥ 4 days) were evaluated as two groups. Patient outcomes were assessed 1 month after surgery.

Results: Of 159 patients (mean age, 49 years; 71 males) with SAHs, 135 (mean age, 51 years; 55 males) underwent early surgery and 24 patients (mean age, 56 years; 16 males) underwent late surgery. The overall post-operative vasospasm rate was 10.7%. The rate of post-operative vasospasm was significantly higher in the late surgery group (41.7%) compared to the early surgery group (5.2%; $p < 0.001$). There were 15 post-operative deaths (9.4%). The mortality rate in the late surgery group (25.0%) was significantly higher than the early surgery group (6.7%; $p = 0.005$).

Conclusions: The present study has demonstrated that early surgery is advantageous over late surgery in patients with SAH with lower post-operative vasospasm and mortality rates.

Key words: Subarachnoid hemorrhage; timing of aneurysmal surgery; intracranial aneurysms; outcomes; vasospasm; mortality.

Introduction

Subarachnoid hemorrhage (SAH), which accounts for approximately 5% of all strokes, is a devastating condition with a high morbidity and mortality (1, 4). There is still no consensus on the optimal timing of surgery for the treatment of aneurysmal SAH (13, 19). The optimal timing of surgery has been addressed in several early non-randomized trials (3, 8, 9, 20) and in one randomized trial (14); however, no difference has been demonstrated between early and late surgery. Additionally, in a recent observational study conducted in the Netherlands (13), no significant difference in outcome was reported between early and late surgery for patients in good clinical condition, and it was reported that outcome was significantly better after early surgery in patients with poor clinical condition on admission. There is a tendency towards the early surgery (1, 11) as it enables the prevention of rebleeding (9, 17, 19, 20), aggressive treatment of vasospasm and treatment of ischemic complications. Moreover, early surgery shortens the duration of hospitalization (1, 17, 20). Although it is advantageous in many aspects, early surgery is often avoided due to the risk of surgical morbidity and mortality (9, 10, 17). In their study reviewing the advantages of delayed surgery against early surgery, Maurice-Williams *et al.* (10) stated that they continued to adhere to a policy of postponed surgery. However, they emphasized that early surgery, but not delayed surgery, was advisable for patients with large intracerebral hematomas causing acute brain compression and for patients in good clinical condition who had a second hemorrhage from which the patient would quickly recover without ill effects (10).

The purpose of the present retrospective, single-center, comparative study was to evaluate the effects of early and late surgery on vasospasm and mortality in patients with SAH who underwent surgical clipping.

Material and methods

In the present single-center, retrospective study, patients with SAH in whom saccular aneurysms

were surgically treated at the Kartal Training and Research Hospital between 1999 and 2005 were evaluated. The data of patients, including operative reports, patient histories, discharge summaries, and radiological examinations were retrospectively reviewed from the hospital records. The eligibility of the patients was assessed according to pre-defined inclusion criteria. The patients admitted to the hospital with SAH based on computed tomography (CT), underwent an angiography within 72 hours of the SAH to confirm an aneurysm as the reason of the bleeding. Patients with a score of 9 or more on the Glasgow Coma Scale were included in the study. All patients with a confirmed aneurysm rupture were offered and received surgical clipping. The patients who were not surgical candidates due to advanced age or the presence of co-morbidities were excluded from the study.

The pre- and post-operative management and anesthesia protocols were identical in all patients. On admission, the clinical condition of each patient was assessed according to the World Federation of Neurological Surgeons (WFNS) scale (21). All patients received steroids, anti-convulsants, a benzodiazepine tranquilizer, opioid analgesics, a laxative, and nimodipine pre-operatively. Therapy with steroids, anti-convulsants, and nimodipine was continued post-operatively. Patients with WFNS grades II-IV were also treated with hypertension, hypervolemia, and hemodilution (triple-H) therapy. Patient outcomes were assessed 1 month post-operatively.

In the present study, early surgery was defined as a surgery performed within 72 hours after SAH, whereas late surgery was performed 4 or more days after SAH.

Statistical Analysis

Statistical analysis was performed using the Statistical Program for Social Sciences (version 15.0; SPSS Inc., Chicago, IL, USA). Categorical variables were expressed as numbers and percentages. Group comparisons were performed using the chi-square test for categorical variables. A p value < 0.05 was considered statistically significant.

Results

Among the 183 patients fulfilling the pre-defined inclusion criteria, 24 were excluded due to advanced age or an existing co-morbidity. Thus, a total of 159 patients (mean age, 49 years; 71 males and 88 females) with SAH who underwent surgical clipping were eligible for the analysis. Of 159 patients, 135 (mean age, 51 years; 55 males [40.7%] and 80 females [59.3%]) underwent early surgery (days 0-3) and 24 (mean age, 56 years; 16 males [66.7%] and 8 females [33.3%]) underwent late surgery (days 4-10). The number of female patients in the early surgery group was significantly higher compared to the number of male patients ($p = 0.019$), whereas the number of male patients were significantly higher in the late surgery group compared to the number of females ($p = 0.019$). Of the 135 patients in the early surgery group, 8 had multiple aneurysms (2 aneurysms in 7 patients and 3 aneurysms in 1 patient). Seven of these patients had bilateral aneurysms; 6 giant aneurysms were identified in these patients. Of 159 patients 30 (18.9%) had intracerebral hemorrhage, whereas 80 (50.3%) had intraventricular hemorrhage. Twenty-five patients (18.5%) in the early surgery group and 5 patients (20.8%) in the late surgery group had intracerebral hemorrhages. Sixty-six patients (48.9%) in the early surgery group and 14 patients (58.3%) in the late surgery group had intraventricular hemorrhages. There were no significant differences between the early and late surgery groups regarding the rates of intracerebral and intraventricular hemorrhages ($p = 0.789$ and $p = 0.394$, respectively). The general characteristics of the entire study population and early and late surgery groups on admission are presented in (Table 1).

Delayed ischemic neurologic deterioration (DIND) attributable to ischemia or vasospasm was encountered in a total of 17 patients (10.7%) during the post-operative period. Five (29.4%) of these patients also had vasospasm on the angiogram taken pre-operatively. The rate of post-operative vasospasm was significantly higher in the late surgery group (41.7% [10 patients]) compared to the early surgery group (5.2% [7 patients]; $p < 0.001$).

There were 15 post-operative deaths and the overall post-operative mortality rate was 9.4%. The mortality rate in the late surgery group (25.0% [6 patients]) was significantly higher than the early surgery group (6.7% [9 patients]; $p = 0.005$).

Discussion

The major controversial issue regarding the management of SAH is the timing of surgery (13, 19). SAH, without treatment, from a ruptured intracranial aneurysm is a serious medical condition with a mortality of 50%-60%, and a morbidity of 20%-30% (16). The importance of early referral to specialized centers and the increasing tendency towards early surgery has been emphasized in the guidelines on the management of SAH (1, 11). The present retrospective study comparing patients undergoing

Table 1

The general characteristics of the study population, and early and late surgery groups on admission

	Study population (n = 159)	Early surgery group (n = 135)	Late surgery group (n = 24)
Gender (F/M)	88/71	80/55	8/16
Mean age, years	49	51	56
WFNS scale (n, %)			
Grade 1	65 (40.9)	58 (42.9)	7 (29.2)
Grade 2	62 (38.9)	53 (39.3)	9 (37.5)
Grade 3	20 (12.6)	17 (12.6)	3 (12.5)
Grade 4	9 (5.7)	5 (3.7)	4 (16.7)
Grade 5	3 (1.9)	2 (1.5)	1 (4.1)
Location of aneurysm (n, %)			
ACoA	52 (32.7)	42 (31.1)	10 (41.7)
MCA	45 (28.3)	39 (28.9)	6 (25.0)
PCoA	25 (15.7)	22 (16.3)	3 (12.5)
ICA	20 (12.6)	19 (14.1)	1 (4.1)
Others	17 (10.7)	13 (9.6)	4 (16.7)

F: Female, M: Male, WFNS: World Federation of Neurological Surgeons, ACoA: Anterior communicating artery, MCA: Middle cerebral artery, PCoA: Posterior communicating artery, ICA: Internal cerebral artery.

early and late surgery for SAH demonstrated that early surgery was superior to late surgery with respect to vasospasm and mortality rates.

There are several studies in which early surgery has been compared with late surgery in patients with SAH; however, the optimal timing of surgery has not been determined (3, 8, 9, 13, 20). In the study by Miyazawa *et al.* (12), the clinical factors affecting the outcome of patients with ruptured distal anterior cerebral artery aneurysms were determined; the clinical grade and timing of aneurysm surgery were reported to be the significant factors affecting the outcomes of patients according to multivariate analysis. The tendency towards early surgery in recent years (1) is principally due to its associated advantages. Early surgery, while eliminating the risk of bleeding (9, 17, 20), may lower the occurrence of vasospasm by enabling lavage of the subarachnoid space. Moreover, early intervention may also render the prevention and treatment of complication possible and shorten the duration of hospitalization (1, 17, 20).

The major drawbacks of early surgery are surgery-associated morbidity and mortality (9, 10, 17). In the study by Haley *et al.* (5), the results of the International Cooperative Study on the Timing of Aneurysmal Surgery (8, 9) were analyzed in the subgroup of patients admitted to North American centers (5). In contrast to the overall results of the International Cooperative Study (8, 9), Haley *et al.* (12) reported that patients undergoing early surgery (0-3 days after SAH) had significantly higher rates of recovery and equivalent overall outcomes with respect to mortality compared to patients undergoing surgery between days 11 and 32. In the prospective phase of a study by Whitfield *et al.* (20), in which patients were assigned to early (0-3 days) or late (after day 3) surgery groups, a tendency towards lower mortality was reported in the early group compared to the late group (11% vs. 22%). Similarly, the mortality rate of the early surgery group (6.7%) in the current study was significantly lower than the late surgery group (25.0%).

Based on the guidelines of SAH management, early surgery is effective in the aggressive therapy of vasospasm (1, 11). In the present study, the effects of early and late surgery on post-operative vasospasm were compared, and it was observed that the rate of post-operative vasospasm was significantly lower in the early surgery group (5.2%). compared to the late (41.7%) surgery group. The incidence of cerebral vasospasm increases between days 7 and 10 following SAH (9, 10, 15, 20). In the International Cooperative Study on the Timing of Aneurysm Surgery, the worst outcomes were reported in patients undergoing surgery between days 7 and 10, and this was attributed to the effects of vasospasm (5, 8, 9). Similarly, we also observed a high frequency of vasospasm in the late surgery group who underwent surgery between days 3 and 10.

Rebleeding is also a major issue related to high mortality in patients with SAH. In the study by Roos *et al.* (15), it has been stated that rebleeding is still the major cause of poor outcome in early surgery, although early surgery is known to lower the rates of

rebleeding (9, 17, 19, 20). Because of the retrospective nature of the present study, rebleeding could not be assessed as a patient outcome, which may be considered a limitation to the study.

Considering that cerebral vasospasm and ischemia are mostly encountered in the intermediate period (days 4-10 of the primary SAH) (9) and that initial bleeding, vasospasm, and re-bleeding are the major causes of morbidity and mortality associated with SAH (2, 6-8, 15), early surgery is recommended (1, 11). The results of the present study demonstrated that early surgery led to lower post-operative mortality and vasospasm rates in patients with SAH who underwent aneurysmal clipping. However, contemporary, prospective, randomized trials with large sample sizes are required to highlight the advantages and disadvantages of early surgery to late surgery in SAH patients.

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