ORIGINAL ARTICLE

The effects of the early and ultra-early intervention on the outcome in aneurysmatic subarachnoid hemorrhage

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ABSTRACT

BACKGROUND: The optimal timing of intervention for aneurysmatic subarachnoid hemorrhage is one of the historically controversial issues in neurosurgery. Although numerous studies investigated the subject, they had many limitations due to the nature of the disease. Early and ultra-early interventions have gained more and more supporters in recent decades. Nevertheless, the effects of the early and ultra-early intervention on the outcome of the disease are far from clarity.

METHODS: A single-center retrospective cohort study was carried out at Trakya University Medical Faculty Training and Practice Hospital. The study includes data on all patients admitted with an aneurysmal subarachnoid hemorrhage between January 1, 2001, and December 31, 2005. Patients were divided into two groups according to their WFNS grade status: Good (I–III) or poor (IV–V) grades. Patients are also classified according to their Glasgow Outcome Scale score: Unfavorable (1–2) or favorable (3–5) outcomes. Data were analyzed statistically, and the effects of the early and ultra-early intervention on the outcome were assessed.

RESULTS: A total of 580 patients were admitted in the study period. Among them, 494 were eligible for the study. The median age (interquartile range) was 55 (18) years. While 244 (49.4%) patients were women, 250 (50.6%) patients were men. Three hundred and fourteen (63.6%) patients were operated, and 25 patients (5.1%) were undergone endovascular treatment. The ultra-early intervention was achieved in 60 (12.1%) patients and 142 patients (28.7%, including the previous ultra-early intervention group) early intervention was achieved. A meaningful outcome difference was present between the poor-grade ultra-early treatment group and the rest (p=0.007). Analogously, a meaningful outcome difference was present between the poor-grade early treatment group and the rest (p<0.001).

CONCLUSION: This study supports the growing trend toward early or ultra-early intervention in aneurysmatic subarachnoid hemorrhage. Our findings showed that both early and ultra-early interventions have positive effects on the outcome in poor-grade aneurysmatic subarachnoid hemorrhage patients. Future studies with more homogenized and larger samples should be realized to clarify the optimal timing of intervention for aneurysmatic subarachnoid hemorrhage.

Keywords: Intracranial aneurysm; outcome; subarachnoid hemorrhage; timing; Turkey.

INTRODUCTION

For aneurysmatic subarachnoid hemorrhage (aSAH), a disease with high mortality and morbidity leading to a substantial burden for the society, the optimal timing of aneurysm intervention is one of the historically controversial issues in neurosurgery.[1–4] Ingall et al.[5] reported that aSAH incidence varies from 5.2/100,000 people/year in Valle d'Aosta to 19.4/100,000 people/year in Central Finland. We carried out this study in Edirne, Turkey, where Simsek et al.[6] reported the incidence of aSAH as 10.3/100,000 people/year for patients who could reach the hospital.

The ratio of rebleeding after aSAH has been reported between 8% and 23% in the first 72 h.[7] In-hospital rebleeding occurs mostly in the first 24 h (5.8%) or between 24 and 72

Cite this article as: Akıncı AT, Aktürk Y, Tütüncüler B, Orakdöğen M, Şimşek O. The effects of the early and ultra-early intervention on the outcome in aneurysmatic subarachnoid hemorrhage. Ulus Travma Acil Cerrahi Derg 2021;27:449-456.

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Ulus Travma Acil Cerrahi Derg 2021;27(4):449-456 DOI: 10.14744/tjtes.2020.49196 Submitted: 27.03.2020 Accepted: 09.06.2020

h time frame after the initial bleeding (1.2%).[8] Overtime, as the median of treatment day decreased from day 4 to day 1, consecutively, the median day of rebleeding decreased from day 5 to day 0, and the in-hospital rebleeding ratios declined from 24% to 17%.[9]

While vasospasm is the cause of death in 10–23% of aSAH patients, it results in disability in 25–50% of survivors; only 30–45% of survivors can return to their previous jobs.[10] Although radiological vasospasm is detected in 67.3% of patients, it leads to a deficit only in 32.6% of patients.[11]

In their study published in 2010, Lovelock et al.[12] reported that mortality due to subarachnoid hemorrhage (SAH) has dropped by about 50% in the past two decades. However, mortality rates were reported as approximately 50% in 1 month after bleeding without treatment.[13] Although aSAH accounts for only 3–5% of all strokes, the loss of productive life years is equal to that of ischemic strokes.[14] Even though this high mortality and morbidity have been reduced overtime thanks to changes on the management such as early or ultra-early surgery and endovascular coiling, the optimal timing of the aneurysm intervention is still unclear, either surgical or endovascular.

Although studies to determine the effect of surgical timing on outcome in SAH are quite numerous, they have many limitations due to the nature of the disease and the historical development of the methods for diagnosis and treatment. Most studies are retrospective, non-randomized, and have small sample volumes.[4,6,15]

The vast majority of these studies in the literature were carried out in socioeconomically developed countries.[6] With the addition of inequalities in diagnosis and treatment opportunities to regional differences in the epidemiology of the disease, the difficulty in projecting limited literature data to a specific country/region becomes more evident.

With this study, the effects of ultra-early and early intervention on the outcome of the disease in aneurysmatic subarachnoid hemorrhage will reveal more information about the optimal timing of aneurysm intervention. More effective treatment of this disease, which has high mortality and morbidity, and therefore a high cost to the society, will help to reduce these burdens of the disease.

In our study, we aimed to determine the effect of ultra-early and early intervention on the outcome by analyzing the demographic, radiological, and clinical data of the patients treated for aneurysmatic subarachnoid hemorrhage. Trakya University Ethics Committee approved the study (Decision number: TUTF-BAEK 2019/383). In such studies, written informed consent was not required due to the retrospective and anonymous nature of the analysis.

MATERIALS AND METHODS

Study Design

This study was planned as a single-center retrospective cohort study. The study was carried out at Trakya University Medical Faculty Training and Practice Hospital. Trakya University Faculty of Medicine, Department of Neurosurgery, is the leading center in the Thrace Region, where the vast majority of patients are referred. Digital subtraction angiography and aneurysm clips set, that is, endovascular and surgical treatment for aneurysmatic subarachnoid hemorrhage can only be applied in our institution.

The study includes all patients admitted to our institution with an aneurysmal subarachnoid hemorrhage (aSAH) between January 1, 2001, and December 31, 2015. We investigated all electronic and printed patient medical files retrospectively. We recorded information of patients who were followed up and treated with the diagnosis of aneurysmatic subarachnoid hemorrhage in our hospital between January 1, 2001, and December 31, 2015.

Inclusion Criteria

The predefined inclusion criteria were as follows: (1) The demonstration of SAH on CT or LP. (2) The presence of a confirmed aneurysm or the death of the patient with SAH with a pattern highly suggesting an aneurysm, before further investigation. (3) The necessary data were complete. The predefined exclusion criteria were as follows: (1) The aneurysm never ruptured (incidental). (2) The etiology of the hemorrhage was not an aneurysm. (3) The necessary data were missing or incomplete.

Data Acquirement

We obtained patients' data from written and electronic medical records. We recorded patients' age, gender, computed tomography, magnetic resonance imaging and digital subtraction angiography, lumbar puncture findings, clinical severity of SAH (evaluated by the World Federation of Neurosurgical Societies [WFNS] Grade), the treatment method and timing, and the outcome (evaluated by the Glasgow Outcome Scale [GOS]) data in a computer database.

Definitions

We defined ultra-early treatment as the treatment performed within 24 h after the rupture of the aneurysm. We defined early treatment as the treatment performed within 72 h after the rupture of the aneurysm. We divided patients into two groups according to their WFNS grade status. A good grade is defined for patients with WFNS Grade I–III and a poor grade is defined for those with WFNS Grades IV or V. Outcome status at discharge was assessed using the GOS score. A GOS score of 3–5 was considered a favorable outcome and a GOS score of 1 or 2 as an unfavorable outcome.

Statistical Analysis

Results are expressed as mean ± standard deviation, as median (interquartile range) or as percentages where appropriate. Average or median values for continuous variables, frequency numbers, and percentages for categorical variables were calculated. Mann–Whitney U and Chi-square tests were performed whenever appropriate. The level of significance was accepted as p≤0.05. IBM© SPSS© Statistics version 21 package program was used for statistical analysis.

RESULTS

We identified a total of 580 patients admitted with aSAH in the study period. Among them, 494 were eligible according to the inclusion criteria; thus, 86 patients were excluded from the study. The median age (interquartile range) of the 494 patients with aSAH was 55 (18) years. While 244 (49.4%) patients were women, 250 (50.6%) patients were men. For the diagnosis of SAH, a CT scan was used for 486 (98.4%) patients, an MRI scan for 84 (17%), and a lumbar puncture for 14 (2.8%) patients.

Data on patients' distribution according to WFNS grades and the dichotomized classification as good or poor are summarized in Tables 1 and 2. For further investigation, a DSA was performed on 258 (52.2%), and an MRI angiography was performed on 95 (19.2%) patients. Seventy-seven patients (15.6%) were operated without further investigation of the aneurysm by DSA or an MRI angiography.

Three hundred and fourteen (63.6%) patients were operated, and 25 patients (5.1%) were undergone endovascular treatment. Sixty (12.1%) patients were treated within 24 h, and 142 patients (28.7%, including the previous 24 h group) were treated within the first 72 h. The average time between the onsets of the hemorrhage to the intervention was 9.6±15.1 days.

The distribution of the patients' outcomes according to GOS and the dichotomized classification as favorable or unfavorable is summarized in Tables 3 and 4, respectively. Rebleeding happened in 41 (8.3%) patients.

Among 221 patients (44.7%) who died, 76 patients were operated, four patients were treated endovascularly, one patient was treated by endovascularly and also surgically, and 142 patients died without any treatment. One hundred and nineteen (24.1% of total) patients died before a further investigation for the aneurysm. The median time to death (interquartile range) was 8 (14.8) days after the onset of the hemorrhage. Survival rates for deceased patients classified according to dichotomized grades and intervention timings are depicted in Kaplan–Meier graphics (Figs. 1a and b; 2a and b). Survival rates for deceased patients classified according to their operational status are depicted in Figure 3.

In the ultra-early treatment group, 21 patients out of 60 died, and in the early treatment group, 45 patients out of 142 died; thus, mortality rates were 35% and 31.7%, respectively. A Chi-square test before any classification showed no statistical difference between the distribution of patients with a favorable outcome and unfavorable outcome between the ultra-early treatment group and the rest (p=0.159).

There was a meaningful difference between the distribution of patients with a favorable outcome and unfavorable outcome between the early treatment group and the rest (p<0.001). Further analysis for good- and poor-grade WFNS subgroups

Table 1. WFNS grades

WFNS grades	Counts	% of Total	Cumulative (%)
1	189	38.3	38.3
2	87	17.6	55.9
3	32	6.5	62.3
4	103	20.9	83.2
5	83	16.8	100.0

WFNS: World Federation of Neurosurgical Societies.

Table 2. Cumulative WFNS Grades

WFNS grades	Counts	% of Total	Cumulative (%)
1–3	308	62.3	62.3
4–5	186	37.7	100.0

WFNS: World Federation of Neurosurgical Societies.

Table 3. Frequencies of Outcome (GOS)

Levels	Counts	% of Total	Cumulative (%)
1	221	44.7	44.7
2	2	0.4	45.1
3	40	8.1	53.2
4	52	10.5	63.8
5	179	36.2	100.0

GOS: Glasgow Outcome Scale.

Table 4. Frequencies of Outcome (1. Unfavorable/2. Favorable)

Levels	Counts	% of Total	Cumulative (%)
1	223	45.1	45.1
2	271	54.9	100.0

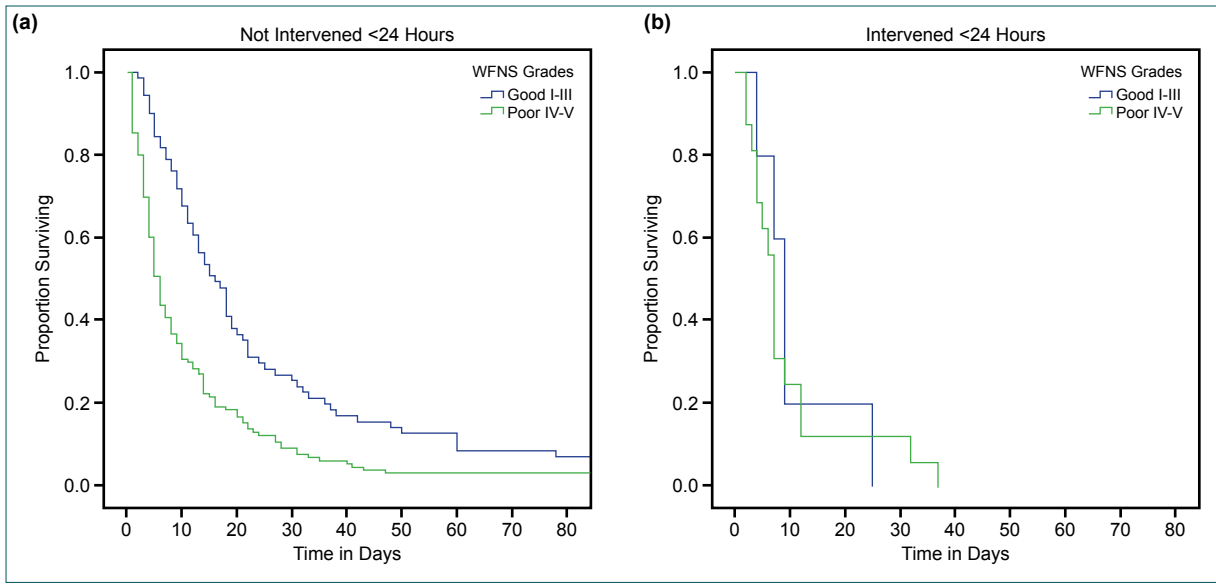

Figure 1. (a, b) Survival graphics of the deceased patients according to the ultra-early intervention and the WFNS grades. WFNS: World Federation of Neurosurgical Societies.

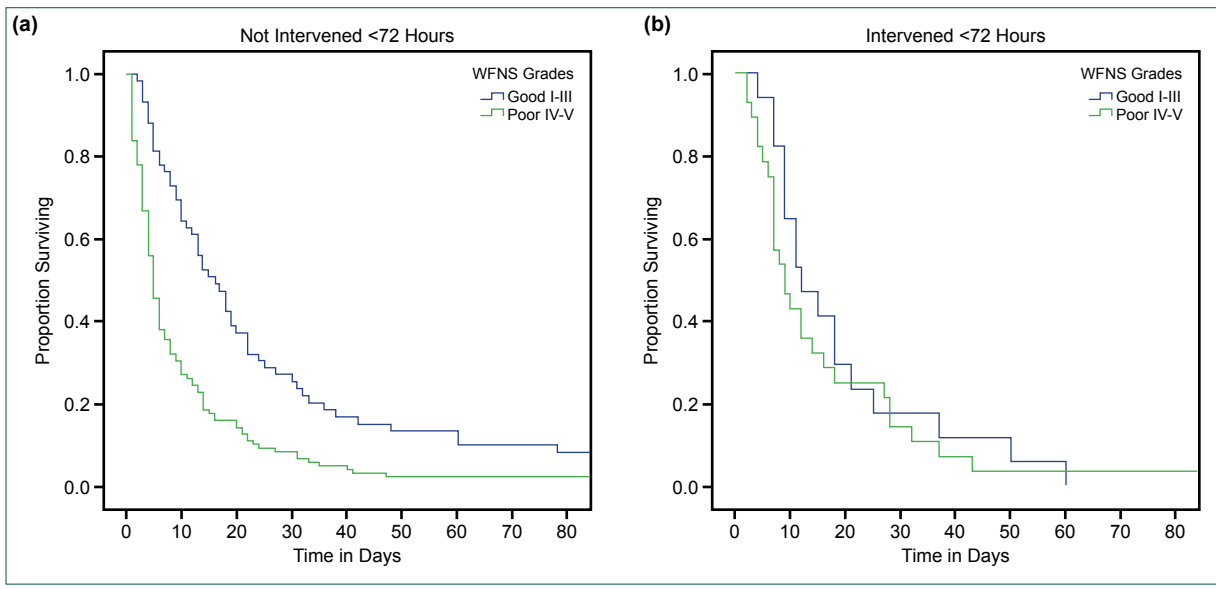

Figure 2. (a, b) Survival graphics of the deceased patients according to the early intervention and the WFNS grades. WFNS: World Federation of Neurosurgical Societies.

showed no statistical outcome difference between the good-grade ultra-early treatment group and the rest (p=0.224), nevertheless, a meaningful outcome difference was present between the poor-grade ultra-early treatment group and the rest (p=0.007).

Further analysis for early treatment group showed a trend for the outcome difference between the good-grade early treatment group and the rest (p=0.058), analogously, a meaningful outcome difference was present between the poor-grade early treatment group and the rest (p<0.001). The results are summarized in Tables 5 and 6 in addition to Figure 1a and b.

DISCUSSION

With the introduction of angiography, McKissock et al.[16–18] started by questioning the effect of surgical intervention on the natural course. Chyatte et al.[19] reported that morbidity and mortality occur primarily as a direct result of severe initial bleeding; therefore, the measured benefits of early surgery might be less than predicted. Öhman and Heiskanen[20] concluded that surgery performed in the acute phase was leading to better results than delayed surgery.

Subsequent large-scale studies have shown that rebleeding and vasospasm are the leading causes of 30-day mortality

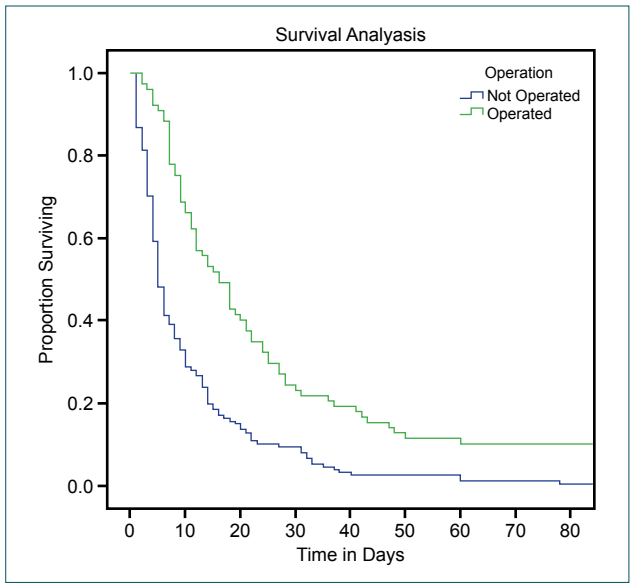

Figure 3. Survival analysis of the deceased patients according to overall surgical intervention.

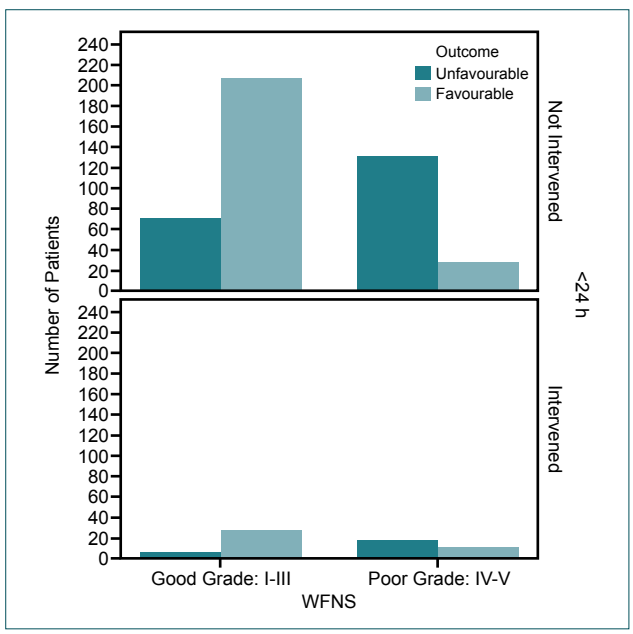

Figure 4. Distribution of the patients according to the ultra-early intervention, the outcome, and the WFNS grades. WFNS: World Federation of Neurosurgical Societies.

and morbidity after SAH.[21,22] Broderick et al.[23] reported that studies excluding patients with poor grades at the time of admission largely underestimate the importance of first bleeding and emphasize the importance of vasospasm. Fogelholm et al.[24] reported that the rate of patients who underwent surgery increased from 14% in the 1970s to 46% in the 1980s and the average time from bleeding to the intervention was shortened from 15 days to 4 days. Although a more active treatment policy was implemented in their institution in the 1980s, the survival improved just slightly.

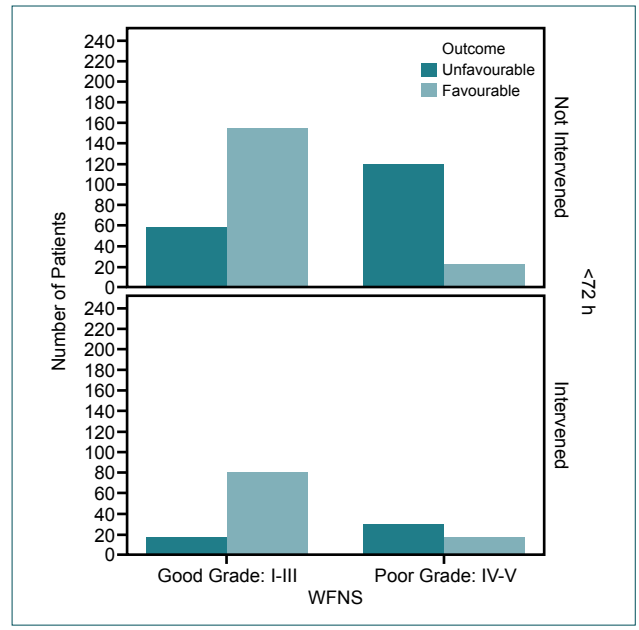

Figure 5. Distribution of the patients according to the early intervention, the outcome, and the WFNS grades. WFNS: World Federation of Neurosurgical Societies.

De Gans et al.[15] reported that both early and mid-term surgical treatment improved the outcome after aneurysmal SAH, especially for patients with functional clinical status at admission. However, they added that this impression was only due to an indirect comparison between different patient groups, and there is still no solid evidence of the best timing of the surgery. They also indicated observational studies with better methods and ideally, a new randomized study requirement.

Our findings correlated with the literature in terms of the benefit of early intervention.[25–27] We found a trend for the outcome difference between the good-grade early treatment group and the rest ($p=0.058$), which is very close to the 0.05 threshold. Furthermore, the outcome difference between the poor-grade early treatment group and the rest was distinctively meaningful ($p<0.001$).

Ultra-early treatment of ruptured aneurysms is associated with better clinical outcomes compared to treatment initiated over 24 h, and this advantage is more evident for coiling than clipping.[28] Wong et al.[29] reported that aneurysm treatment over 24 h was associated with a better outcome and halved the risk of clinical rebleeding in patients with poor-grade aneurysmal SAH. Mees et al.[30] also supported the current practice for early aneurysm treatment. They reported that the risk of an unfavorable outcome is highest when treatment is done after day 10th and that postponing treatment is not recommended in patients eligible for treatment between 5 and 10 days after SAH.

In our analysis, the positive effect of the ultra-early intervention on the outcome was prominent for the poor-grade group

Table 5. Effects of the ultra-early Intervention on the outcome according to WFNS grades

Grade (good/poor)	First day intervention	Outcome (unfavorable/favorable)		Total
		Unfavorable	Favorable	
Good	Not Intervened	70	206	276
	Intervened	5	27	32
	Total	75	233	308
Poor	Not Intervened	131	27	158
	Intervened	17	11	28
	Total	148	38	186
Total	Not Intervened	201	233	434
	Intervened	22	38	60
	Total	223	271	494

WFNS: World Federation of Neurosurgical Societies.

Table 6. Effects of the early intervention on the outcome according to WFNS grades

Grade (good/poor)	First 3 days intervention	Outcome (unfavorable/favorable)		Total
		Unfavorable	Favorable	
Good	Not Intervened	58	153	211
	Intervened	17	80	97
	Total	75	233	308
Poor	Not Intervened	119	22	141
	Intervened	29	16	45
	Total	148	38	186
Total	Not Intervened	177	175	352
	Intervened	46	96	142
	Total	223	271	494

WFNS: World Federation of Neurosurgical Societies.

($p<0.001$). Nevertheless, analogously to the early treatment, the outcome difference between the good-grade ultra-early treatment group and the rest was not significant.

Our findings also showed that we had high mortality: 221 patients out of 494 (44.7%) were deceased. We think that the main reason for this finding is our lack of optimal intensive care conditions. The early and ultra-early interventions seem to have positive effects on the outcome. Our belief is that as our intensive care conditions and technical facilities improve, the positive effects on the results will become more evident. This study supports the growing trend toward performing early or even ultra-early intervention in aneurysmatic subarachnoid hemorrhage.[31–34] Our findings showed that both early and ultra-early interventions have positive effects on the outcome in poor-grade aneurysmatic subarachnoid hemorrhage patients. Future studies with more homogenized and larger samples should be realized to clarify the optimal timing of intervention for aneurysmatic subarachnoid hemorrhage.

Ethics Committee Approval: All procedures performed in studies involving human participants were following the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Trakya University Faculty of Medicine Ethics Committee approved the study (Date: 06.11.2019, Decision number: TUTF-BAEK 2019/383).

Peer-review: Internally peer-reviewed.

Authorship Contributions: Concept: A.T.A., M.O., O.Ş.; Design: A.T.A., M.O., O.Ş.; Supervision: A.T.A., M.O., O.Ş.; Resource: A.T.A., Y.A., O.Ş.; Data: A.T.A., Y.A., O.Ş.; Analysis: A.T.A., Y.A., B.T., O.Ş.; Literature search: A.T.A., Y.A., B.T., O.Ş.; Writing: A.T.A., Y.A., B.T., M.O., O.Ş.; Critical revision: A.T.A., Y.A., B.T., M.O., O.Ş.

Conflict of Interest: All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

Financial Disclosure: The authors declared that this study has received no financial support.

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ORİJİNAL ÇALIŞMA - *ÖZ*

Erken ve ultra-erken müdahalenin anevrizmatik subaraknoid kanamada sonuç üzerine etkileri

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AMAÇ: Anevrizmatik subaraknoid kanama için optimal müdahale zamanlaması nöroşirürjide tarihsel olarak tartışmalı konulardan biridir. Çok sayıda çalışma konuya değinmesine rağmen, hastalığın doğası nedeniyle bu çalışmaların birçok sınırlamaları vardır. Erken ve ultra-erken müdahaleler son yıllarda giderek daha fazla destekçiye ulaşmıştır. Bununla birlikte, erken ve ultra-erken müdahalenin hastalığın sondurumu üzerindeki etkileri netlik kazanmamıştır.

GEREÇ VE YÖNTEM: Trakya Üniversitesi Tıp Fakültesi Eğitim ve Uygulama Hastanesi'nde tek merkezli geriye dönük bir kohort çalışması yapıldı. Çalışma, 1 Ocak 2001 ve 31 Aralık 2015 tarihleri arasında anevrizmal subaraknoid kanama ile başvuran tüm hastalara ait verileri içerdi. Hastalar WFNS Derecelerine göre "İyi Derece (I-III)" veya "Kötü Derece (IV-V)" olmak üzere iki gruba ayrıldı. Hastalar ayrıca Glasgow Sondurum Skalası puanlarına göre "Olumsuz (1–2)" veya "Olumlu (3–5)" sondurum olarak sınıflandırıldı. Veriler istatistiksel olarak analiz edilerek, erken ve ultra-erken müdahalenin sondurum üzerindeki etkileri değerlendirildi.

BULGULAR: Çalışma döneminde toplam 580 hasta kabul edildi. Bunlar arasından 494 hasta çalışma için uygun bulundu. Ortanca yaş (çeyrekler arası aralık) 55 (18) yıl idi. İki yüz kırk dört hasta (%49.4) kadın iken 250 hasta (%50.6) erkekti. Üç yüz on dört hasta (%63.6) ameliyat edildi ve 25 hastaya (%5.1) endovasküler tedavi uygulandı. Ultra-erken müdahale 60 hastada (%12.1), erken müdahale 142 hastada (%28.7) (bu grup ultra-erken müdahale grubunu da kapsamaktadır) sağlandı. Düşük dereceli ultra erken tedavi grubu ile diğerleri arasında anlamlı bir sondurum farkı mevcuttu ($p=0.007$). Benzer şekilde, düşük dereceli erken tedavi grubu ile diğerleri arasında anlamlı bir sondurum farkı vardı ($p<0.001$).

TARTIŞMA: Bu çalışma, anevrizmatik subaraknoid kanamada erken veya ultra-erken müdahaleye yönelik artan eğilimi desteklemektedir. Bulgularımız, hem erken hem de ultra-erken müdahalenin düşük dereceli anevrizmatik subaraknoid kanama hastalarında sondurum üzerinde olumlu etkileri olduğunu göstermiştir. Anevrizmatik subaraknoid kanama için en uygun müdahale zamanını açıklığa kavuşturmak için daha homojen ve büyük örneklerle yeni çalışmalar gerçekleştirilmelidir.

Anahtar sözcükler: İntrakraniyal anevrizma; sondurum; subaraknoid kanama, Türkiye; zamanlama.

Ulus Travma Acil Cerrahi Derg 2021;27(4):449-456 doi: 10.14744/tjtes.2020.49196