Ultra-Early Versus Early Aneurysm Surgery After Subarachnoid Hemorrhage: A Retrospective Outcome Analysis

Tratamento cirúrgico precoce versus ultra precoce de aneurismas cerebrais: Análise retrospectiva

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Abstract

Object The timing of definitive management of ruptured intracranial aneurysms has been the subject of considerable debate, although the benefits of early surgery (until 72 hours postictus) are widely accepted. The aim of the present study is to evaluate the potential benefit of ultra-early surgery (until 24 hours) when compared with early surgery, in those patients who were treated by surgical clipping at the Neurosurgery Department of the Coimbra Hospital and University Centre.

Methods A 17-year database of consecutive ruptured and surgically treated intracranial aneurysms was analyzed. Outcome was measured by the Glasgow Outcome Scale (GOS). Baseline characteristics were analyzed by the Fisher exact test, the chi-squared and Mann-Whitney tests. Logistic regression was used to assess the impact of good grade according to the World Federation of Neurological Surgeons (WFNS) scale and ultra-early surgery in a good GOS outcome.

Results 343 patients who were submitted to surgical clipping in the first 72 hours postictus were included, 165 of whom have undergone ultra-early surgery. Demographics and preoperative characteristics of ultra-early and early surgery patients were similar. Good-grade patients according to the WFNS scale submitted to ultra-early surgery demonstrated an improved GOS at discharge and at 6 months. Poor-grade patients according to the WFNS scale submitted to ultra-early surgery demonstrated an improved GOS at discharge.

Keywords

- aneurysm
- early surgery
- subarachnoid hemorrhage
- ultra-early surgery
- neurosurgical clipping

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Conclusions Ultra-early surgery for aneurysmal subarachnoid hemorrhage patients improves outcome mainly on good-grade patients. Efforts should be made on the logistics of emergency departments to consider achieving treatment on this timeframe as a standard of care.

Resumo

Objetivos O *timing* de tratamento dos aneurismas intracranianos rotos tem sido objeto de debate considerável, embora os benefícios da cirurgia precoce (até 72 horas após ictus) sejam amplamente aceitos. O objetivo do presente estudo é avaliar o potencial benefício da cirurgia ultra precoce (até 24 horas) sobre a cirurgia precoce nos pacientes tratados por abordagem cirúrgica no Departamento de Neurocirurgia do Centro Hospitalar e Universitário de Coimbra.

Métodos Foi usada uma base de dados de 17 anos de aneurismas intracranianos que sofreram rotura e que foram tratados cirurgicamente. O resultado foi avaliado pela Escala de Glasgow de desfecho (GOS, na sigla em inglês). As características da população foram analisadas pelo teste de Fisher, qui-quadrado e Mann-Whitney. A regressão logística foi usada para avaliar o impacto do bom estado clínico à admissão (World Federation of Neurological Surgeons [WFNS]) e da cirurgia ultra precoce sobre o bom desfecho (GOS).

Resultados Foram incluídos 343 pacientes submetidos a clipagem cirúrgica nas primeiras 72 horas pós-ictus, 165 dos quais foram submetidos a cirurgia ultra precoce. As características demográficas e pré-operatórias dos pacientes submetidos a cirurgia ultra precoce e precoce foram semelhantes. Pacientes com bom WFNS submetidos a cirurgia ultra precoce demonstraram melhoria do desfecho na alta e aos 6 meses. Os pacientes com WFNS de baixo grau submetidos a cirurgia ultra precoce demonstraram melhoria do desfecho na alta.

Conclusões A cirurgia ultra precoce para pacientes com hemorragia subaracnoidea aneurismática melhora o resultado principalmente em pacientes com bom estado clínico à admissão (WFNS). Esforços devem ser feitos na logística dos departamentos de emergência, a fim de considerar o tratamento nesse período como *timing* preferencial.

Palavras-chave
- aneurisma cerebral
- cirurgia precoce
- cirurgia ultra precoce
- clipagem neurocirúrgica
- hemorragia subaracnoideia

Introduction

Besides the clinical impact of a primary aneurysmal subarachnoid hemorrhage (SAH), rebleeding and vasospasm are the major factors responsible for a poor outcome. Aneurysm treatment is the key to avoid rebleeding and may also have an important role on vasospasm occurrence and management.[1,2] Early surgery (within 72 hours) was shown to be safe and cost-effective as compared with delayed surgery. Considering that rebleeding rates may be maximal within the first 24 hours after aneurysmal SAH, ultra-early treatment (within the first 24 hours) seems an attractive strategy to lower rebleeding rates and improve the outcome.[3,4]

To date, the few studies designed to evaluate ultra-early aneurysm treatment effect have not demonstrated in an unambiguous way the beneficial effects from this time treatment.[1,5–10]

Currently, two treatment approaches are relevant, depending on the clinical status of the patient and the characteristics of the aneurysm: the endovascular technique and microsurgery – neurosurgical clipping. In this study, only patients undergoing surgical clipping were considered.

Since 2000, the Neurosurgery Department of the Coimbra Hospital and University Centre (CHUC) has treated patients admitted with SAH according to the early surgery protocol (first 72 hours). With the evolution of scientific knowledge and local logistic resources available (24 hours surgical prevention team), the ultra-early program (first 24 hours) was gradually implemented and currently is the gold-standard.

We undertook a retrospective audit of outcomes to assess the potential benefit of ultra-early surgery compared with early surgery, after outcome analysis of patients that were operated in Neurosurgery Department (ND) of CHUC.

Methods and Materials

A database of all intracranial aneurysms presented to this neurosurgery department was maintained prospectively over a 17-year period (2000 to 2016). The database was prospectively updated with long-term clinical outcome data. Patients with proven aneurysmal SAH who were submitted to surgery within the first 72 hours postictus were included. This series represents 343 cases of aneurysmal SAH treated by means of surgical clipping within the 0 to 72 hours postictus timeframe.

Patient demographics, World Federation of Neurological Surgeons (WFNS) clinical grade on admission, aneurysm location, time between SAH ictus and clipping were collected. The ictus was defined as the onset of headache or collapse. Clinical outcomes were measured at discharge and 6 months using the Glasgow Outcome Scale (GOS).

Subarachnoid hemorrhage was confirmed either by brain computed tomography (CT) or lumbar puncture and cerebrospinal fluid analysis. Intracranial aneurysms were diagnosed by CT angiography or by Digital Subtraction Angiography. Surgeries were performed by a team consisting of an experienced neurovascular surgeon (a total of four performed all of the surgeries), a neuroanesthesiologist and specially trained nurses. The policy of this Institution is to treat every ruptured aneurysm within 72 hours postictus, but preferably as soon as feasible, and efforts were made to perform ultra-early surgery whenever possible. The cases submitted to early surgery were not consequent to clinical decision but to other nonclinical factors such as delayed transfers from other hospitals, late diagnosis and hospital logistical delays.

Prophylactic nimodipine is initiated as part of the standard medical management of SAH in this institution. We do not routinely use antifibrinolytic drugs. Symptomatic hydrocephalus was managed either by external ventricular derivation or ventriculoperitoneal shunt. The treatment of vasospasm and delayed ischemic neurological deficits were managed on a case-by-case basis and included hyperdynamic therapy and, eventually, endovascular treatment.

The baseline characteristics were analyzed by the Fisher exact test, the chi-squared and Mann-Whitney tests. Logistic regression was used to assess the impact of good grade in WFNS and ultra-early surgery in a good GOS outcome.

The present study was developed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Ethical approval was obtained from the CHUC ethical commission.

Results

A total of 165 cases (48.1% of the total) of ruptured supratentorial aneurysms treated with microsurgical clipping within the first 24 hours are referred to as 'ultra-early'. The other 178 cases (51.9% of the total) also treated with microsurgical clipping in the time frame of 24 to 72 hours post aneurysmal SAH are referred to as 'early'. Demographics and clinical status of these groups prior to treatment are detailed on ►**Table 1**. No statistically significant pretreatment differences between groups were observed.

The measured overall mortality rate was of 10.8%. The mortality rate was of 7.3% on ultra-early surgery group, while in the early surgery group it reached 13.5%, but this difference was not significative ($p = 0.061$).

Aneurysm location is detailed on ►**Table 2** and no statistically significant differences were found between ultra-early and early groups.

For each time, at discharge and 6 months after surgery, patients were divided into two groups according to the GOS outcome: the group of patients who had poor outcome (GOS 1 to 3) and the group that had good outcome (GOS 4 and 5). Patient WFNS grading scale data was also dichotomized into good-grade (WFNS grading scale 1 to 3) and poor-grade (WFNS grading scale 4 and 5).

At discharge, good outcome was observed in 73.3% of ultra-early patients and in 61.8% of early patients ($p = 0.018$),

Table 1 Patient demographics and preoperative clinical status: Comparison of ultra-early and early treatment groups

	Ultra-early N (%)	Early N (%)	All N (%)	*p-value*	Statistical test used
N	165 (48.1)	178 (51.9)	343		
Mean of Age (min. - max.)	55 (46–64)	58 (44–71)	56 (45–68)	0.295	Mann-Whitney
Gender				0.785	Chi-squared
M	57 (34.5)	64 (36.0)	121 (35.3)		
F	108 (65.5)	114 (64.0)	222 (64.7)		
WFNS				0.292	Chi-squared
1	79 (47.9)	95 (53.3)	174 (50.7)		
2	45 (27.3)	39 (21.9)	84 (24.5)		
3	9 (5.5)	14 (7.9)	23 (6.7)		
4	24 (14.5)	27(15.2)	51 (14.9)		
5	8 (4.8)	3 (1.7)	11 (3.2)		
WFNS dichotomized				0.541	Chi-squared
Good-grade	133 (80.6)	148 (83.1)	281 (81.9)		
Poor-grade	32 (19.4)	30 (16.9)	62 (18.1)		

Abbreviations: N, Number; WFNS, World Federation of Neurological Societies.
Values are expressed as median and interquartile range or number (%).

Table 2 Aneurysm location: Comparison of ultra-early and early treatment groups

Aneurysm location	Count	Ultra-early N (% within location)	Early N (% within location)	N (% of total)
OA		2 (50%)	2 (50%)	4 (1.2%)
ICA		11 (57.9%)	8 (42.1%)	19 (5.5%)
PCoA		25 (47.2%)	28 (52.8%)	53 (15.4%)
AChoA		0 (0.0%)	1 (100.0%)	1 (0.3%)
ACA		8 (50.0%)	8 (50.0%)	16 (4.7%)
ACoA		60 (47.2%)	67 (52.8%)	127 (37.0%)
MCA		34 (50.8%)	33 (49.3%)	67 (19.5%)
PICA		1 (50.0%)	1 (50.0%)	2 (0.6%)
VA		1 (100.0%)	0 (0.0%)	1 (0.3%)
BA		1 (50.0%)	1 (50.0%)	2 (0.6%)
Other location		0 (0.0%)	2 (100.0%)	2 (0.6%)
Multiple aneurysms		22 (44.9%)	27 (55.1%)	49 (14.3%)
Total		165 (48.1%)	178 (51.9%)	343 (100.0%)

Abbreviations: ACA, anterior cerebral artery; AChoA, anterior choroidal artery; ACoA – anterior communicating artery; BA, basilar artery; ICA, internal carotid artery; MCA – medial cerebral artery; N – number; OA, ophthalmic artery; PCoA, posterior communicating artery; PICA, posterior inferior cerebellar artery; VA, vertebral artery.

a difference of 11.5% of patients favorable to the ultra-early group. Poor outcome was obtained in 26.1% of ultra-early patients and in 38.2% of early patients, a difference of 12.1% of patients favorable to the early group. After 6 months, 82.4% of the ultra-early group and 71.9% of the early group obtained good outcome ($p = 0.004$), a difference of 10.5% of patients favorable to the ultra-early group. Poor outcome was verified in 5.8% of the ultra-early patients and in 24.7% of the early patients, a difference of 18.9% of patients favorable to the early group (►**Table 3**).

Subgroup analysis of good-grade patients submitted to ultra-early surgery demonstrated both an improved GOS at discharge ($p = 0.045$) and an improved GOS at 6 months ($p = 0.007$). On the other hand, subgroup analysis of poor-grade patients submitted to ultra-early surgery demonstrated improvement on GOS at discharge ($p = 0.031$) but it did not reach statistical significance at the 6-month outcome ($p = 0.064$).

Logistic regression was performed with dichotomized GOS as the dependent variable, to assess the impact of good-grade on WFNS and ultra-early surgery on a good outcome.

Evaluation of the logistic regression found better outcomes at both discharge and 6 months for the ultra-early surgery group of patients over the early group of patients, when adjusted for clinical grade on admission (WFNS) (►**Table 4**).

A rebleeding rate of 3.8% ($n = 13$) was found after the first rupture. Five of these patients were submitted to ultra-early surgery and the other eight were submitted to early surgery. However, the result was not statistically significant ($p = 0.577$).

Discussion

Aneurysm rebleeding is one of the most severe complications of ruptured brain aneurysms, frequently leading to death or disability. Since rebleeding after the initial ictus is estimated to reach higher rates in the first hours, ultra-early treatment seems to be a reasonable approach.[3,4] Historically, several factors were evoked to support delayed microsurgical clipping of ruptured aneurysms, mainly: difficult access due to brain swelling, increased risk of intraoperative aneurysm rupture, higher need for application of temporary clips and for the use of brain retractors.[1] Despite this, in the early nineties, a prospective, observational clinical trial was conducted by the International Cooperative Study on the Timing of Aneurysm Surgery to determine the best time for surgical treatment. The authors concluded that early surgery was neither more hazardous nor beneficial than delayed surgery, and that the postoperative risk following early surgery was equivalent to the risk of rebleeding and vasospasm in patients waiting for delayed surgery.[3,4] Due to those results, early treatment (treatment within the first 72 hours postictus) became the mainstay of aneurysmal SAH management worldwide. In fact, the American Heart Association / American Stroke Association (AHA/ASA) 2012 revised Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage have a Class I recommendation to perform aneurysm treatment as early as feasible (B level of evidence).[11] Consequently, despite the fact that either a specialized neurosurgical vascular team or an endovascular team available on a 24-hour basis could be a logistical problem for many hospitals, earlier treatment of aneurysmal SAH is becoming the standard of care.

The ultra-early treatment has been proposed based on the rate and outcome of early rebleeding following aneurysmal SAH. Multiple studies have shown that incidence of rebleeding is maximal in the first 24 hours (4.1–17.3% rebleeding rates) with high rates of fatal outcome (65–80%).[12–15] There are not many exclusive surgical series showing that ultra-early treatment can be beneficial for good-grade and poor-grade patients at discharge and after 6 months, simultaneously. Only three of them showed better outcome for ultra-early timing, but none with these assumptions.[5,6,8] Phillips et al concluded that treatment within 24 hours was associated with improved clinical outcome at 6 months.[8] This study included surgical as well as endovascular treated patients and the authors concluded that the outcome benefit was exclusive to the coiling subgroup whereas no difference in outcome was observed between ultra-early and early surgical patients.

Better results were seen in the poor-grade (WFNS grading scale 4 to 5) patients submitted to ultra-early treatment, as recorded in the Wong et al 2012 study.[10] In fact, the Melbourne case series of clipping within 12 hours for poor-grade aneurysmal SAHs stated previously that the high ultra-early rebleeding rates observed among this subset of patients indicates the need for urgent treatment.[7] Wong et al suggested that the outcome improvement with this subgroup of patients was due mainly to the reduction of rebleeding rates with ultra-early treatment.

A recent study on Nationwide Inpatient Sample analysis in the US demonstrated that ultra-early aneurysm surgery not only improves outcome but also decreases hospitalization costs.[9]

Table 3 Outcome and mortality subgroup analysis between ultra-early and early surgery patients stratified by the Glasgow outcome scale grading

	Ultra-early N (%)	Early N (%)	All N (%)	*p-value*	Statistical test used
N	165 (48.1)	178 (51.9)	343		
Overall Mortality	12 (7.3)	24 (13.5)	36 (10.5)	0.061	Chi-squared
GOS discharge				0.00048	Chi-squared
1	7 (4.3)	14 (7.9)	21 (6.1)		
2	5 (3.0)	12 (6.7)	17 (5.0)		
3	31 (18.8)	42 (23.6)	73 (21.3)		
4	73 (44.2)	40 (22.5)	113 (32.9)		
5	48 (29.1)	70 (39.3)	118 (34.4)		
Lost to follow-up	1 (0.6)	0	1 (0.3)		
GOS discharge dichotomized	165 (48.1)	178 (51.9)	343	0.018	Chi-squared
Good outcome (4–5)	121 (73.3)	110 (61.8)	231 (67.4)		
Poor outcome (1–3)	43 (26.1)	68 (38.2)	111 (32.3)		
Lost to follow-up	1 (0.6)	0	1 (0.3)		
GOS 6 months				0.0086	Chi-squared
1	11 (6.7)	23 (12.9)	34 (9.9)		
2	2 (1.2)	4 (2.2)	6 (1.8)		
3	7 (4.2)	17 (9.6)	24 (6.9)		
4	32 (19.4)	17 (9.6)	49 (14.3)		
5	104 (63.0)	111 (62.3)	215 (62.7)		
Lost to follow-up	9 (5.5)	6 (3.4)	15 (4.4)		
GOS 6 months Dichotomized	165 (48.1)	178 (51.9)	343	0.004	Chi-squared
Good outcome (4–5)	136 (82.4)	128 (71.9)	264 (77)		
Poor outcome (1–3)	20 (5.8)	44 (24.7)	64 (18.7)		
Lost to follow up	9 (5.5)	6 (3.4)	15 (4.4)		

Abbreviations: GOS, Glasgow Outcome Scale; N, Number.

Table 4 Logistic regression analysis with WFNS and time of surgery as covariates for good outcome of Glasgow outcome scale

	GOS discharge		GOS 6 months	
Variables	**HR (95% CI)**	***p-value***	**HR (95% CI)**	***p-value***
WFNS (good grade)	8.129 (4.329-15.264)	<0.0005	4.652 (2.200-9.838)	< 0.0005
Time of surgery (ultra-early)	2.029 (1.221-3.370)	0.006	3.214 (1.562-6.609)	0.002

Abbreviations: CI, Confidence interval; HR, Hazard ratio; WFNS, World Federation of Neurological Societies.

No previous study showed an unequivocal benefit of ultra-early surgery on patient outcome both at discharge and at 6 months in subgroups of poor and good-grade patients.

At the neurosurgery department of the CHUC, virtually all ruptured anterior circulation aneurysms are treated by surgical clipping, and the present study only analyzed surgical cases, not endovascular ones. As seen in our patients, all clinical grades were treated by surgery, meaning that clinical status was not a sufficient reason for patients to be treated by endovascular methods.

Aneurysmal rupture with a different location than Middle Cerebral Artery (ACM), more specifically in the anterior communicating artery (ACoA), is a poor prognostic factor.[16,17] However, in our study, a significant relationship was not found on mortality and on outcome.

A trend toward a lower mortality was found on patients submitted to ultra-early surgery ($p = 0.061$). The mortality rate of the ultra-early group was 7.3% versus 13.5% of the early group, which means that early surgery has a mortality rate almost twice that of ultra-early surgery.

In the present study, good-grade patients benefit from ultra-early surgery both at discharge as at 6 months follow-up ($p = 0.045$ and $p = 0.007$, respectively), whereas poor graded patients have benefit only at discharge ($p = 0.031$).

These results are in conformity with the previous concept of better results for poor-grade patients, but the improvement does not stand on follow-up. On the other hand, for the good-grade patients, the present study demonstrates that ultra-early surgery improves outcome not only at discharge but also at the 6-month follow-up.

These solid results strengthen the concept that ultra-early surgery should be the mainstay in the context of aneurysm treatment.

These results are relevant because the ultra-early and early groups are homogeneous (which means that no difference between presurgical clinical status were observed).

The rebleeding rate was higher in the early group (5 patients on ultra-early and 8 patients on early timing) but this difference was not significative ($p = 0.577$). The number of patients that suffered this complication was similar and can be the reason that justifies this result. The objective of the present study was not to compare directly the rebleeding rate between groups. However, we need more surgical cases to analyze the benefit of ultra-early surgery on the prevention of rebleeding. Nevertheless, the rebleeding prevention effect of ultra-early treatment could be the major contributing factor for this difference.

The limitations of the present study include the ones usually associated with retrospective analyses. No difference between WFNS grading was observed between the two groups of patients. Another weakness of the present study is the lack of detailed information of the clinical condition of the patients, such as brain swelling, acute hydrocephalus or intracranial hypertension and of intraoperative aspects such as duration of surgery, use of temporary clipping or the need for brain retractors.

We believe that patient selection bias can be a limitation, but it was minimized by the fact that the timing of surgery was determined only by logistical hospital issues, a limitation which in a way mimics real life situations, where all such difficulties (surgical team available) are often encountered. In the last few years, at the neurosurgery department of the CHUC, there is a team on call which allows the ultra-early protocol surgical treatment for the huge majority of these patients, which is nowadays the gold-standard time of care.

Conclusion

The present work is a retrospective single center surgical series of consecutive aneurysmal SAH patients submitted to treatment within the first 72 hours postictus, prospectively updated with long-term clinical outcome data. Good-grade WFNS patients submitted to ultra-early surgery demonstrated an improved outcome (both at time of discharge as at 6-month GOS outcome). Poor-grade WFNS patients submitted to ultra-early surgery demonstrated an improved time of discharge outcome. Efforts should be made on the logistics of emergency departments to consider achieving treatment of aneurysmal SAH patients on the first 24 hours after ictus as a standard of care.

Ethical Approval

Ethical approval was obtained from the Coimbra Hospital and University Centre ethical commission.

Conflict of Interests

The authors have no conflict of interests to declare.

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