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Microsurgical clipping in forty patients with unruptured anterior cerebral circulation aneurysms

An investigation into cognitive outcome

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ABSTRACT

Objective: It is a consensus that most unruptured intracranial aneurysms (UIA) can be treated with acceptably low morbidity. However, some studies recently reported postoperative cognitive impairment, suggesting that it could be attributable to surgical damage. Our goal is to evaluate cognitive function before and after microsurgical clipping in patients with UIA. **Method:** A consecutive series of 40 patients who underwent microsurgical clipping for UIA were studied. The cognitive assessment (Mini Mental State Examination, MMSE) was performed immediately before and at least one month after surgery. Paired Student's "t" test and analysis of variance (ANOVA) were used for statistical purposes. **Results:** The mean MMSE score in the preoperative analysis was 28.12 (SD, 1.34). In the postoperative period the mean MMSE score was 28.40 (SD, 1.46). Paired Student's "t" test was applied to the scores and no significant difference was found (p=0.315). ANOVA did not find independent associations between MMSE scores and age, hypertension, smoking, dyslipidemia, education, aneurysm location, number, laterality or size. **Conclusion:** The present study suggests that microsurgical clipping for UIA does not result in major cognitive dysfunction as determined by the MMSE.
Key words: cerebral aneurysm, surgical clipping, cognitive impairment, mini mental state examination.

Clipagem microcirúrgica em 40 pacientes com aneurisma de circulação cerebral anterior não-roto: uma investigação cognitiva

RESUMO

Objetivo: É consenso que a maioria dos aneurismas intracranianos não-rotos (AINR) podem ser tratados com aceitável taxa de morbidade. Entretanto, alguns estudos reportaram déficits cognitivos no pós-operatório, sugerindo que poderiam ser atribuídos ao dano cirúrgico. O objetivo desse estudo é avaliar a função cognitiva antes e após clipagem microcirúrgica em pacientes com AINR. **Método:** Uma série de 40 pacientes com AINR submetidos à clipagem microcirúrgica foi estudada. A avaliação cognitiva (Mini Exame do Estado Mental, MEEM) foi realizada antes e após a intervenção cirúrgica. A análise estatística foi realizada com teste "t" de Student e análise de variância (ANOVA). **Resultados:** A média dos escores do MEEM na análise pré-operatória foi 28,12 (DP, 1,34). No período pós-operatório, a média dos escores foi 28,40 (DP, 1,46). Não houve diferença estatística (teste "t" de Student; p=0,315). A ANOVA não encontrou associações independentes entre os escores de MEEM e idade, hipertensão, tabagismo, dislipidemia, educação e características dos aneurismas (topografia, número, lado e tamanho). **Conclusão:** O presente estudo sugere que a clipagem microcirúrgica não está associada a danos cognitivos maiores em pacientes com AINR.
Palavras-chave: aneurisma cerebral, clipagem cirúrgica, déficit cognitivo, mini exame do estado mental.

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In recent years the debate over the best treatment for patients with unruptured intracranial aneurysms has intensified. Incomplete and conflicting data about the natural history of these lesions and the risks associated with their repair have complicated this discussion[1-3].

Intracranial aneurysms can be treated with either microsurgical clipping or endovascular coiling. Clipping is the most popular treatment[2]. This procedure aims to exclude the aneurysm from circulation by placing a clip across the neck. In the past decade, endovascular coiling has grown in popularity as an alternative to clipping. This procedure aims to obstruct the aneurismal lumen with a detachable coil, with the intent of inducing secondary thrombosis of the aneurysm. Coil embolization has the potential advantage that the patient is spared invasive intracranial surgery[4,5].

It is a consensus that most unruptured intracranial aneurysms can be treated with acceptably low morbidity and mortality[6-8]. Recently, an international study of unruptured intracranial aneurysms (ISUIA)[2] suggested that the high surgical morbidity was largely attributable to impaired cognitive status. The same study suggested that the endovascular treatment might be associated with less immediate risk of morbidity and mortality.

After the publication of ISUIA in 2003, a series of well designed, methodologically sound studies appeared with conflicting results. Tuffiash et al.[9] and Otawara et al.[7] showed that neurosurgical clipping of unruptured intracranial aneurysms was not associated with cognitive dysfunction. On the other hand, Ohue et al.[10] reported that neuropsychological function had deteriorated in 40% of the patients one month after neurosurgical clipping. Due to the contradictory data available to date, new complementary cognitive studies are needed to clarify the current issue.

The objective of the present study is to evaluate the cognitive function measured with the Mini Mental State Examination (MMSE) before and after neurosurgical clipping in patients with unruptured intracranial aneurysms.

METHOD

Patient population

All patients treated for unruptured intracranial aneurysms at Hospital São José / Complexo Hospitalar Santa Casa by the authors in a 4 years period (2004-2008) were initially selected (n=59 patients).

The inclusion criteria for the present study were as follows: diagnosis of unruptured saccular intracranial aneurysm in the anterior cerebral circulation; age between 21 and 70 years old; and signed informed consent.

Patients with obvious cognitive impairments (I.Q. lower than 80), inability to read or to understand the consent form, past medical history of psychiatric disorder, or subarachnoid hemorrhage were excluded.

Forty patients (33 female, 7 male) filled the above criteria and were included in the final cohort.

Ethical approval was granted by the Institution (Comitê de Ética em Pesquisa / Complexo Hospitalar Santa Casa - protocolo 1040/05).

Therapeutic procedure: neurosurgical clipping

Standard neurosurgical approaches (classic pterional or anterior interhemispheric) were performed using the operating microscope. After widely opening of the CSF cisterns, self retractors were intermittently used on the frontal and/or temporal lobes. The aneurysms were excluded from circulation by the placement of a clip (Vicca®) across the neck. All operations were performed by the same neurosurgical team (senior author JLK).

Cognitive assessment

The cognitive assessment was performed one day before and at least one month after neurosurgical clipping. The tests were performed by a trained neuropsychology group.

The cognitive test used was the Mini Mental State Examination[11]. The MMSE test is a brief 30-point questionnaire test that is usually used to screen for cognitive impairment. It is commonly used in medicine to screen for dementia. It is also used to estimate the severity of cognitive impairment at a given point in time and to follow the course of cognitive changes in an individual over time, thus making it an effective way to document an individual's response to treatment. The assessment contains 11 questions and required 5 to 10 minutes to complete during a face-to-face interview. All the following domains were evaluated in this test: orientation, retention, attention, calculation, evocation, language, and visual constructive ability. Any score greater than or equal to 25 points (out of 30) is effectively normal (intact). Below this, scores can indicate severe (≤9 points), moderate (10-20 points) or mild (21-24 points). Low to very low scores correlate closely with the presence of dementia, although other mental disorders can also lead to abnormal findings on MMSE testing[12,13].

All MMSE cognitive data obtained and also additional standard information were documented for all patients in an SPSS (Statistical Package for Social Sciences, version 12.0, SPSS Inc., Chicago, IL, USA) database.

Sample calculation and statistical analysis

The sample calculation was performed with PEPI Software (Programs for EPIdemiologists; Version 4.0). The minimum number of patients needed for the study was 26 (α=0.05; test power 80%).

All data were analyzed with help of the SPSS Software. Statistical analysis was performed with Ppaired Student's

"t" test ($p<0.05$). Analysis of variance (ANOVA, $\alpha=0.05$) was also applied in order to investigate independent associations between MMSE scores and age, risk factors for intracranial aneurysm (hypertension, smoking, dyslipidemia), education, number of aneurysms, aneurysm topography, aneurysm size and aneurysm laterality.

RESULTS

Patients

The final number of patients included in the study was 40 (7 males and 33 females). Ages ranged from 22 to 70 years old (mean, 53.2). Characteristics of the patients and aneurysms are provided in Table 1 and Table 2 respectively.

Conditions leading to the diagnosis of an unruptured intracranial aneurysm and enrollment in the treatment group included: incidental finding in computerized tomography (CT) or magnetic resonance imaging (MRI) (38 patients), cranial nerve deficit / visual impairment (1 patient), transitory ischemic cerebrovascular accident (1 patient).

Imaging definitive diagnosis of the aneurysms was made based on angiotomography plus digital cerebral angiography (26 patients), only digital cerebral angiography (7 patients), angio-MRI plus digital cerebral angiography (5 patients), only angiotomography (2 patients) and a combination of angiotomography, angio-MRI and digital cerebral angiography (1 patient).

Table 1. Patients characteristics.

Characteristic	Neurosurgical group
Number of patients	40
Female-to-male ratio	33:7
Age (mean)	22-70 yr (53.2 yr)
Number of years of education (mean)	11.5 yr
Risk factors	n
Hypertension	18
Cigarette smoking	13
Familial history of aneurysm	4
Hypercholesterolemia	3
Type 2 diabetes	2
Polycystic kidney disease	1

Table 2. Aneurysms characteristics.

Characteristic	Result
Aneurysm location	n
Single aneurysms	36
MCA	16
Ophthalmic	6
PCom	3
Paraclinoidal	8
Carotid bifurcation	1
ACoA	1
Pericalosal	1
Aneurysm location	n
Multiple aneurysms	4
ACoA + MCA + PCom	1
Ophthalmic + PCom	1
MCA + MCA	1
Carotid bifurcation + A2 + PCom	1
Side of aneurysms	n
Left	22
Right	18
Size of aneurysms (mean)	3-20 mm (6.58 mm)

MCA: middle cerebral artery; PCom: posterior communicating artery; ACoA: anterior communicating artery.

Surgical results

Surgery was performed with the pterional approach in 39 cases. For clipping the neck of anterior communicating aneurysms, a small part of rectal gyrus was always aspirated. Anterior interhemispheric approach was performed in only 1 case (pericallosal aneurysm). All patients had only one surgery, independent of the number of aneurysms that needed treatment.

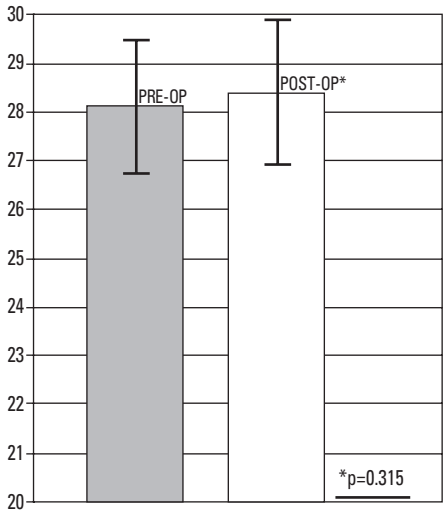
All aneurysms diagnosed were definitively treated, i.e. excluded from cerebral circulation with the placement of a clip across the neck. In one patient, a small aneurysm diagnosed at the time of microsurgical approach was only coated with Teflon® material.

Surgical morbidity was observed in 2 patients. In a patient with a 20 mm ophthalmic aneurysm, a mild visual impairment occurred after surgery and in a patient with an internal carotid / posterior communicating artery aneurysm moderate dysphasia plus mild right hemiparesis were seen in the postoperative period resulting from a small basal infarct confirmed by CT-scan. In both patients, all symptoms were reversed within three weeks.

Systemic morbidity also occurred in the immediate postoperative period: phenytoin toxicity (4 patients), hyponatremia and seizures (1 patient), and psychomotor agitation (1 patient). There were no deaths in this series. After one month, all patients were intact according to Glasgow Outcome Scale (GOS=5).

Cognitive assessment

The mean Mini-Mental State Examination score in the preoperative analysis was 28.12 (SD, 1.34). In the postoperative period (at least one month after the surgery) the mean Mini-Mental State Examination score was 28.40 (SD, 1.46) (Figure). Scores in both evaluations ranged from 25 to 30, consistent with the absence of cognitive impair-



PRE-OP: preoperative values; POST-OP: postoperative values.

Figure. Mini-Mental State Examination scores.

ment before and after the neurosurgical approach. Paired Student's "t" test was applied to the Mini-Mental State Examination scores and no significant difference was found (p=0.315). Analysis of variance were also applied and there were no independent associations between Mini-Mental State Examination scores and age (p=0.738), risk factors (hypertension, p=0.464; smoking, p=0.079; dyslipidemia, p=0.970), education (p=0.382), number of aneurysms (p=0.623), aneurysm topography (p=0.231), aneurysm size (p=0.270) or aneurysm laterality (p=0.582).

DISCUSSION

The management of unruptured intracranial aneurysms remains one of the most intriguing topics in neurosurgery. The conflicting data about the natural history of these lesions and the inconsistent results with respect to surgical morbidity and mortality have contributed to the difficulty of this discussion[2,3,14].

Although the morbidity and mortality of aneurysm surgery clearly depends on the particular neurosurgeon and medical center being evaluated, several studies have attempted to formulate generalizable results. While no consensus has been reached, there is agreement that most unruptured intracranial aneurysms can be managed with reasonably low morbidity and mortality[6-8,15].

With the advent of improved technology and operative techniques, it is certain that the risks associated with unruptured aneurysm surgery have trended down over time[15,16]. Solomon et al.[17] documented outcomes after 202 consecutive surgeries for microsurgical clipping of unruptured cerebral aneurysms. Overall, minor complications, major complications, and death occurred in 5, 7, and 3.5% of patients, respectively. Additional cohort analysis showed that in patients with incidental aneurysms (17%), the mortality rate was 2.9%. Raaymakers et al.[8] published a meta-analysis of 61 studies about surgical treatment for unruptured intracranial aneurysms and found that clipping was associated with a mortality of 2.6% and a morbidity of 10.9%. The results also showed that half the patients with surgical morbidity became dependent in daily life. Bederson et al.[18] related comparable values: range from 0 to 7% for death and from 4 to 15% for complications. Ogivy and Carter[19] retrospectively reviewed their series of 604 unruptured aneurysms and found rates of morbidity and mortality for the entire group were 15.9 and 0.8% respectively. Moroi et al.[20] published their results after treating 549 unruptured aneurysms at Research Institute for Brain and Blood Vessels. Their reported outcome results were remarkable with 0.3% mortality and 2.2% morbidity overall. More specifically, for aneurysms smaller than 10mm, their mortality and morbidity rates were only 0.0 and 0.6 %, and for aneurysms larger than 10 mm, these rates were 1.2 and 6.1%.

In both reports from The International Study of Unruptured Intracranial Aneurysms investigators[1,2], prospective assessments of the morbidity and mortality rates associated with surgical intervention were obtained. In the initial report published in 1998[1], the overall surgical morbidity and mortality rate for patients with no history of subarachnoid hemorrhage was 15.7%. The follow-up ISUIA results published in 2003[2], revealed a surgical morbidity and mortality rate of 12.6%. In this part of the study, the authors suggested that the high surgical morbidity was attributable to cognitive impairment, as demonstrated on the Mini-Mental State Examination. Patients underwent to postoperative cognitive evaluation and they were found to have 10.6% incidence of impaired cognitive status at 30 days and 1 year after surgery. However, there is an issue with this study that must be considered. Because no preoperative evaluation was obtained, it is unknown what proportion of impaired cognition was a direct result of brain surgery and related complications.

Some authors suggest that cognitive decline may represent a form of underdiagnosed morbidity related to aneurysm clipping. Fukunaga et al.[21] evaluated the cognitive function of 30 patients with unruptured intracranial aneurysms before and after neurosurgical clipping. The authors reported a significant deterioration in cognitive tests in 17 patients (55%) after the first month. However, three months after the operation, all patients recovered to preoperative levels in a second cognitive evaluation. Hillis et al.[6] also performed detailed cognitive evaluation in 12 patients with diagnosis of unruptured intracranial aneurysms. The authors noted significant differences between preoperative and postoperative performance only on a few tests (measures of word fluency, verbal recall and

Stroop test). The significance of those results was considered questionable. Another interesting study of cognitive deterioration was performed by Ohue et al.[10]. The authors analyzed 43 patients with unruptured aneurysms before and after clipping and found that in 17 (40%) neuropsychological function had deteriorated 1 month after surgery. On follow-up 6 months later, six patients had completely recovered, five patients partially recovered, and three patients had not recovered.

On the other hand, some recent published papers showed that neurosurgical clipping of unruptured intracranial aneurysms is not associated with cognitive dysfunction. Tuffiash et al.[9] studied a consecutive series of 25 patients who underwent surgical clipping to unruptured aneurysms. The patients were submitted to a battery of neuropsychological tests 1 week preoperatively and again postoperatively (before hospital discharge and at 3-month follow-up if they had deficits at discharge). The authors found no evidence of long-term cognitive deficits resulting from aneurysm clipping. Another recent study with favorable cognitive results was published by Otawara et al.[7]. The authors performed a detailed cognitive analysis before and after surgery for unruptured aneurysms in 44 patients. They found that neurosurgical clipping did not impair cognition in their series.

The present study also showed favorable general and neuropsychological outcome for all the forty patients submitted to clipping. Surgical morbidity was observed only in 2 patients (5%), while systemic morbidity occurred in 6 (15%). Since all morbidity was transient and there were no deaths in the series, these results compare favorably with the most positive rates found in literature. However, it is important to reflect on some aspects of the systemic morbidity. Phenytoin toxicity was seen in 4 patients (10%), unusually high rate compared to the incidences reported in literature. In more recent cases, phenytoin toxicity was not seen with such high frequency.

The cognitive results obtained in the present series with the Mini-Mental State Examination can also be considered remarkable, even though this test was the sole cognitive instrument performed. The Mini-Mental State Examination is one of the most widely used clinical instruments for quickly detecting cognitive impairment. This test, through its seven domains, can be used to screen for cognitive impairment, to estimate the severity of cognitive impairment at a given point in time, to follow the course of cognitive changes in an individual over time, and to document an individual's response to treatment[12,13]. However, although the Mini-Mental State Examination can detect major cognitive information, the authors agree that it does not substitute a full neurocognitive test battery.

In conclusion, the present study suggests that neurosurgical clipping for unruptured intracranial aneurysm does not result in major cognitive dysfunction as determined by the Mini-Mental State Examination. Further studies are necessary to confirm this hypothesis.

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