



Factors Influencing Intraoperative Rupture of Intracranial Aneurysms

Intrakraniyal Anevrizmaların İntraoperatif Rüptürünü Etkileyen Faktörler

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ABSTRACT

AIM: The study deals with intraoperative rupture of intracranial aneurysms (IOR) during microsurgery, analyzing factors that may be connected with IOR.

MATERIAL and METHODS: During the three-year period (2006-2008), 934 patients were operated for aneurysms at the Institute of Neurosurgery, CCS, Belgrade. In total, 536 patients were observed.

RESULTS: IOR occurred in 14.7%. Male gender, seizures and timing of surgery proved to be risk factors for IOR. All other tested features had no significance. Localization (IOR rate 11.93% in ACM, 17.06% in ACA and 17.26% in ACI) and size (small: IOR in 68/439 (15.49%), large: 8/74 (10.8%), and very large: 3/23 (13.04%)) of aneurysm seemed to have an influence, but this could not be proved. The majority of IORs (58.23%) occurred in early surgery. Early operated patients: IOR occurred in 46/167 (27.54%), intermediary: 25/103 (24.27%), and delayed: 8/266 (3%) – with highly significant differences.

CONCLUSION: Age, hypertension, diabetes mellitus, cardiomyopathy, pregnancy, higher Fisher score, previous IOR, or the presence of vomiting and headache did not affect the occurrence of IOR, whereas the timing of surgery, male gender and epileptic seizures increased the risk. Localization and size of aneurysm tend to have an influence but statistical significance was not proved in this study.

KEYWORDS: Intracranial aneurysm, Intraoperative rupture, Risk factors

ÖZ

AMAÇ: Çalışma mikrocerrahi sırasında intrakraniyal anevrizmaların intraoperatif rüptürünü (IOR) incelemekte ve İOR ile ilişkili olabilecek faktörleri analiz etmektedir.

YÖNTEM ve GEREÇLER: Üç yıllık dönemde (2006-2008) Belgrad'da CCS Nörocerrahi Enstitüsünde 934 hasta anevrizma için ameliyat edilmiştir. Toplam olarak 536 hasta izlenmiştir.

BULGULAR: İOR %14,7 hastada görülmüştür. Erkek cinsiyet, nöbetler ve cerrahinin zamanının İOR için risk faktörü olduğu bulunmuştur. Diğer test edilen özelliklerin bir önemi bulunmamıştır. Anevrizmanın lokalizasyonu (IOR oranı ACM ile %11,93, ACA ile %17,06 ve ACI ile %17,26) ve büyüklüğü (küçük: IOR 68/439 (%15,49), büyük: 8/74 (%10,8) ve çok büyük: 3/23 (%13,04)) bir etkiye sahip gibidir ama bu ispatlanamamıştır. İOR'lerin çoğunluğu (%58,23) erken cerrahiyle oluşmuştur (erken ameliyat edilen hastalar: IOR 46/167 (%27,54), orta dönem: 25/103 (%24,27) ve geç: 8/266 (%3)) ve farklar yüksek ölçüde önemlidir.

SONUÇ: Yaş, hipertansiyon, diabetes melitus, kardiyomiyopati, hamilelik, daha yüksek Fisher puanı, önceki İOR, veya kusma ve bulantı bulunması İOR varlığını etkilemezken cerrahinin zamanlaması, erkek cinsiyet ve epileptik nöbetler riski arttırmıştır. Anevrizmanın yeri ve büyüklüğünün bir etkisi var gibidir ama bu çalışmada istatistiksel önem ispatlanamamıştır.

ANAHTAR SÖZCÜKLER: İntrakraniyal anevrizma, İntraoperatif rüptür, Risk faktörleri

INTRODUCTION

Intracranial cerebral aneurysms remain a top neurosurgical challenge despite the remarkable achievements of modern neurosurgery and are still accompanied by high morbidity and mortality. Many patients with ruptured cerebral aneurysm pass before reaching the hospital, while half of treated patients die or live with severe disability after hemorrhage. Quick and accurate diagnosis is essential in patients with subarachnoid hemorrhage (SAH). The treatment may be

surgical and it involves microsurgical dissection by clipping or endovascular methods (coiling included). Risk of re-hemorrhage is the highest in the first hours after the initial rupture and can occur at any time. Intraoperative aneurysmal rupture (IOR) is the least desired and potentially lethal complication of neurosurgical treatment. Meticulous micro dissection techniques, detailed planning of surgical stages and predicting possible incidents can lead to the reduction of mortality and morbidity. Intraoperative rupture of cerebral aneurysms is scarcely mentioned in literature.

Data from the literature suggest that the incidence of IOR of cerebral aneurysms is estimated at 5-50%, (2, 9, 15, 25). In older studies (11, 19), IOR is more common, probably as the result of the lack of surgical experience in the pioneering era of micro neurosurgery. Today's rate of IOR is much lower during endovascular procedures and is considered to be between 2.4% and 2.9%, depending on the published series (10, 24, 25).

Although undesired and uncontrolled bleeding can occur at any stage of surgery, there are certain factors that are associated with a higher risk of intraoperative rupture. According to the literature, the risk of IOR of cerebral aneurysms increases with giant aneurysms, aneurysms of the basilar artery, and anterior communicating artery (8, 15, 20), but the relationship between localization and the occurrence of IOR is not clearly defined. Batjer and Samson (3) showed that intraoperative rupture of aneurysm can be expected at three moments: initial phase of surgery- during craniotomy, opening the dura or retraction of the brain (mortality 75%, and incidence of 7%); second phase during aneurysm preparation for clipping as a result of blunt or sharp preparation of aneurysm (incidence 48%) and in the third phase - during clip placement - (incidence 45%). The intensity of IOR bleeding can be divided into minor, moderate and severe (15). The intensity of bleeding due to IOR is in direct correlation with the outcome, as the occurrence of neurological complications is more certain in the case of massive bleeding than in the case of bleeding that can be resolved by simply closing the clip.

Sluzewski et al. indicates that the size of aneurysm substantially affects the appearance of IOR, smaller diameter of aneurysm is associated with the lower rate of IOR (22). According to several authors, the use of temporary clip in dissection of aneurysms dramatically reduces the incidence of IOR (1, 23, 25). While the experience of the operating neurosurgeon has been shown not to affect the incidence of IOR, it has a positive effect on the ability to find a solution for disastrous bleeding, it reduces the time of temporary clipping, reduces surgical mortality and thus improves the outcome (13). Anticipating difficulties and continuous skill improvement enhance the effectiveness of surgeons, ultimately leading to better outcomes. IOR is very likely to increase the chance of permanent neurological deficit or death, and may be a risk factor for the development of vasospasm and delayed ischemia (4).

This study aims to present our experience in the surgical treatment of aneurysms and point out the factors that may influence IOR of intracranial aneurysms.

MATERIAL and METHODS

Over the three-year period from 1 January 2006 to 31 December 2008 at the Neurosurgery Division of the Clinical Center of Serbia, Belgrade, a total of 934 patients were operated for brain aneurysms. The 536 patients who met the criteria and whose medical records were available for analysis were selected for inclusion in the study (aneurysm surgery after subarachnoidal hemorrhage, highly experienced surgeon). A retrospective - prospective study was designed to analyze factors associated with IOR of intracranial aneurysms, pre and during treatment. A questionnaire was designed for the purpose of data statistical processing. The relevant parameters obtained from the questionnaire were then entered in a computerized database, and processed using the Windows XP Pro operating system, Microsoft Office 2003/2007 Pro software package and SPSS for Windows v.13. Results: Among 536 analyzed patients, IOR occurred in 79 (14.74%), which is consistent with the data from recent literature. An analysis of demographic data showed that IOR was present in male patients in 57% compared to 43% in female patients. The difference is statistically significant and the male gender is associated with high rate of IOR (Table I). The average age was approximately 50 years in both groups (with and without IOR), and the age of patients was not confirmed to be a risk factor (Table II). One of the issues that arise empirically is, whether the occurrence of IOR is significantly associated with the history of hypertension. The data is presented in Table III. We did not find any significant difference between the groups. Hypertension was not a risk factor for the occurrence of IOR. The presence of cardiomyopathy in patients with and without IOR is shown in Table IV. There was no statistically significant difference. The presence of diabetes mellitus (DM) in our series was lower than in general population; the data is given in Table V with no significant differences. Pregnancy itself as a risk factor in female patients was analyzed and data presented in Table VI. There was no statistically significant difference in the occurrence of IOR, and pregnancy cannot be considered a risk factor for IOR. In our study, 21 people had been operated previously, and 1 had IOR during first surgery. The data are shown in Table VII,

Table I: Gender Distribution of IOR of Intracranial Aneurysms

	Gender				Total	
	Male		Female			
IOR	n	%	n	%	n	%
Yes	45	57.0	34	43.0	79	100
No	156	34.2	301	65.8	457	100
Total	201	37.6	335	62.4	536	100

These data were analyzed using the method of chi-square test, contingency tables, and on the basis of test results ($\chi^2=14.9$, $df=1$, $p<0.001$), we showed that in a population of patients with IOR, a statistically significant difference frequency IOR by gender, and that the total number of events significantly more common in males, so male gender can be considered a risk factor for the occurrence of IOR.

no significance was found in connection with previous IOR. In the analysis of preoperative symptoms, we found that the presence of headache and/or vomiting was even more frequent in the group of patients who did not subsequently experience IOR; however, the differences were not statistically significant, and the presence or absence of headache/vomiting is not a predicting factor.

Table II: Age of Patients and IOR

	IOR		Total
	Yes	No	
\bar{x}	50.56	52.51	51.60
Sd	12.32	11.57	11.93
Median	50	53	52
The minimum value	11	2	2
The maximum value	75	76	76

There was no statistically significant difference ($t=1.31$, $DF=534$, $p=0.19$).

The frequency of most commonly reported complaints of headaches and vomiting, occurring individually or together, is shown in Table VIII. The data of IOR depending on the seizures, or history of epilepsy, are shown in Table IX, and analyzed by *chi square* test. Statistical significance was found for epilepsy, and also epileptic seizures or history of epilepsy increased the risk of IOR.

Values of Fisher score on admission are presented in Table X, showing that Fisher score on admission was not prognostic for latter IOR. Table XI shows the distribution of IOR and localization of aneurysm. Analysis of the data showed no significant difference, and localization of aneurysm was not a predictor of IOR in this study. Nevertheless, the frequency of IOR was not equal in groups in terms of localization. Out of a total number of aneurysms localized in carotid artery (ACI), IOR occurred in 20/116 (17.24%), in the anterior communicating artery (ACA) - 36/211 (17.06%), middle cerebral artery (ACM) - 21/176 (11.93%), and posterior circulation (PC) - 2/33 (6.06%), indicating that carotid and anterior communicating artery aneurysms tend to rupture during surgery more frequently. Statistical significance could not be documented in this study.

Table III: Hypertension and IOR

IOR	Hypertension				Total	
	No		Yes		n	%
	n	%	n	%		
Yes	47	59.5	32	40.5	79	100
No	239	52.2	218	47.8	457	100
Total	286	53.3	250	46.7	536	100

We analyzed whether hypertension can be identified as major risk factor for IOR. Chi-square test showed no significance in differences $p < 0.05$ according to the frequency of hypertension between the groups of patients with and without IOR. Frequency of hypertension, on average, was about 46.7% in both groups.

Table IV: Patients by IOR and Cardiomyopathy

IOR	Cardiomyopathy				Total	
	No		Yes		n	%
	n	%	n	%		
Yes	75	94.9	4	5.1	79	100
No	411	90	46	10	457	100
Total	486	90.7	50	9.3	536	100

Between groups with and without IOR we found no statistically significant difference in presence of cardiomyopathy ($chi-square=1.95$, $DF=1$, $p=0.16$). Therefore, the presence of cardiomyopathy, in this sample, it is not essential for the occurrence of rupture, but clinical experience suggests that its presence can not be ignored. In both groups cardiomyopathy was present in 9.3% of cases.

Table V: IOR in Correlation with DM

IOR	DM				Total	
	No		Yes		n	%
	n	%	n	%		
Yes	77	97.5	2	2.5	79	100
No	442	96.8	15	3.2	457	100
Total	519	96.9	17	3.1	536	100

Further testing using the chi squares, showed not a statistically significant difference between groups ($chi-square=0.1$, $DF=1$, $p=0.75$) with or without diabetes mellitus. Thus, the comorbidity of DM does not increase the frequency of intraoperative rupture. In both groups in the study we found 3.1% DM.

Table VI: Pregnancy and IOR

IOR	Pregnancy				Total	
	No		Yes		n	%
	n	%	n	%		
Yes	34	100	0	0	34	100
No	298	98.4	5	1.6	303	100
Total	332	98.6	5	1.4	337	100

Between patients with and without pregnancy there was no statistically significant difference in IOR ($p = 1.00$). Thus, the pregnancy itself, at least in this sample, it is not crucial for the occurrence of intraoperative rupture in female patients.

Table VII: Patients with IOR and Previous Intraoperative Rupture

IOR	Previous IOR				Total	
	No		Yes		n	%
	n	%	n	%		
Yes	78	98.7	1	1.3	79	100
No	437	95.6	20	4.4	457	100
Total	515	96.1	21	3.9	536	100

In our study, very few of those who had previous IOR, and we applied a Fisher's test which did not show a statistically significant difference ($p=0.34$) in relation to the existence of a previous rupture, between the groups of patients with and without IOR.

Table VIII: Patients with IOR, and Headaches and/or Vomiting

IOR	Headache and / or vomiting				Total	
	No		Yes		n	%
	n	%	n	%		
Yes	11	13.9	68	86.1	79	100
No	15	3.3	442	96.7	457	100
Total	26	4.9	510	95.1	536	100

The analysis of the frequency of headache and/or vomiting—using chi square test, we found significance in differences, more frequent in the group with no IOR. ($\text{chi-square}=16.4$, $DF=1$, $p<0.001$). A headache and/or vomiting may not be a prognostic sign for later IOR.

Table IX: IOR and Epilepsy

IOR	Epilepsy				Total	
	No		Yes		n	%
	n	%	n	%		
Yes	26	32.9	53	67.1	79	100
No	218	47.8	239	52.2	457	100
Total	244	45.6	292	54.4	536	100

Using the chi-square test, we found out that epilepsy is significantly more often in group with IOR. History or occurrence of epilepsy are associated with high risk of IOR ($\text{chi-square} = 6.02$, $DF=1$, $p=0.014$). Epilepsy may be considered a risk factor for IOR.

Table X: Fisher score and IOR

	Fisher score in IOR group	Fisher score in group without IOR	Total
\bar{x}	2.41	2.53	2.47
Sd	1.07	0.71	0.89
Median	2	2	2
Minimal value	1	1	1
Maximal value	4	4	4

In relation to the value of Fisher scores we have not documented statistically significant differences between the two groups of patients ($U=3191$, $p=0.22$). That is, Fisher score on admission is not prognostic factor for later IOR.

Table XII presents the size of aneurysm and IOR. The percentages of IOR in groups depending on aneurysm size were as follows: 68/439 (15.48%) in the small group, 8/74 (10.81%) in the medium and 3/23 (13.08 %) in the very large group without any significant differences.

Analyzing the timing of surgery (Table XIII) showed that 46/79 (58.23%) of IOR happened in early surgery, 25/79 (31.6%) in the intermediary period and 8/79 (10.13%) in delayed surgery. In the early surgery group, IOR occurred in 46/167 (27.54%); in the intermediary surgery group (period between 4-10 days after SAH), IOR occurred in 25/103 (24.27%); while in the delayed surgery group, IOR occurred in 8/266 (3%) with

a significant statistical difference between groups. (Tables XIII, XIV)

DISCUSSION

Data from the literature suggest that the incidence of intraoperative rupture of cerebral aneurysms (IOR) is estimated to be 5-50%, (2, 13, 25). In older surgical series, intraoperative rupture was more common and was probably the result of surgical inexperience in the pioneer era of micro neurosurgery. Hence, Pertuiset (19) published the incidence of intraoperative rupture in 61%, with the rupture in distal aneurysmal sac in 90% of cases. Other authors including Kassell

Table XI: Patients by IOR and the Localization of the Aneurysm

Localizatin	IOR				Total	
	Yes		No		n	%
	n	%	n	%		
ACI	20	25.3	96	21.0	116	21.6
ACA	36	45.6	175	38.3	211	39.4
ACM	21	26.6	155	33.9	176	32.8
PC	2	2.5	31	6.8	33	6.2
Total	79	100.0	457	100.0	536	100.0

Both chi-square test and ANOVA method of proportions, showed no statistically significant difference ($\chi^2=4.56$, $df=3$, $p=0.21$) in relation to the localization of the aneurysm between the groups with and without IOR. In other words, it is not possible from the localization of the aneurysm to predict the IOR.

Table XII: Distribution of Patients According to the Size of Aneurysms

Size of aneurismal sack	IOR				Total	
	Yes		No		n	%
	n	%	n	%		
Small (<12mm)	68	86.1	371	81.2	439	81.9
big (12-25mm)	8	10.1	66	14.4	74	13.8
Giant (>25mm)	3	3.8	20	4.4	23	4.3
Total	79	100.0	457	100	536	100

Between patients with and without IOR we found no statistically significant difference in the size of sac ($\chi^2 = 1.16$, $DF = 2$, $p = 0.56$), which implies that the size of the aneurysm also has no prognostic significance for IOR.

Table XIII: Timing of Surgery Divided in Two Groups (in first 72 Hours and Later) After SAH

	IOR		Without IOR		total	
	n	%	n	%	n	%
Early surgery in first 72 hours	46	27.54	121	72.45	167	100
3 and more days after SAH	33	8.94	336	91.05	369	100
Total	79	14.7	457	82.26	536	100

Analyzing differences between groups by timing of surgery, early operated and others we found $p=0.000$, showing high significance between groups. IOR is more likely to occur in early surgery of ruptured aneurysms.

Table XIV: Timing of Surgery Divided in Three Groups (in First 72 Hours, 3-10 Days, and 11 or more Days After SAH)

	IOR		Without IOR		Total	
	n	%	n	%	n	%
Early surgery (first 72 hours)	46	27.54	121	72.45	167	100
Intermediar 3-10 days after SAH	25	24.27	78	75.72	103	100
Delayed 11 or more days after SAH	8	3.0	258	96.92	266	100
Total	79	14.7	457	82.26	536	100

Analysis of differences between three groups by timing of surgery showed differences between all groups to be very significant ($p=0,000$), IOR is more likely to occur in early than in intermediar surgery. In intermediar group IOR is less likely to occur than in early group, but more likely than in delayed group.

et al. recorded significantly lower incidence of intraoperative rupture of 26% (11); Graf and Nibbelink showed a surprisingly low incidence of intraoperative rupture of 18% in randomized cooperative studies (9). However, in this series of 228 patients, postoperative complications were present in more than 70% of the operated with an overall mortality rate of 44% after six months of surgery. The incidence of IOR in the latest surgical series was significantly reduced, hence in the series published by Leipzig et al. (15), the overall incidence of IOR is 6.7%. Even less IORs occur during endovascular procedures: 2.4 to 2.9% (10, 24, 25).

The incidence of IOR in our study was 14.34 %. The variable incidence of intraoperative rupture of aneurysms is due to different definitions by different authors, some series also include minor bleeding that occurred during clip application.

Chandler et al. define the IOR as bleeding that stops and changes the order of microsurgical procedures, and do not include minor bleeding which is easily controlled surgically. We have followed this definition (5). Similar, Giannota et al. in his report does not include minor bleedings that occur during clip application and can easily be controlled by closing the clip (8). However, Le Roux et al. include minor IOR bleeding (14).

In our study, IOR occurred more frequently in male patients, and in those with seizures of epileptic history. Both results are interesting and very hard to comment. Surprisingly, none tested co-morbidities influencing higher occurrence of IOR. We could not find similar data in literature to compare with our results. These findings certainly deserve further analysis.

The relationship between the localization of aneurysm and the occurrence of IOR is not clearly defined. Sundt et al. (23) did not find a correlation between the location of aneurysm and IOR. Schramm and Cedzich (20) indicate more frequent intraoperative rupture in aneurysms of the anterior communicating artery while it could not be confirmed statistically (8) in other series. Aneurysms of the middle cerebral artery in the individual series are associated with a

lower incidence of IOR. Leipzig et al. (15) indicates a higher incidence of intraoperative rupture in aneurysms on posterior inferior cerebellar artery (PICA), anterior communicating (ACA) and posterior communicating artery (ACoPost). Localization of the aneurysm of the basilar artery is particularly unfavorable and the bleeding very difficult to control in case of IOR (4).

We were not able to prove significant differences of IOR depending on the localization of aneurysm, although the absolute number of IOR is highest in ACA, and this localization accounts for 45% of all IORs.

In our series IOR was less common in ACM - (21/176) 11.93%, and PC aneurysms (2/33) 6.06%, and more common in ACI - (20/116) 17.24%, and ACA (36/211) 17.06%.

According to literature data, the size of aneurysm substantially affects IOR with the smaller aneurysm diameter being associated with the lower rate of IOR (22). The percent of IOR in groups depending on the size was as follows: in the small aneurysm group, it was 68/439 (15.48%), large 8/74 (10.81%), giant 3/23 (13.04%), without significant differences, therefore we can conclude that the size of aneurysm was not proved to be a predictor of IOR.

Although the time of the surgical procedure is not probable to impact IOR, it is believed that the delayed surgery reduces the risk of intraoperative ruptures (14, 15). Analysis of surgery timing showed that 46/79 (58.23%) of IOR happened in early surgeries (in the first 72 hours after SAH), 46/167 (27.54%) in intermediary period (4-10th day after SAH) and 25/103 (24.27%) in delayed surgeries (11th day and later) 8/266 (3%). IOR in early surgery group compared to other two groups merged together, as shown in the early group 46/167 (27.54%), and 33/369 (8.94%) in other two groups, with high significance of difference. Furthermore, when the data was separated into three groups by time of surgery, we found differences between groups to be significant showing that IOR is most likely to occur in early and far less likely in delayed surgeries. Having in mind that the risk of re-rupture without surgery is extremely high in the first days after SAH (5% in the

first 3 days, and in the first two weeks 20%), and the mortality rate of 70%, the benefits of early surgery are evident although early surgery is associated with more IORs as the bleeding can be controlled and aneurysms clipped.

CONCLUSION

Hypertension, diabetes mellitus, cardiomyopathy, pregnancy, and Fisher score on admission did not affect the occurrence of IOR of intracranial aneurysms, and neither did the most common symptoms such as nausea and vomiting. Surprisingly, male gender and epileptic seizures increased the risk of IOR in our study. Early surgery was associated with more frequent IOR, but it has benefits due to the prevention of uncontrolled rupture and high mortality rate of untreated patients. The influence of size and localization seemed to exist although it could not be proved in this study.

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