TREATMENT OPTIONS OF CEREBRAL ANEURYSMS

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Thesis mentor: Prof. dr. sc. Darko Ledić, dr. med.

The graduation thesis was graded on _____ in Rijeka,
before the Committee composed of the following members:

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3. Izv. prof. dr. sc. Ingrid Škarpa-Prpić dr. med.

The graduation thesis contains 28 pages, 1 figure, 2 tables, 31 references.

Contents

Abbreviations

CT Computed tomography scan

CTA Computed tomography angiography

EVD External ventricular drain

GCS Glasgow-Coma-Scale

HH Hunt-Hess score

IADSA Intra-arterial digital subtraction angiography

KBC Klinički bolnički centar (eng. Clinical Hospital Centre)

MRA Magnetic resonance angiography

1 Introduction

This thesis focuses on intracranial aneurysms and their treatment. The various success rates of the typical treatment methods are examined. Currently, the most common treatment for an intracranial aneurysm is coiling. Coiling is not performed at Kliničkibolnički centar (eng. Clinical Hospital Centre) (KBC)-Rijeka. Patients who should receive this type of therapy are transferred to Zagreb. There are typically two treatment options at the Rijeka Hospital, where the data used in this paper had been collected: Clipping and conservative management of the disease. In the following paper, the success rates of the different therapies will be explained in more detail. Since no one has looked into the data of intracranial aneurysms from KBC-Rijeka in recent years, assumptions about the expected results are pure speculation. By the end of this work a clearer understanding should be achived. However, the aim of this paper is not only to concentrate on the results of the therapy's success. This work also wants to draw attention to negative and positive habits that inevitably arise in a long daily routine at the clinic. By looking at the treatment as a whole, from admission to discharge, the patient's well-being should be permanently increased. As a final point of this work, other factors that have an influence on the success of a patient's therapy will also be discussed. It can be assumed with a high degree of certainty that increased age is a negative prognostic factor. However, since as already described, no examination of the data from the Clinics of Rijeka has taken place in recent years, no one can say whether this is to be confirmed in the data. Other values that could influence the prognosis of a patient are Glasgow-Coma-Scale (GCS), Hunt-Hess score (HH), Fischer grade, sex, time since onset of symptoms and length of stay. All these values will be examined in the following paper.

1.1 Aneurysm

"Intracranial aneurysms are a common condition in the general population, estimated to affect 3-6% of the population [1] " It should be noted that fortunately, about 50-80% of aneurysms do not rupture in a patient's lifetime [2]. This leads to the fact that diagnosis is often incidental. In addition, despite the relatively high prevalence in the population, mortality rates are low. It should be noted that unruptured aneurysms are usually asymptomatic and go unnoticed by the patient. However, some patients experience symptoms that can be connected with the rupture of an aneurysm, such as headache, dizziness or oculomotor nerve palsies [1] . The two typical

active treatment options for subarachnoid aneurysm haemorrhage are clipping and coiling. The passive treatment would be a conservative management that can include a craniotomy or the placement of an External ventricular drain (EVD). Classical surgical treatment started in 1937 by clipping before in 1990 Coiling was developed [3] and has become an increasingly popular treatment option. The most important risk factors for being affected by an aneurysm are: Female gender, (66-70% of those affected are female), Old age (which is also a known risk factor), in some congenital diseases the risk is also increased. Notably, polycystic kidney disease stands out as a significant factor, doubling the risk to approximately 10% compared to the general range of 3.6-6%. Moreover, other conditions, including Marfan syndrome, neurofibromatosis type 1, multiple endocrine neoplasia type 1, pseudoxanthoma elasticum, hereditary hemorrhagic telangiectasia, and Ehlers-Danlos syndrome, are associated with an increased susceptibility [1].

1.2 Clipping

Clipping is one of the two typical treatments for a cerebral aneurysm. The first obliterative clipping was performed in 1938 by Walter Dandy at John Hopkins Hospital in the USA [4]. Since then, it has been the typical treatment for such a condition for many years. Clipping is performed by performing a craniotomy and then using a vascular clip to close the aneurysm from the outside. In the case of a ruptured aneurysm, this also stops the bleeding. The advantage of this procedure is that the risk of a new aneurysm forming is significantly reduced. The disadvantage is that this procedure is much more invasive than coiling. In recent decades, the popularity of clipping has declined as the new technique of coiling has been introduced. Nevertheless, clipping remains a recognised and reliable method of treating patients with cerebral aneurysms [5].

1.3 Coilling

Coiling is the second typical treatment for a cerebral aneurysm. Coiling was first performed in 1990 by Guido Guglielmi. It is an endovascular treatment that closes an aneurysm without opening the patient's skull. As this is a demanding procedure, it requires state-of-the-art technology. It is therefore only logical that it took many years longer compared to clipping until the possibility for this therapeutic option arose. In coiling, a coil, usually made of platinum, is inserted through an arterial or venous route to the aneurysm. There are also coils made of biopolymer and hydrogel-coated coils. Coils come in all shapes. Length, diameter and cross-

section can be chosen according to preference and requirement. In the procedure, one or more coils are placed in the aneurysm. The aneurysm is closed by the thrombotic effect of the blood which adheres to the coil. From then on, the blood flows past the coil with the clotted blood. The typical danger of a coil is that it can cause thrombosis and vascular occlusion, which can lead to a stroke. The insertion of the coil can also cause the aneurysm to rupture. In recent years, the percentage of aneurysms treated in this way has increased. This is explained by the lower complication rate and the higher success rates of the therapy [6, 7].

2 Aims and Objectives

This study aims to find out whether there is a significant difference between endovascular treatment at the KBC-Zagreb and non-endovascular treatment at the KBC-Rijeka. Treatment in Rijeka typically involves clipping. However, the treatment spectrum also includes craniotomies, the placement of an EVD and general management. In the following, they will be grouped as conservative therapy as none of these treatment options acts on the aneurysm itself. The patients considered in this study were transferred to Zagreb exclusively for endovascular treatment. The Rijeka Hospital currently does not have the possibility to perform endovascular treatment. In Rijeka, patients requiring interventional radiological treatment are therefore transferred 167 km to Zagreb by ambulance. The first objective is to assess and compare various options for treating an acutely symptomatic aneurysm and identify the most effective approach. The second goal is to explore the possibility of improving current procedures to ensure a faster and better allocation of patients. By determining a better choice of approach in the future, long-term costs due to rehabilitation measures could be reduced and patient well-being permanently increased. Furthermore, the data from KBC-Rijeka will be compared with the current state of research. In the discussion section, other research will be compared to the data from Rijeka and similarities and differences will be highlighted. Another task of this paper is to create a data basis. This should enable future studies to draw a comparison. Only in this way is it possible to determine an improvement or worsening of the treatment success. In recent years, no paper has been written that deals with the data on aneurysms from Rijeka, so this paper also serves as a baseline from which can be worked upon.

3 Participants and Study Design

This work is conducted in the design of a retrospective cohort study. For this purpose, the data of all patients admitted to the neurosurgery department of KBC-Rijeka were anonymised and differentiated according to diagnosis. The analysis of this data resulted in 82 patients with the diagnosis of cerebral haemorrhage, who presented to the Emergency Department of the KBC-Rijeka in the period under consideration from 01.01.2020 to 09.12.2022. Of these 82 patients with a cerebral haemorrhage, 42 patients presented with an acutely symptomatic aneurysm, and it is precisely these patients who will be considered in this paper.

In the following, it will be explained on what data the patients were evaluated. To determine the baseline situation, the time since onset of symptoms, the GCS score Table 1, the HH Table 2 and the diagnostic method used to detect an aneurysm were recorded if possible. In order to assess the influence of other factors, the age of the patients, their sex and the length of stay in the hospital were also determined. To compare the treatment options, the place of treatment, the chosen therapy, the control-diagnostic method and the patient's condition when leaving the hospital compared to the time of the patient's admission were recorded. The effectiveness of the therapy is also to be determined from the last parameter. The assessment of whether the patient's symptoms had changed compared to the time of admission was the responsibility of the discharging physician. In the discharge letter from the hospital, the doctor recorded whether the patient's clinical condition had improved, worsened or remained unchanged. In the following, these values are compared with each other. It was also calculated whether there was a correlation between the various factors considered. GraphPad Prism 8.3.0 was utilized to assist with the statistical analysis, including the Kolmogorov-Smirnov test to examine normality. For correlation testing, the nonparametric Spearman correlation was used, with a correlation considered significant if the resulting P-value was less than 0.05 ($p < 0.05$).

Table 1: Glasgow-Coma-Scale (Source: Waterhouse [8])

Feature	Response	Score
Best eye response	Open spontaneously	4
	Open to verbal command	3
	Open to pain	2
	No eye opening	1
Best verbal response	Orientated	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No verbal response	1
Best motor response	Obeys commands	6
	Localising pain	5
	Withdrawal from pain	4
	Flexion to pain	3
	Extension to pain	2
	No motor response	1

Table 2: Hunt-Hess score (Source: Shah et al. [9])

Grades	Criteria
1	Asymptomatic, mild headache, slight nuchal rigidity
2	Moderate to severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy
3	Drowsiness, confusion, mild focal neurological deficit
4	Stupor, moerate to severe hemiparesis
5	Deep Coma, decerebrate posturing, Moribund apperance

4 Results

4.1 Treatment Options

Of the total 42 patients, 23 (54.8%) were referred to KBC-Zagreb for endovascular therapy. 19 patients (45.2%) remained in Rijeka for further treatment. It can be concluded from this that the allocation of patients in Rijeka is decided in a balanced way. In Rijeka, clipping was performed 9 times (47.4%) and conservative therapy 10 times (52,6%). This shows that the most frequently performed therapy is conservative management.

Now the discharge conditions of the patients are to be taken into consideration. We have data available for 19 patients who received treatment in Rijeka, while for Zagreb we have information on 23 patients. Of 19 treated in Rijeka, 8 were discharged in an improved general condition. This results in a rate of 42.1%. In Zagreb, 14 of the 19 known patients improved. This results in a rate of 73.7%. It must be also mentioned that one Patient died in the following days of the Therapy (5,3%). In the following, the endovascular therapy in Zagreb, the clipping in Rijeka and the other therapies in Rijeka consisting of EVD, craniotomy and a conservative approach are compared. As described above, 14 out of 19 patients improved with the endovascular treatment in Zagreb which is 73.7%. When clipping was performed in Rijeka, which was the case in 9 patients, 6 patients had a successful treatment at the time of discharge, so 66.7% of the patients. In the days following clipping two patients died (22,2%) .If treatment in Rijeka did not include clipping, 2 out of 10 patients showed an improvement in their general condition at discharge which is 20%. If one looks at the correlation of this value, one can see that there is a clear connection between therapy and outcome. With an R-value of 0.41, there is a relatively strong correlation between these parameters ($r = 0.41$; $p = 0.010$; $n = 38$).

In order to exclude the possibility of a shift in the data due to age, the age of the different treatments should be considered in the following. The 23 patients who received endovascular treatment have an average age of 56.9 years. The median age is 59.9 years. The average age for clipping in Rijeka is 58.7 years. The median age is 59 years. With a Conservative approach, the average age is 62.7 years. The median age is 60.7 years. This shows that patients who receive endovascular treatment are on average 1.8 years younger, i.e. 3.1% younger. The median age is 0.9 years, i.e. 1.5% older. With conservative treatment, patients are on average 4 years older, i.e. 6.8%. The median age is 1.7 years, i.e. 2.9% older. All Percentages are compared to clipping. From the calculations on the correlation between age and therapy, it can be concluded that there

is no correlation.

4.2 Age

When looking at the age, it can be said that the cases are concentrated in the second half of life, the youngest patient was 35.8 years old, and the oldest person was 88.1 years old. The average age is 57.3 years, the median is 59.2 years. It can be said that women, with an average of 60.1 years and 62.7 in the median, are older than men, who are 56.9 years old on average and 57.4 years old in the median. This is also visible in Figure 1. This makes an age difference of 3.2 years on average and 5.3 years on median, or 5.3% and 8.5%. From the calculations of the correlation between sex and age, it can be concluded that there is no correlation.

In the following, the effects of age are compared with the success of the therapy. Of the 22 patients considered who were younger than 60 years of age and for whom it is known how they were doing at the time of discharge compared to the time of admission, therapy was successful in 16 patients. That is 72.7%. In contrast, 15 patients were older than 60 years and for whom therapy success could be estimated at the time of discharge. Of these, 5 had successful therapy at the time of discharge. That is 33.3%. If one now looks at the correlation between the outcome and the age, a clear connection can be established. With an R-value of -0.46, there is a relatively strong correlation ($r = -0.46$; $p = 0.004$; $n = 38$).

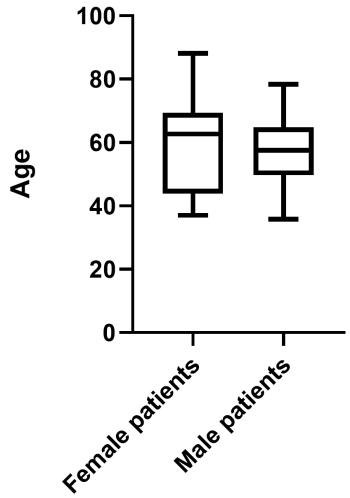

Figure 1: Overview of patient age

4.3 Sex

There was no discernible trend in the sex distribution. Of the 42 patients considered, 23 were women, i.e. 54.8%. 19 of the patients considered were male, i.e. 45.2%. If we look at the influence of the gender factor, the following results emerge. Of the 21 women whose general condition was known before and after the therapy, 11 had a successful therapy. This is 52.4%. Of the 16 men with a known course of therapy, 10 improved when looking at the clinical discharge symptoms. This is 62.5%. From the calculations on the correlation between sex and outcome, it can be concluded that there is no correlation.

4.4 Length of Stay

With this value, it should be noted that patients from KBC-Zagreb cannot be taken into account, which is due to the fact that the length of stay of the transferred patients in Rijeka is not known. From the 9 clipping cases considered in Rijeka, the average length of stay is 23.6 days. The median length of stay is 21 days. The other treatments in Rijeka, 10 in number, which are not further differentiated, have an average length of stay of 14.1 days. The median is 12.5 days. The average length of stay was thus reduced by 9.5 days for a non-clipped patient. This is also true for the median reduction of 3 days. The difference was 40.6% on average and 24% in the median. If one looks at the correlation between length of stay and therapy success, one can also establish some correlations. Here, the influence of the length of stay will only be considered in the case of clipping, since the other treatment methods had too little success to recognise a trend. Of the 4 patients who were treated in the clinic for less than 21 days, an improvement in the general condition was observed in 2, i.e. 50%. When looking at patients who were treated at KBC-Rijeka for 21 days or longer, a difference can be observed. Of the 5 patients who met the above criteria, 4 were discharged in a clinically improved condition. This is 80% of the patients. From the calculations on the correlation between length of stay and outcome, it can be concluded that there is no correlation, at least in the case of clipping.

4.5 Time Until Arrival

The average time taken by a patient from the onset of symptoms to arrival at the emergency department was 6.5 hours, with a median time of 4 hours. In the following, the time of arrival is compared with the success of the treatment. Of the 12 patients who presented to the emergency

department after 4 hours from symptom onset, 10 patients improved clinically. This is 83.3%. Only 6 of the 12 patients (50%) who presented within 4 hours showed significant improvement after treatment. From the calculations of the correlation between the onset of symptoms and outcome, it can be concluded that there is no correlation.

4.6 Glasgow Coma Scale

When the 35 patients with known GCS arrived at the emergency department of KBC-Rijeka, the average GCS score was 10.9 and the median score was 13. Of 20 patients with a known therapy result and GCS score > 8, 14 left the clinic in an improved condition so 70%. In contrast, 11 patients with GCS ≤ 8 and known therapy success, 6 of whom left the clinic in an improved general condition. This is 54.5% of the patients. From the calculations of the correlation between GCS and outcome, it can be concluded that there is no correlation.

4.7 Hunt-Hess Score

The HH score was recorded in 12 patients and averaged 2.2 with a median of 2. The influence on the success of the therapy proved to be insignificant. Of the 4 patients whose general condition was determined at discharge and who had a HH score of ≥ 3, 3 improved clinically, i.e. 75%. Of the patients with a HH of ≤ 2, 4 out of 5 showed an improvement at discharge. This results in 80%. From the calculations on the correlation between HH and outcome, it can be concluded that there is no correlation.

4.8 Diagnostics

In 41 of the 42 cases, Computed tomography scan (CT) and Computed tomography angiography (CTA) were performed for diagnostic clarification of the aneurysm, i.e. in 97.6% of the cases.

5 Discussion

This section is separated into 3 parts. The first puts the results of the data collected for this paper in perspective to international studies. The second part will discuss the Problems of this paper and the problems in obtaining the data for the purpose of this paper. The third part asks questions that can be tackled in further papers about this topic.

5.1 Discussion of the Results

5.1.1 Considerations Regarding Therapy

The success rate of endovascular treatment at the KBC-Zagreb was 73.7%. Clipping performed at KBC-Rijeka showed an improvement rate of 66.7%. Brinjikji et al.[10] showed in their paper ”Effect of age on outcomes of treatment of unruptured cerebral aneurysms: a study of the National Inpatient Sample 2001-2008” that coiling is the most successful therapy. In their data, mortality was only 0.9%, compared to 2.5% of patients treated with clipping. Overall, however, it can be said that older patients had significantly higher complication rates. This topic will be discussed later in this paper. The authors conclude that older patients (over 65 years of age) benefit most from endovascular therapy by comparing their results with other studies that were current at the time. Brinjikji et al. also point out that in this group of patients, endovascular therapy also reduces the time patients spend in the hospital . Brinjikji et al.[11] also describe in ”Age-related trends in the treatment and outcomes of ruptured cerebral aneurysms: a study of the nationwide inpatient sample 2001-2009” that coiling is the better treatment choice, especially in older patients. They consider it positive that between 2001 and 2009 the mortality of all patient groups decreased, which is attributed to a better individualised and adapted choice of therapy for both clipping and endovascular treatment. It is even described that in the middle cerebral artery, clipping achieves better therapeutic success (46% in coiling and 87% in clipping) . Since the data set of this work is too small, no trend can be determined with regard to the success rate and therapy selection. For this, a larger number of cases is required. The authors also quote from the paper ”Could late rebleeding overturn the superiority of cranial aneurysm coil embolization over clip ligation seen in the International Subarachnoid Aneurysm Trial?” in which it is described that, from the point of view of the authors Mitchell et al. [12], clipping is the preferred therapy option for patients aged 40 years and younger. This is justified by the fact that long-term protection from SAH is better in these patients and a longer life expectancy

can be reached . If one now looks at the concrete values from the work from 2001-2009, the authors describe that in 33.7% of the patients, a negative result occurred. In Rijeka, 33.3% of Patients had a negative outcome. When looking at the values for coiling, according to the authors the rate is 23.2%. For Zagreb, the rate is 27.3% according to the data for this study [11]. Another paper should bring a further perspective on the situation. Bryan et al.[13] describe in the paper "The treatment of acutely ruptured cerebral aneurysms: endovascular therapy versus surgery", that 75% of patients can expect successful endovascular treatment. This result is in line with the 73.1% from Zagreb. For the treatment option of clipping, the same authors give a success rate of 68% for survival in the first month. This compares with 66.7% of patients who had an improvement in their general condition at the time of discharge. Conservative treatment showed improvement at discharge in only 20% of cases. This is a topic on which the database is very thin. Maurice-Williams et al.[4] describe in their 2003 paper "Intracranial aneurysm surgery and its future", that patients admitted with a grade 1 aneurysm who survive the first 4 days have a 90% chance of surviving the next 2 years without treatment . Another perspective is provided by a 1984 study named "Cooperative study of intracranial aneurysms and subarachnoid haemorrhage: a long-term prognostic study: II. Ruptured intracranial aneurysms managed conservatively". Nishioka et al.[14] describe that 66.5% of patients died within a period of 16-24 years, 40% of them within the first 6 months. Bryan et al.[13] advise in the already mentioned paper "The treatment of acutely ruptured cerebral aneurysms: endovascular therapy versus surgery", against treating patients conservatively, citing high mortality and morbidity in patients treated this way. They describe that conservatively treated ruptured aneurysms have a rebleeding chance of about 20% in the first 2 weeks after rupture.

All in all, it can be said that conservative management of patients is very rarely if ever, recommended. However, as described at the beginning, the data on this is thin. The data collected from this study with a 20% success rate leads one to conclude that this therapy option is not to be recommended. In this study, there was a clear correlation between therapy and outcome and when compared to other scientific studies in this field, the same picture emerges. The best therapy option should be chosen according to age and place of onset of the disease. The clear correlation between therapy and outcome is also confirmed in studies whose data basis lies outside Europe and can therefore be assumed to be reliable. The data collected for the purpose of this study, therefore, fit seamlessly into the current research situation. An influence of age on the selected treatment option of 1.5-6.8% can be considered as not significant. According to

this, it can not be said that patients with a better prognosis were selected for a specific treatment.

5.1.2 Considerations Regarding Age

This study shows that age is a significant factor in prognosis. There is a clear trend that acute aneurysms are a disease of the second half of life. The average age of the patients treated at KBC-Rijeka is 57.3 years for men and 60.1 years for women. Other studies on this topic show similar results. Yamashita et al.[15] describe in the analysis "Cerebral aneurysms in the elderly in Yamaguchi, Japan: analysis of the Yamaguchi Data Bank of cerebral aneurysm from 1985 to 1995" that there is a clear relationship between age and outcome. Furthermore, it is described that patients of advanced age have a significantly increased risk of admission with a Hunt and Kosnik score (a modification of the HH with a 0 and 1a in grading[16]) of 4 or 5. Zhao et al.[17] also describe in "An analysis of 1256 cases of sporadic ruptured cerebral aneurysms in a single Chinese institution" that aneurysms occur mainly in the second half of life. They also describe that women are slightly older than men with 55.2 to 51.6 years. Zheng et al.[18] describe in their study "Influence of age-related complications on clinical outcome in patients with small ruptured cerebral aneurysms", that age has a significant impact on many factors. They found out that patients of advanced age suffer from significantly more neurological deficits. It was also reported that old patients are hospitalised for significantly longer. They also reported that, as confirmed in other studies and this one, they have a statistically relevant worse outcome than those affected at a younger age. With a successful treatment rate of 72.7% in patients under 60 and a rate of 33.3% in patients over 60, a strong correlation could be established. This is also shown in other research that came to the same conclusions. The somewhat older average age of women could also be proven internationally. The data collected from KBC-Rijeka thus confirm the current state of research.

5.1.3 Considerations Regarding Sex

When looking at the different data between men and women, it's possible to see that women are on average 5.3% older than men. A trend can be seen here, but according to the calculations it cannot be considered significant. When looking at other research results on this topic, the same can be seen. Li et al.[19] describe in their work "Prevalence of Unruptured Cerebral Aneurysms in Chinese Adults Aged 35 to 75 Years" that there is no significant difference regarding age. In both, the age of highest incidence was 55 to 64 years. This also confirms that the highest

prevalence occurs in the second half of life, as already described in the previous part. The paper ”Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis” by Vlak et al.[20] clearly describes that there is an increased risk for women over 50. This is due to the fact that they suffer more frequently from larger (>5mm) aneurysms which have an increased risk of rupture. This also explains why, in the data collected for this study, women were 5.3% older on average and 8.5% older on the median. Therefore, it can be said that the results of KBC-Rijeka are in line with the international results. A correlation could also be rejected when investigating whether gender has an influence on the success of the therapy. Fuentes et al.[21] wrote in their paper ”sex differences in cerebral aneurysms and subarachnoid hemorrage” that it has been known for some time that women are more likely to carry an unruptured aneurysm. This is also shown in this paper: women presented 9.6% more often with an aneurysm than men. Furthermore, the authors describe that some studies have already looked at the influence of gender on the outcome of therapy. However, this was not the primary aim of these studies, just as it is not the case in this paper. Nevertheless, these studies also conclude that there is no correlation between gender and outcome. The data set on which this paper is based supports this assumption.

5.1.4 Analysis of Test Scores

The GCS has long been established in clinical practice and produces a clear snapshot of patients [22]. In the following, the influence of this value on the prognosis of aneurysms is described. In the data on which this paper is based, there was a difference in treatment success of 15.5% depending on whether the patients had a GCS score of more than 8 points or not. However, there was no correlation. Patients were only assessed for GCS on admission, so no pre-operative and post-operative comparison can be drawn from this data. When looking at other data on this topic, the following picture emerges. Aulmann et al.[23] describe that even in their data from the paper ”Validation of the prognostic accuracy of neurosurgical admission scales after rupturing of cerebral aneurysms”, there was little evidence of a correlation. This was the case for almost all scores in their work. Surprisingly, they found the HH to be the best measure of prognosis. The paper by Catapano et al.[24] called ”The prognostic significance of a cast fourth ventricle in ruptured aneurysm patients with intraventricular hemorrhage in the Barrow Ruptured Aneurysm Trial (BRAT)” also describes that although patients with the same GCS were studied, the outcome varied greatly depending on the underlying other scores. In this study, the

HH was also considered to be more decisive. Thus, it is described that besides an age of >55 years, as well as having a so-called cast fourth ventricle (high amount of blood in the ventricle), a HH of >3 is a decisive risk factor that has a negative effect on the expected outcome. All in all, it can be said that the GCS cannot be assumed as a reliable prognostic factor in the case of an aneurysm. Instead, HH should be relied upon to estimate future prognosis. In the data for this study, there was no correlation between GCS and outcome.

When looking at the HH score, which is a proven tool in neurosurgery for assessing the condition of a patient with SAH [25], the picture is similar to that of the GCS. The success of treatment occurred, with a HH of greater than or equal to 3, just 5% more frequently than in the case of a HH of less than or equal to 2. From this data situation, there is no correlation and thus, from the point of view of this study, no possibility of assessing the prognosis of a patient on the basis of this parameter. In contrast to the data described in this paper, the authors Lubicz et al.[26] report in "Endovascular treatment of ruptured intracranial aneurysms in elderly people" that there is a significant correlation between the HH at admission and the clinical outcome. In their paper, they mainly discussed the difference between patients with HH 1-3 and 4-5. It is not possible to analyze the impact of HH due to the small number of patients in this paper. The authors of the before mentioned paper suggest delaying treatment for patients with a HH score of 4 or higher until their condition improves. Overall, however, the chance of a worse outcome of therapy remains increased. That a high HH (4-5) is associated with a worse prognosis is also described by Sedat et al.[27] in the paper "Endovascular treatment of ruptured intracranial aneurysms in patients aged 65 years and older: follow-up of 52 patients after 1 year". They write that 77% achieved an improvement in HH 1-2 and only 16% in HH 4-5. A second group showed a similar result with 88.5% to 41%. From this, it can be concluded that there is probably a connection between HH and the outcome of a patient. The papers used for comparison included more patients and they were more differentiated. Also, the data collected for the purpose of this study, with a number of 12 patients with known HH, are to be considered very unreliable. The absence of any patients with a HH of 5 in this study further emphasizes the unreliability of the database regarding this particular factor.

5.1.5 Examination of Other parameters

Now the influence of the time until arrival at the clinic should be taken into perspective. The data suggest that there is no correlation between arrival time at the clinic and therapy success.

Contrary to an initial assumption, patients who arrived after 4 hours from the onset of symptoms had a 33% higher rate of successful therapy. Patients who arrived within 4 hours of symptom onset showed improvement in 50% of cases. This compares to 83.3% who presented 4 hours or more after the onset of symptoms. One reason for this could be the more severe symptomatology of the patients who then visit the hospital earlier. However, since no data is available on this topic, this is pure speculation. This is what Maurice-Williams et al.[4] describe in their 2003 paper "Intracranial aneurysm surgery and its future". They report that only 45% of patients who present to a hospital within 24 hours can be described as having a grade 1 or 2. For patients who take more than 7 days to present to a hospital, the rate is 85%. For this reason, it seems logical that more severe diagnoses are done earlier. Overall, the scientific situation on this topic is relatively thin. Most scientific papers only address the issue of delaying surgery. For example, Deruty et al.[28] in the study "Management of the ruptured intracranial aneurysm-early surgery, late surgery, or modulated surgery?" conclude that in younger patients (age $<$50) it is advisable to perform surgery earlier, while in older patients or patients with impaired consciousness, it is advisable to wait a little longer. However, since this study is from 1991 when endovascular treatment was not as common as it is today, another study should also be considered. The work by Maurice-Williams et al.[4] from 2003, which has already been cited, asks precisely the question of whether surgery should be delayed, which was a major question of the 1970s. They describe that it makes no difference, as the amount of patients who are admitted at grades 1-3 who die from rebleeding while still waiting for surgery is about the same number of patients who die when switching to an early surgical technique. It can be said that the time factor plays a subordinate role. Furthermore, the authors describe that with the introduction of endovascular treatment, discussion is no longer necessary, as there is no reason to postpone endovascular treatment. From this, it can be concluded that good cooperation between KBC-Rijeka and KBC-Zagreb is crucial, as all patients requiring endovascular treatment must be transferred. As a rule, these transfers are carried out within 24 hours at KBC-Rijeka.

Looking at the length of stay proved to be difficult. The first problem is that no data from Zagreb are available and therefore could not be included in the evaluation. But also some patients from Rijeka cannot be evaluated. These are the patients treated conservatively, since only 2 out of 10 of these showed therapeutic success, no trend can be recognised from this data. For the conclusions on length of stay and outcome, only the patients clipped at KBC-Rijeka are to be considered. The difference in symptomatic improvement was 30%. Patients treated for less

than 21 days had a 50% success rate, while patients treated for 21 days or longer had an 80% success rate. However, there was no correlation between length of stay and outcome. In their study ”Impact of hospital-related factors on outcome after treatment of cerebral aneurysms”, Berman et al.[29] describe that a shorter hospital stay with a better outcome for the patient can be achieved by an experienced team at a maximum care provider. In the case of a ruptured aneurysm, an improvement of up to 20% less adverse outcomes was observed at a maximum care hospital compared to smaller hospitals. The fact that length of stay in itself has a positive effect on the therapeutic outcome is not described at all. Since an experienced team with a shorter length of stay achieves a better outcome, a correlation between length of stay and outcome cannot be assumed. Overall, it can be said that conservative treatment is associated with a shorter length of stay so that a median reduction of 24% can be achieved. However, whether this is to the advantage of the patient remains questionable with an improvement rate of just 20% of patients treated conservatively. Although no data on the difference in length of stay between patients who were clipped and patients who were treated with coiling was collected in this study, it should be briefly discussed here. Hoh et al. write in ”Length of stay and total hospital charges of clipping versus coiling for ruptured and unruptured adult cerebral aneurysms in the Nationwide Inpatient Sample database 2002 to 2006” that clipping in patients with a ruptured aneurysm is associated with a 1.2-fold increase in length of stay and thus also with increased costs. Looking at the length of stay proved to be difficult. The first problem is that no data from Zagreb are available and therefore could not be included in the evaluation. But also some patients from Rijeka cannot be evaluated. These are the patients treated conservatively, since only 2 out of 10 of these showed therapeutic success, no trend can be recognised from this data. For the conclusions on length of stay and outcome, only the patients clipped at KBC-Rijeka are to be considered. The difference in symptomatic improvement was 30%. Patients treated for less than 21 days had a 50% success rate, while patients treated for 21 days or longer had an 80% success rate. However, there was no correlation between length of stay and outcome. In their study ”Impact of hospital-related factors on outcome after treatment of cerebral aneurysms”, Berman et al.[29] describe that a shorter hospital stay with a better outcome for the patient can be achieved by an experienced team at a maximum care provider. In the case of a ruptured aneurysm, an improvement of up to 20% less adverse outcomes was observed at a maximum care hospital compared to smaller hospitals. The fact that length of stay in itself has a positive effect on the therapeutic outcome is not described at all. Since an experienced team

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5.1.6 Considerations Regarding Diagnostics

When looking at the diagnostics, CT and CTA were used in 97.6% of the cases. As this is the typical method of diagnosing an intracranial aneurysm, this was to be expected. Keedy[31] describes in his paper, "An overview of intracranial aneurysms", that there are three main methods of diagnosis Intra-arterial digital subtraction angiography (IADSA), CT/CTA and Magnetic resonance angiography (MRA). Each of these methods has its advantages and disadvantages. Due to the highest spatial resolution, IADSA remains the gold standard. The disadvantage of this method is that a contrast medium is needed. Thrombi can also be visualised more poorly compared to the other two methods. Another problem with IADSA is that it is expensive and has a complication rate of 2-4%. MRA has the advantage that no contrast medium is needed, but it can be given to obtain a better image. MRA is particularly helpful in patients with kidney damage, but also in patients who have problems tolerating contrast media. Compared to an IADSA, an MRA can visualise a thrombus better. A CT and CTA can also show calcification and, similar to MRA, a developed thrombus is better demarcated than is the case with IADSA. It is also described that the sensitivity of the methods decreases significantly with the smaller size of the aneurysm to be found. Overall, it can be said that smaller aneurysms are better detected in a CTA than in an MRA. Based on these factors, the author suggests that CTA has more advantages than the gold standard IADSA. According to the current state of research on the diagnosis of aneurysms, nothing should be changed in the diagnostic procedure in Rijeka.

5.2 Limitations

As this paper was done on a small scale with only 41 patients having an acute aneurysm, the conclusion drawn from this study can‘t be counted as conclusive for depicting the treatment options as a whole. Also, only the data from the Rijeka hospital were used, which makes the data very one-sided and perhaps highlights regional problems that do not exist in hospitals in the rest of the country. Furthermore, a study over three years is too short to make decisions based only on these results. Probably the biggest problem that also made the data collection of this work particularly difficult is the opaque data situation. In order to make future work more

meaningful and easier, a protocol for the inclusion of these patients should be created at (KBC-Rijeka). This should include the Onset of Symptoms, GCS, HH but also the Fischer grade. The latter was detected only twice in the 42 patients considered. Unfortunately, it is currently the case that the admitting physician does not have any guidelines and, accordingly, several of these parameters are often missing. This also makes data collection much more difficult, as one has to spend a long time clicking through doctor's letters to find the required data, which is then often not found. Fixed criteria should also be defined. Based on these criteria, it should be decided whether the clinical symptoms of a patient have improved, worsened or remained unchanged. Currently, this is the responsibility of the discharging doctor. The parameters on the basis of which this is assessed remain opaque and are nowhere clearly defined. Another major problem with the data used for this study is that there is no data on the long-term success of the treatment. The current data sets only reflect the condition of the patients when they leave the hospital and even then only whether they are better, worse or unchanged compared to their admission. Yet it is precisely the long-term success of a therapy that is of decisive importance. Here, it would be advisable to carry out a semi-annual or annual check-up to ensure that the treatment also has the desired success over a longer period of time. In addition, it is possible to find out whether there are differences between endovascular therapy in Zagreb and therapy in Rijeka in the long term. But there is also a qualitative problem with the evaluation of the general condition of the patient at discharge. It is not recorded whether the patient is much better or only a little better, so it is also necessary here to name objective criteria that can be used to determine how much better the patient is.

5.3 Outlook

This raises some questions for future studies. How does the data from Rijeka compare to other Croatian or European cities? Since in this paper, only two clinics were studied and only the endovascular cases from Rijeka for the KBC-Zagreb, this is not sufficient to make a general statement. What are the long-term successes and failures? As discussed in the previous part, this paper completely lacks a look at long-term successes. How does the success of therapy in the last three years compare to the last ten or twenty? As already described in the aims and objectives part, the aim of this work was to create a data basis. Extending this data into the future and past and putting it into perspective and substantiating or falsifying results is an important part of future work.

6 Conclusion

As it is possible to see, there are still many unanswered questions and there are still some things that can be changed in order to write papers with a more solid database. This was to be expected given the fact that this paper is the first to deal with aneurysm data from KBC-Rijeka. Nevertheless, some conclusions can be drawn from the data of the last three years.

Possible improvements to ensure high-quality therapy in the KBC-Rijeka are: An admission protocol should be developed urgently. Doctors must determine a GCS, HH score and Fischer grade, otherwise an objective perspective cannot be taken at all. The absence of GCS recordings in 7 patients indicates the need for further improvements. Additionally, the low incidence of HH recordings in only 12 patients and Fischer grade recordings in only 2 patients highlights this poor result. It is also to be criticised that these scores were only determined on the arrival of the patients. In order to ensure good care, these scores should also be checked regularly during the patient's stay in the hospital, especially in the case of patients with a long stay. In addition, the said scores must also be carried out when the patient is discharged to make the successes or failures of a therapy objectifiable.

The choice of treatment should also be changed in the future. If you look at the study results, endovascular treatment is considered the best option in most cases and is accordingly chosen more often. In Rijeka, 54.8% of patients receive this treatment. It should be considered more often to transfer a patient to Zagreb for endovascular therapy. The most important conclusion that should be drawn from this study is that the results of clipping in Rijeka are very satisfactory and are also above the averages of the studies used in this study. It is therefore incomprehensible that over 50% of the patients who remained in Rijeka received conservative therapy. In the future, more patients should receive clipping instead. When managing fewer patients conservatively patient well-being and quality of life could be increased, while long-term costs for treatment and care would go down. Logically, every patient is different and therefore a personalised approach is recommended. From this, it can be concluded whether it is advisable to perform an endovascular treatment or a clipping for the respective patient.

However, this work did not only lead to conclusions about therapy. For example, it was shown that age is a significant risk factor for suffering an aneurysm, as was assumed in the beginning. It also showed that women who suffer from an aneurysm are on average 5.3 years older than men. Explaining the probable reasons for this would go beyond the scope of this paper and requires a separate study.

The time of arrival since the onset of symptoms proved to be a negligible factor. There was a tendency for patients who came earlier to the clinics to have a worse outcome. However, there was no significant correlation. We can only speculate about the reason for this. It is most likely that patients presenting with an aneurysm with more severe symptoms go to the hospital earlier and therefore have a worse prognosis.

There were only correlations between therapy and outcome and between age and outcome. The GCS was not suitable as a prognostic factor in this study or in international studies. The HH score was also not shown to be a prognostic factor in this study, but in other studies, it is described as more reliable than the GCS. If one wants to use a trend direction for the success of a patient's therapy, it follows from the research for this paper that the HH score should be chosen. The accuracy of this parameter on the result, however, remains controversial.

The performance of a CT and CTA in Rijeka is to be regarded as exactly right. This should not be changed in the future as the standard diagnostic procedure.

Another positive aspect is the good cooperation between KBC-Rijeka and KBC-Zagreb. This is satisfactory and the transfer of patients within a maximum of 24 hours can be considered as good. The therapeutic successes in Zagreb are also comparable to the studies used for this paper.

7 Summary

In summary, it can be said that both clipping and endovascular treatment in the KBC-Rijeka can be compared to international therapeutic successes. In the future, fewer patients should be treated conservatively. The admission and discharge protocols need to be revised so that the different scores are performed and recorded more reliably. Overall, the data collected for this paper were consistent with the current state of research. This work largely supports the current data and research situation. Age and therapy can probably be described as the biggest factors influencing patient outcomes. GCS and HH are both not reliable prognostic factors, with HH performing slightly better. CT and CTA can be confirmed as the best diagnostic option.

Aneurysm, Cerebral aneurysm, Clipping, Coilling, Conservative Therapy, Rijeka, Zagreb

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9 Curriculum Vitae

Alfred Gramelt was born in Weimar, Germany on October 9th, 1998. He received his high school diploma from Armin-Knab-Gymnasium in Kitzingen, Germany. In 2017, he began his integrated undergraduate and graduate studies at the Faculty of Medicine, University of Rijeka in Croatia. In 2020/21, he completed a three-month internship in internal medicine at Diakonissen-Stiftungskrankenhaus Speyer. Additionally, Alfred participated in voluntary internships in general practice and neurosurgery during his summer breaks. Throughout his studies in Croatia, he has achieved proficiency in speaking Croatian at a B1 level.