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Endovascular Treatment of Carotid In-Stent Restenosis

Thesis

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INTRODUCTION

Stroke is the most common significant manifestation of cerebrovascular disease and is the second greatest cause of disability and death globally. 87% of the cases manifest as ischemic stroke, up to 20% of these as the proximal internal carotid artery (ICA) lesion due atherosclerosis. Despite the advances in medical treatment, the invasive treatment of these lesions by an endovascular or surgical approach remains an important option of stroke prevention, in symptomatic and asymptomatic cases alike. The recent large randomized trials comparing the safety and efficacy of carotid stenting (CAS) vs. endarterectomy (CEA) showed similar outcomes in stroke prevention with both methods, initiating a shift in the treatment paradigm from favoring endarterectomy towards equal acceptance of both modalities. A drawback of both CEA and CAS is the development of neointimal hyperplasia resulting in a progressive, significant in-stent recurrent stenotic lesion (ISR). The underlying pathology and the composition of the material causing luminal narrowing is completely different compared to the original atherosclerotic plaque. The neointimal tissue is covered with endothelium and there is no debris material within the plaque, therefore the risk of increased thrombogenicity and embolization is minimal. However, rapid progression of the luminal narrowing can lead to decreased blood flow velocity and may ultimately result in a thrombotic occlusion of the ICA. Accordingly, a significantly increased risk of ipsilateral stroke has been reported in patients with in-stent restenosis by multiple randomized trials, also there is evidence of significant correlation between luminal narrowing and cognitive impairment, underlining the importance of timely diagnosis and effective treatment of ISR lesions. The literature on the treatment of ICA ISR is relatively sparse and randomized trials are lacking. Available treatment options include repeated CAS, endarterectomy or reangioplasty (re-PTA) using a conventional or a drug-eluting balloon (DEB). Although the safe and effective application of paclitaxel-eluting DEBs is well established for the treatment of ISR in other vascular territories including the coronary, peripheral and intracranial arteries, results of a mere 33 DEB re-PTA procedures of ICA ISR have been published in case series in the literature altogether.

AIMS

The present examination is characterized as a retrospective study conducted at a single site, focusing on patients who experienced carotid in-stent restenosis. Multiple randomized trials have indicated a significant rise in the likelihood of ipsilateral stroke in individuals with in-stent restenosis. At the same time, the CREST-H study aims to evaluate cognitive outcomes in individuals diagnosed with cerebral hypoperfusion and cognitive impairment. Hemodynamically significant "asymptomatic" carotid disease may represent one of the few examples of treatable causes of cognitive impairment. If cognitive decline can be reversed in these patients, then it will be established a new indication for carotid revascularization independent of the risk of recurrent stroke. Therefor both symptomatic and asymptomatic carotid stenoses emphasize the need of promptly diagnosing and treating ISR lesions, setting up the indication for neurointervention.

The primary objectives of this study were to determine:

1. The dynamics of the development of in-stent restenosis (ISR) following internal carotid artery (ICA) stenting.
2. The effectiveness and safety of angioplasty using drug-eluting balloons (DEB) in the management of ISR occurring in the ICA.
3. The incidence of secondary restenosis subsequent to the effective management of primary restenosis with DEB angioplasty.

Primary endpoints were death resulting from vascular disease, transient ischemic attack (TIA), and stroke related to the treated ICA. The secondary endpoint was a recurrent ISR lesion during follow-up.

Methods

Patient cohort, detection of ISR and prepocedural imaging

The present study is a retrospective cohort investigation conducted at Moritz Kaposi Teaching Hospital in Kaposvár, Hungary. The study utilized clinical and imaging data for analysis of the total of 950 stent-PTA procedures performed in our institution between March 2013 and March 2021, following multi-disciplinary team (MDT) decision. Postprocedural follow-up included outpatient visits every 3 months in the first year and every six months thereafter. Carotid Doppler ultrasound (DUS) exam was performed at each visit, with Doppler velocity measurements using proper angle correction techniques and B-mode imaging assisted by color-duplex. Peak systolic velocity (PSV) ratios in the stented ICA segment and the CCA greater than two were used as cutoff values for significant (>50%) in-stent restenotic lesions. We utilized peak systolic velocity (PSV) values of 220 cm/s and 300 cm/s as thresholds to classify luminal narrowing rates above 50% and 70% as moderate and severe in-stent restenosis (ISR), respectively. In case of a suspected ISR lesion, verification was achieved by supraaortic-intracranial CTA performed on a dual-source CT scanner (Figure 1)

Treatment with DEB

Procedure

Patients with high-grade (>50%) ISR lesions were scheduled for DEB re-PTA. Before the intervention, the patients signed a consent form in each case after adequate information. Procedures were performed in local anesthesia, with an anesthesia team present in stand-by, using a 6 French femoral or radial access. All patients received an IV dose of 5000 IU Na-heparine after access was secured. The degree of ISR lesions was first verified with selective injection of the common carotid artery (CCA) on the affected side, followed by the insertion of a 6F guide catheter into the CCA. A filter device was not applied. A 0.014 inch microwire was advanced through the ISR lesion into the petrosal segment of the ICA, 0.5 mg atropine was administered IV as premedication for the prevention of extreme bradycardia/asystole during the dilatation of the ICA bulbus and a 6x30 mm paclitaxel-eluting balloon (Elutax, Aachen Resonance, Aachen, Germany) was inflated under manometer control to nominal pressure (6 atm) for 30 seconds. The inflation time was shortened and the balloon was

deflated immediately if the patients' heart rate fell under 50 bpm. Following deflation, the balloon was removed and control series were performed to document the effect of re-PTA and to exclude intracranial emboli. At the end of the procedure, the femoral access sites were closed by closure device (Angio-Seal, Terumo, Tokyo, Japan) and the radial access sites were closed by manual compression.

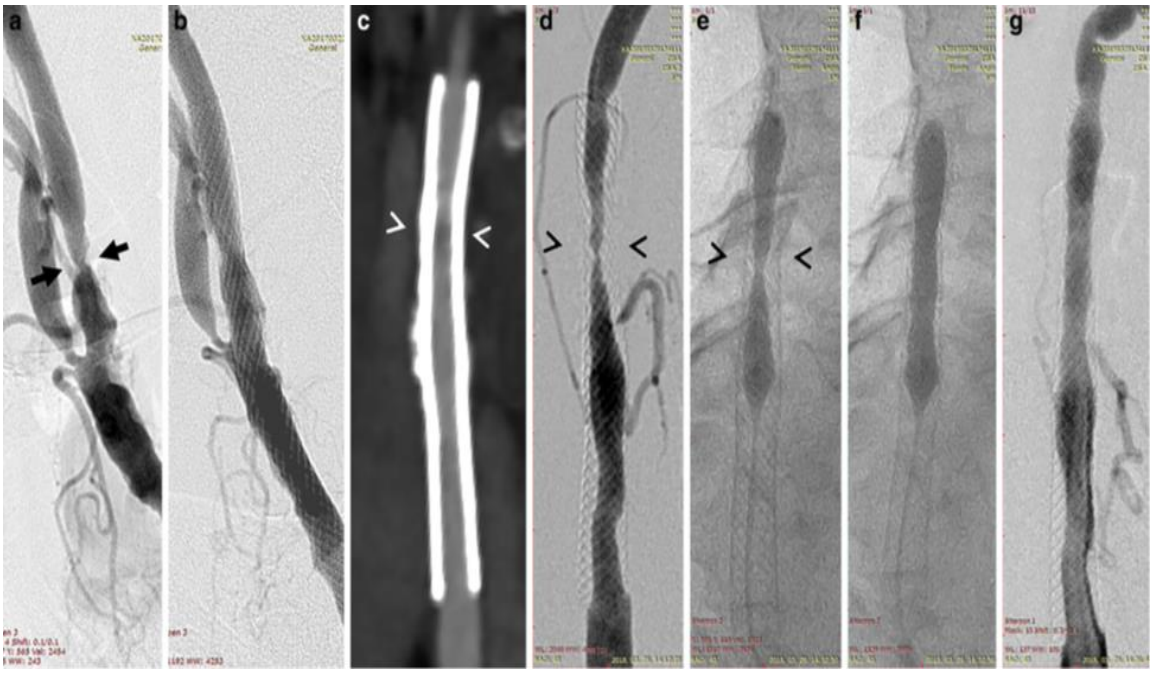

Figure 1. Illustrative case demonstrating the DEB re-PTA procedure of an ISR lesion of the right-sided ICA in a 63-year-old female patient. A highgrade stenotic lesion in the proximal portion of the right ICA (*arrows* in **a**) was treated with stent implantation, followed by angioplasty with good result (**b**). The DUS after 6 months suggested a high-grade ISR in the location of the original lesion, which was verified by dual-source CTA (**c**) and catheter angiography (**d**, *arrowheads* in **c**–**e** point to the stenotic lesion). **e**, **f** Angioplasty using a paclitaxel eluting balloon was performed with good morphological results (**g**). The patient had the last follow-up DUS 52 months after the DEB re-PTA procedure, showing no signs of a recurrent ISR.

ICA internal carotid artery, *DEB* drug-eluting balloon, *ISR* in-stent restenosis, *DUS* Doppler ultrasound, *PTA* percutaneous transluminal angioplasty, *CTA* computed tomography angiography

Medication

At the beginning of the procedure (DEB re-PTA), all patients were administered an intravenous dose of 5000IU of sodium heparin. A regimen of oral dual antiplatelet medication consisting of 100mg of acetylsalicylic acid and 75mg of clopidogrel was administered for a duration of 6 months, followed by the continuation of clopidogrel monotherapy. Patients receiving long-term single or dual antiplatelet therapy (SAPT or DAPT) were consistently assessed using the Multiplate test (Roche Deutschland Holding GmbH, Grenzach-Wyhlen, Germany) to assess the effectiveness of SAPT/DAPT and, if needed, to administer alternative antiplatelet medication.

Postprocedural Follow-up

The postprocedural follow-up protocol resembled that which occurred after the original stent-PTA procedure. This entailed scheduling outpatient appointments every 3 months in the first year and every six months thereafter. DUS examination was conducted during each session. In case of a suspected repeated ISR lesion, verification was achieved by CT angiography. If CTA confirmed a recurrent ISR lesion, the clinical and imaging data were reviewed by a multi-disciplinary team consisting of neurologists, vascular surgeons and interventional neuroradiologists for treatment decision. According to the MDT decision, an additional re-PTA procedure using the same technique and DEB balloon was performed, as described above. Primary endpoints were vascular death, transient ischemic attack (TIA), and stroke related to the treated ICA. The secondary endpoint was a recurrent ISR lesion during follow-up.

Data Collection and Statistical Analysis

The collected initial data included demographic information such as age and sex, as well as medical history including hypertension, atrial fibrillation, diabetes, dyslipidemia, smoking history, and presence of a neoplastic condition prior to and after the re-PTA intervention. The preprocedural parameters that were gathered encompassed the stent type, as well as the dates of the original stent-PTA, identification of ISR, and the subsequent re-PTA treatment. The quantification of luminal narrowing resulting from intimal hyperplasia was determined on non-subtracted DSA images using the methodology employed in the ECST trial. The location of vascular access and the specific type of anti-aggregation medicine were also documented. The parameters

used to assess technical success and outcomes in this study included the rate of successful re-PTA, which was defined as achieving less than 50% residual stenosis. Other parameters assessed were procedural complications, specifically ischemic stroke resulting from distal emboli, as well as postprocedural adverse events such as access site complications. The length of the follow-up period was also considered, along with the modified Rankin scale (mRS) score at the last follow-up. Additionally, the occurrence of any stroke during the follow-up period was recorded. As a result of the COVID-19 epidemic, the majority of the subsequent follow-up appointments were conducted via telephone interviews. In the event of a patient's passing during the follow-up period, efforts were made to document the reason of death, if ascertainable.

RESULTS

During the period from March 2013 to March 2021, our institution conducted endovascular treatment on 46 high-grade (>50%) ISR located at the origin of the internal carotid artery. This treatment involved the use of angioplasty with a drug-eluting balloon (DEB). A total of 45 patients, with a median age of 64.9 years (ranging from 46.9 to 75.8 years) and a male-to-female ratio of 3.2:1, underwent this procedure. Among these patients, only one developed bilateral ISR. During the aforementioned time frame, a total of 950 ICA-PTA procedures were conducted at the same medical facility. This resulted in an estimated incidence of ISR of around 5%. However, it should be noted that the precise rate of ISR could not be determined due to the lack of extensive examination of the cases without ISR. In all, 16 lesions (35%) were observed in the Roadsaver group, 30 lesions (65%) in the Wallstent group. Out of the initial 46 lesions in the internal carotid artery, 52% (24/46) were symptomatic when the stent was implanted. However, only 2% (1/46) of the lesions that developed in-stent restenosis (ISR) exhibited symptoms, specifically mild hemiparesis, homonymous hemianopsia, and central facial palsy. The remaining lesions that developed ISR were asymptomatic and were identified during routine follow-up using duplex ultrasound (DUS). The imaging work-up in cases of a suspected in ISR on DUS always included a CTA in order to exclude false positive DUS readings, before performing invasive imaging (DSA). A CTA positive for ISR could be confirmed by the DSA series in all the cases. The study found that the median duration between the stent-PTA and the identification of ISR lesions was 8.2 months, with a range of 1.4 to 186.2 months.

Additionally, it was observed that 24% (11 out of 46) of the ISR lesions appeared more than 1 year after the CAS treatment.

The luminal narrowing induced by in-stent restenosis (ISR), as evaluated on the digital subtraction angiography (DSA) images, had an average value of 70±2% (standard error of mean). The observed range of luminal narrowing varied from 50% to 90%. In all instances, technical success was achieved, as shown by the presence of a residual stenosis that was less than 50%. The average rate of residual stenosis was found to be 27±2%, with a range spanning from 5% to 49%. No intraprocedural or postprocedural complications were observed. Figure 2 displays an illustrative example. Clinical follow-up data was collected from all 45 patients (100%) through various methods. These methods included direct communication during personal or telemedical follow-up visits, telemedicine interviews with relatives or the general practitioner, and accessing follow-up data from the National eHealth Infrastructure (EESZT) database. The average follow-up time was 31.7 months, ranging from 1 to 96 months. None of the patients experienced any recurring strokes within the region of the treated internal carotid artery (ICA). Out of the total sample size of 45 patients, a proportion of 9 individuals (20%) experienced mortality during the designated follow-up time. The reason for passing away in six cases was attributed to neoplasms, with four cases involving pulmonary neoplasms, one case involving renal neoplasm, and one case involving head and neck cancer. Additionally, one case was attributed to the consequences of anterior spinal artery syndrome, while the cause of death in the remaining two cases remains unknown. Out of the six fatal neoplasms, three (50%) had already been diagnosed before to the DEB re-PTA procedure. Two patients, whose cause of death was unclear, were no longer being monitored 3 and 24 months following the re-PTA surgery. Relatives verified their deaths through telephone interviews, but the specific reason could not be determined in both cases.

The subsequent imaging findings of DUS following the initial drug-eluting balloon (DEB) re-PTA were obtained for all 46 lesions. The median follow-up duration was 24 months, ranging from 1 to 96 months. These results showed the presence of an asymptomatic, high-grade (>50%) recurrent in-stent restenosis (ISR) lesion in 4 cases (8.7%). The recurrence was further confirmed by computed tomography angiography (CTA). All of the recurring lesions manifested in male individuals and were subjected to a second drug-eluting balloon (DEB) percutaneous transluminal angioplasty (PTA), as previously detailed, followed by continued monitoring of clinical and imaging

outcomes. Throughout the follow-up period, there were no observable signs of ischemia in the hemisphere that was impacted. One instance of a third occurrence of neointimal hyperplasia, which was of high grade and asymptomatic, was identified in a single patient, accounting for 2% of the total cases, occurring 12 months after the second drug-eluting balloon re-percutaneous transluminal angioplasty (DEB re-PTA). The aforementioned lesion had a third DEB re-PTA, and a subsequent follow-up after a period of 36 months revealed no evidence of a fourth occurrence of ISR.

Discussion

Carotid stenosis is a pathological state distinguished by the narrowing of the carotid arteries. The main goal of treatment is to decrease the stroke incidence by the efficient management or elimination of plaque buildup and the prevention of blood clot formation. The majority of people afflicted with carotid stenosis often do not exhibit any symptoms until the arterial passage experiences significant constriction or the formation of a clot occurs. The initial manifestation of symptoms is commonly observed in the form of a transient ischemic attack (TIA). The symptoms have a brief duration lasting only a few minutes, followed by complete dissipation, resulting in the individual's return to their baseline condition. It is essential to not overlook TIAs due to their potential significance as a precursor to an oncoming ischemic stroke.

Treatment of ICA stenosis

The recent large randomized trials that have compared the safety and efficacy of carotid stenting (CAS) and endarterectomy (CEA) have demonstrated similar outcomes in terms of stroke prevention. These findings have led to a change in the treatment approach, shifting from a preference for endarterectomy to a more balanced acceptance of both methods. Both CEA and CAS have a disadvantage in the form of the emergence of neointimal hyperplasia, which leads to the gradual and substantial recurrence of stenotic lesions within the stent, known as in-stent restenosis (ISR).

Treatment of ICA in-stent restenosis

According to the most recent guidelines from the European Society for Vascular Surgery (ESVS), it is recommended to utilize the identical treatment criteria employed for the selection of symptomatic patients with primary atherosclerotic stenosis.

Therefore, it is suggested to treat symptomatic restenosis (50-99%) with carotid endarterectomy (CEA) or carotid artery stenting (CAS) within 14 days after the onset of symptoms. However, the topic of asymptomatic restenosis remains a source of significant controversy in academic discourse. Although there is a common perception that asymptomatic restenosis is often benign, the aforementioned recommendations propose that in cases with post-CEA 70-99% asymptomatic restenosis, reintervention might be contemplated after a thorough evaluation by a multidisciplinary team. It has been observed that a severe asymptomatic restenosis above 70% following carotid endarterectomy (CEA) is indeed linked to a notably elevated likelihood of experiencing a late ipsilateral stroke. When faced with the need for revascularization in patients with restenosis, the selection between redo carotid endarterectomy (CEA) or carotid artery stenting (CAS) should be determined through a comprehensive evaluation by a multidisciplinary team, taking into account the expertise of local surgeons and interventionists, as well as the preferences expressed by the patient.

Regarding the indication of treatment of asymptomatic ICA ISR lesions, the situation is more controversial. According to the European Vascular Surgery recommendation, there is IA evidence supporting the use of medical therapy instead of intervention for the treatment of asymptomatic high-grade carotid in-stent restenosis (ISR). This recommendation is supported by the meta-analysis conducted by Kumar, which revealed a significant reduction in the risk of stroke on the same side as the restenosis, with a reduction of only 0.8%. In-stent restenosis was present, and the adverse clinic does not appear to be tightly associated, which raises doubts about the purpose of re-PTA according to their research**.**

In our opinion, the meta-analysis by Kumar et al. has its limitations. For example, the validation of the in-stent restenosis (ISR) in their study was only conducted using DUS. The PSV cut-off values applied in the studies analyzed by Kumar et al. exhibited a significant degree of variability. The meta-analysis included data from 11 prospective studies, in six of those a PSV of 210 cm/s was used as cut-off criteria for >70 % restenosis, no relevant information on PSV cut-off was given in two studies and only in the remaining three used PSV values that can be found as standards in the literature and are also applied routinely in our clinical practice (220 cm/s >50 %, 300 cm/s > 70 % ISR). In our opinion, this resulted in the inclusion of patients with minor degree of ISR into this meta-analysis, substantially diluting the specificity of the study.

On the other hand the median follow-up duration of patients was 4 years and the study does not provide any insights into the probable progression of the ISR beyond this time period. ISR is a late complication of the stenting procedure and even late progression of the condition can lead to complete occlusion of the treated ICA. To our knowledge, there is no solid evidence in the literature showing that occlusion of a stented ICA would always be asymptomatic. Therefore, we believe that an effective and safe treatment modality for ICA ISR (DEB re-PTA) is non-inferior to no treatment. An additional point is the effect of ICA luminal narrowing on cognitive function. A number of recent studies documented a positive correlation between “asymptomatic” narrowing of the ICA lumen and cognitive impairment. The phenomenon is similar to angina pectoris resulting from coronary artery stenosis or claudication resulting from atherosclerotic stenotic lesions of the lower limb arteries. Based on these results, the CREST-H randomized trial was initiated and is still recruiting patients to investigate the clinical significance of the hemodynamic effects caused by ICA stenosis. In this regard, the hemodynamic effect of luminal narrowing caused by an atherosclerotic plaque or intimal hyperplasia does not seem to differ. As stated in the previous paragraph, we believe that a safe and effective treatment option for ICA ISR might play an important role in the prevention of cognitive impairment as a result of ICA ISR.

Treatment of ICA in-stent restenosis with DEB re-PTA

In the management of in-stent restenosis of the carotid artery (ICA ISR) the therapeutic options that can be considered include repeated carotid artery stenting (CAS), endarterectomy, or reangioplasty (percutaneous transluminal angioplasty) (rePTA) utilizing either a conventional balloon or a drug-eluting balloon (DEB). While the use of paclitaxel-eluting drug-eluting balloons (DEBs) for the treatment of in-stent restenosis (ISR) in various vascular territories such as the coronary, peripheral, and intracranial arteries has been extensively studied and proven to be safe and effective, there is a limited amount of published data on the application of DEBs specifically for the treatment of ICA ISR.

The present study examines the safety and effectiveness of a paclitaxel-eluting balloon for treating in-stent restenosis of the extracranial carotid artery by a retrospective cohort analysis of 45 patients (46 cases). There were no cases of vascular mortality, transient ischemic attack (TIA), or stroke in the treated internal carotid artery (ICA)

area, which were the key endpoint events. A reoccurrence of an in-stent restenosis (ISR) lesion after a drug-eluting balloon (DEB) re-percutaneous transluminal angioplasty (PTA) operation was observed as a secondary endpoint in 8.7% of the lesions. These recurrent ISR lesions were effectively managed with a subsequent re-PTA procedure, with one case requiring a third re-PTA procedure. Notably, no additional cases of recurrent ISR lesions were observed throughout the follow-up period.

In the current investigation, all internal carotid artery in-stent restenosis lesions were solely treated with drug-eluting balloon (DEB) angioplasty. This study was conducted based on the promising outcomes of a previous research, in which the authors examined the effectiveness of drug-eluting balloons (DEB) compared to conventional balloons in the re-percutaneous transluminal angioplasty (re-PTA) of 63 intracranial in-stent restenosis (ISR) lesions. The earlier study revealed a significant decrease in the recurrence rate of ISR, with DEB demonstrating a rate of 9% compared to the 50% recurrence rate observed with conventional balloons. The recurrence rate of ICA ISR in our study is 8.7%, which closely aligns with the recurrence rate of 9% published in other studies on intracranial drug-eluting balloon (DEB) re-percutaneous transluminal angioplasty (PTA). Additionally, our findings indicate that our recurrence rate is approximately one third of the recurrence rate (27-28%) reported in other studies that utilized traditional balloons. The incidence of in-stent restenosis (ISR) recurrence after drug-eluting balloon (DEB) percutaneous transluminal angioplasty (PTA) is comparable to the reported rate of 8.2% observed in a subsequent carotid artery stenting (CAS) procedure. It is important to acknowledge that the management of sequential recurrent lesions can be effectively addressed through repeated drug-eluting balloon (DEB) percutaneous transluminal angioplasty (PTA) procedures. However, it should be recognized that the same level of ease may not be achieved with repeat carotid artery stenting (CAS) interventions, as the implantation of a third or even a fourth co-axial stent in the same vessel segment can present challenges.

The present study has several limitations. Firstly, its design is observational and nonrandomized, which introduces methodological and selection biases that are typical to this type of study. The imaging data were not validated by a central laboratory. The retrospective dataset may contain bias as a result of patients lost to follow-up and missing data. A comprehensive examination of the main stent-PTA procedures was

not conducted. The present cohort only utilized a single kind of drug-eluting balloon (DEB). It is reasonable to hypothesize that variations in drug type, concentration, and the technique employed to secure the drug to the balloon may have a substantial impact on the effectiveness of different DEBs.

Conclusion

The use of a paclitaxel-eluting balloon in the treatment of extracranial carotid in-stent restenosis (ISR) has been found to be a safe and successful alternative to other available therapeutic methods. The primary rates of recurrence are approximately one third of the rates described in the existing literature for re-PTA using traditional balloons. The recurring lesions might be effectively treated by performing further drug-eluting balloon (DEB) percutaneous transluminal angioplasty (PTA) operations, ultimately leading to the successful prevention of in-stent restenosis (ISR). While there is an expanding amount of evidence about the efficacy of drug-eluting balloon (DEB) technology in the therapy of carotid in-stent restenosis (ISR) based on retrospective case series, there is a significant need for larger-scale prospective, controlled studies to firmly establish the role of this technology in the toolbox of neurovascular interventionists.

THESES

The main results of the present thesis are the following:

1. The overall incidence of in-stent restenosis (ISR) in the internal carotid artery (ICA) in our investigated cohort is 5%, with a peak development time of 6-8 months.
2. Based on our analysis of the largest ICA ISR patient cohort known to date, the treatment of ISR of the extracranial ICA using angioplasty with paclitaxel-eluting balloon (DEB) is effective and safe.
3. The incidence of a recurring (ISR) lesion following DEB angioplasty was 8,7% identified as a secondary outcome following DEB angioplasty. The recurring ISR lesions were successfully re-treated with a follow-up re-PTA procedure, and in one case, a third re-PTA treatment was necessary. No further occurrences of recurring ISR lesions were detected over the whole follow-up duration, emphasizing the efficacy of the procedure.
4. The primary endpoints, including vascular death, transient ischemic attack (TIA), and stroke were not reached in any of the cases, underlining the safety of the procedure.
5. The results provide markedly superior outcomes in preventing the reoccurrence of stenotic lesions compared to alternative methods described in current literature.

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