

# Intracranial Atheromatosis Disease (ICAD) and Stent Supported Angioplasty. A Long-Term Follow-up

## *Doença Ateromatosa Intracraniana (DAIC) e angioplastia com stent . Um seguimento a longo prazo*

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### RESUMO

**Objetivos:** A doença ateromatosa intracraniana sintomática possui prognóstico desfavorável. A indicação do tratamento endovascular com angioplastia transluminal percutânea (ATP) assistida com stent deve ser realizada de acordo com a eficácia, segurança, complicações e o risco de re-estenose a longo prazo.

**Material e Métodos:** Estudo realizado entre 1996 e 2008 inclui 28 pacientes, todos sintomáticos mesmo sob tratamento anticoagulante. Foram identificados 30 casos de estenose, localizados na artéria carótida interna (11), artéria basilar (14) e artéria vertebral (5), com grau de estenose > 60% (média nde 83,5%).

**Resultados:** Houve redução significativa do grau de estenose (inferior a 50%), com estenose média residual de 36,8%. Ocorreram duas complicações, com hematomas de reperfusão (6,6%). No seguimento a longo prazo, encontrou-se um único caso de reestenose e nenhum paciente apresentou acidente vascular cerebral isquêmico transitório ou definitivo.

**Conclusão:** O tratamento das estenoses intracranianas com angioplastia assistida com stent é eficiente, com baixo índice de complicação e de reestenose nesta série.

**Palavras Chave:** Estenose intracraniana, angioplastia, AVC-i, Stent.

### ABSTRACT

**Objectives:** Symptomatic intracranial atheromatous disease has an unfavorable prognosis. The endovascular treatment with percutaneous transluminal angioplasty (PTA) stent assisted must be held in accordance with the efficacy, safety, complications and the risk of restenosis in the long term.

**Materials and methods:** A study conducted between 1996 and 2008, includes 28 patients with 30 cases of stenosis located in the internal carotid artery (11), basilar artery (14) and vertebral artery (5). All cases were symptomatic even under anticoagulation treatment and the stenosis grade > 60% (average 83.5%).

**Results:** There was a significant reduction in the degree of stenosis (less than 50%), with an average residual stenosis of 36.8%. There were two complications, with reperfusion bruising (6.6%). In the long term monitoring, we found a single case of restenosis and no patient had a transient or permanent ischemic stroke.

**Conclusion:** The treatment of intracranial stenosis with stent-assisted angioplasty is effective, with a low complication rate and restenosis in this series.

**Keywords:** intracranial stenosis, angioplasty, ischemic stroke, Stent.

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## INTRODUCTION

Intracranial atheromatous disease (ICAD) may evolve with a chronic hypoperfusion condition, emboli and arterial occlusion. It constitutes an important cause of ischemic strokes, especially in the black, hispanic and asian population, corresponding to about 10% of all cerebral ischemic events in the U.S., totaling between 70,000 to 90,000 ischemic strokes / year. In patients with stenosis greater than 50%, the annual risk of recurrent stroke can reach 15% and in cases of stenosis between 70% and 99% the risk of death ranges from 2% to 4 % per year. Intracranial stenosis is associated with several risk factors such as: hypertension, diabetes mellitus, smoking, dyslipidemia, and no Caucasian race. Most studies define this type of lesion as radiologically significant when it presents stenosis greater than 50% of the normal artery caliber, combined with infarction in the region of the affected artery in the absence of sources of embolism<sup>3</sup>.

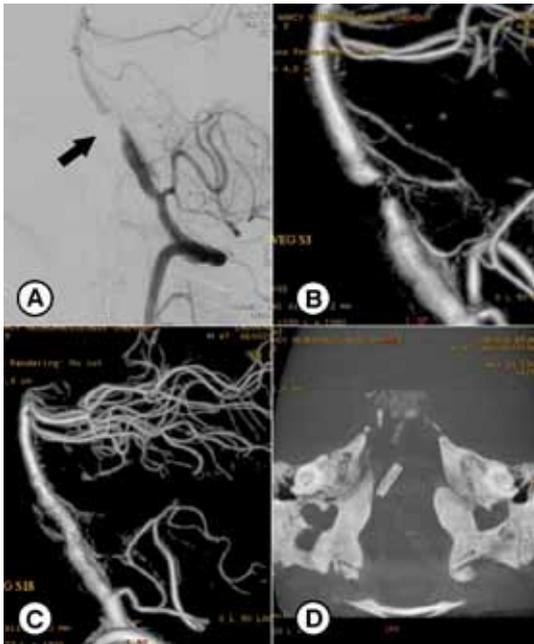
The evolution to an ischemic event can occur in different ways as perfusion failure with a compensation disability of collateral circulation, local thrombosis, arterio-arterial embolization and occlusion of perforating vessels. In a systematic review of retrospective studies of the circle of Willis arteries, separately analysed, the internal carotid artery is the most frequently affected, in about 50% of cases, with annual risk of ipsilateral ischemic stroke ranging from 3.1 to 8.1 % for ICA, up to 7.8% for MCA and up to 8.7% in the vertebral basilar system. The location of the arterial lesion has a direct influence on the annual death rate for stroke, with an annual average of 6.8% in the MCA stenosis, 11.6% in the vertebral basilar stenosis and 12.4% in the ICA stenosis, with a potentially variable risk represented by stenosis in different intracranial arteries<sup>17</sup>. A prospective multicenter study, GESICA<sup>23</sup>, showed that 60.7% of patients with significant hemodynamically stenosis had recurrent stroke or transient ischemia, in an average follow-up of 23.4 months, even with medical treatment and the combination of anticoagulant and antiplatelet at maximum doses. In a critical analysis of the natural history of intracranial atheromatous disease, a high potential for positive results with the endovascular treatment of severe stenosis was found<sup>16</sup>.

## MATERIALS AND METHODS

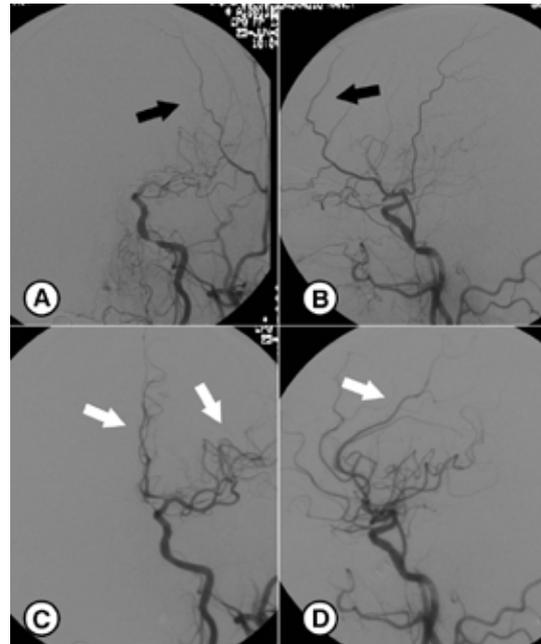
Between November 1996 and August 2008, 28 patients with 30 diseased vessels (Fig. 1), aged between 41 and 82 years old, average of 63.8 years, with symptomatic intracranial atheromatous disease, were treated with endovascular treatment with stent angioplasty, in the Service of Neuroradiologie du Centre Hospitalier et Universitaire (CHU) of l'Université Henri Poincaré Nancy-France and CINN Maringá, Brasil : 25 male patients, aged from 41 to 82 years old and average age of 62.8 years and three females aged 44 to 76 years old, average of 68 years. Gender rate was 8♂ : 1♀ .

Inclusion criteria were: (1) older than 18 and younger than 82 years old, (2) incidence of recurrent transient ischemic attack or ischemic stroke in maximum anticoagulant and antiplatelet therapy (100-325 mg of aspirin daily, 250mg per day of ticlopidine or clopidogrel 75 mg per day), (3) atheromatous stenosis greater than or equal to 60% or less than 99% diagnosed by digital subtraction angiography method WASID<sup>26</sup>, (4) stenosis affecting the major intracranial artery - the internal carotid artery (including petrous and cavernous segment), basilar artery and vertebral artery (V4 segment), (5) having at least two vascular risk factors: hypertension, diabetes, hypercholesterolemia, smoking, history of coronary artery disease, peripheral arterial disease, preexisting atheromatous stenosis in another location or presence of plaques in the aorta, (6) absence of intraluminal thrombus, (7) NIHSS less than 15 at enrollment, (8) absence of permanent neurological deficit.

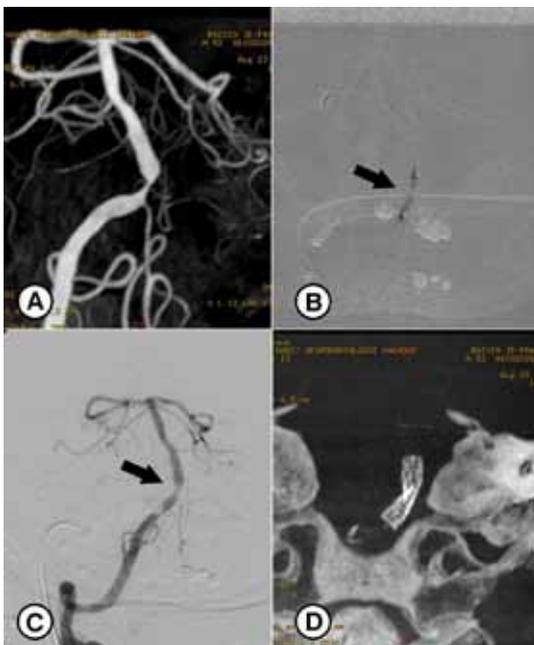
The vast majority of cases had stenosis greater than or equal to 60%, and in three cases (8.1%), symptomatic lesions amenable to treatment were found in more than one artery (Fig.1, 2 and 3).



**Figure 1 A, B, C and D:** AB stenosis 95%, ASD lateral (black arrow) (A) ; DSA 3D (B) ; control angiography immediately after balloon angioplasty and undersized stenting, in DSA 3D with residual stenosis 10% (C) ; and tomographic reconstruction of the stent (D).



**Figure 3 A, B, C and D:** Mori A Type stenosis of the left ICA. DSA PA showing 85% stenosis (A) ; and lateral (B) ; and an anticipation of the time pressure of the superficial temporal artery (black arrows) in relation to MCA. Control by DSA PA (C) and lateral (D) after angioplasty followed by stenting with a 100% reperfusion and an major intracranial perfusion improvement with the return of the intracranial circulation of the MCA (white arrow) in anticipation of the superficial temporal as well as the perfusion of the ACA (white arrow).



**Figure 2 A, B, C and D:** Right VA stenosis Mori B Type in 70%, DSA 3D (A) ; Angioplasty procedure and stenting undersized (black arrow) (B) ; DSA PA control showing a 20% residual stenosis (black arrow) (C) ; and tomographic reconstruction of the stent showing the modification of the mesh by calcified plaque (D).

## THERAPEUTIC INTERVENTIONAL PROCEDURE

All patients were previously treated with antiplatelets, starting three days before the procedure, at a dose of 75 mg clopidogrel (Plavix®, Sanofi, Inc) and aspirin 325 mg. After the procedure they remained in the intensive care unit for 24 hours. GP IIb / IIIa (Abxycimab - ReoPro®) inhibitor was available for an eventual necessity.

The procedure was performed under general anesthesia. During the procedure intravenous heparin infusion with 5.000UI in bolus, after femoral puncture and 40ui/Kg/h. Before angioplasty, a selective diagnostic angiography via the femoral artery with 4F or 5F vertebral catheter, held in the carotid and vertebrobasilar system was performed. In the case of ICA stenosis, a common carotid angiography was done, in order to assess the difference in extra and intracranial arterial time. Then, selective catheterization of the internal carotid artery or vertebral artery in its V3 segment with a 6F

guide catheter (6F Guider Boston) and 0.035 mm hydrophilic guide, keeping continuously infused under pressure. Following the acquisition of 3D images, the diameter of the vessel in its normal segment, as well as the diameter of the stenotic segment, are analyzed by the software AW3D ANALYSIS GE MS (General Electric Medical Systems) on a Butterfly biplanar device or captorplan monoplanar Innova GE MS (General Electric Medical Systems). The percentage is calculated by the equation: stenosis percent =  $[(1 - (D_{STENOSIS} / D_{NORMAL})) \times 100]$ .

### Angioplasty and Stenting

The endovascular treatment strategy varied according to lesion location and type of injury, according to the Mori classification tipe A, B or C. In the Mori type C stenosis cases, > 95%, angioplasty procedure was performed initially, independently of the stent preference, with MAVERICK balloon (Boston Scinetific - Galway - Ireland). The techniques used were percutaneous transluminal angioplasty (PTA) followed by stent deployment, with coronary stent NeuroLink® (Guidan Corporation - Indianapolis, IN).

With the negative images of the angiographic arterial system ("road mapping"), a GT Terumo microguide 0.016"/90° (Terumo - Tokyo - Japan) and a Rapid Transit™ microcatheter (Cordis - AA Roden - The Netherlands) or a GT Terumo microguide 0.012"/90 (Terumo - Tokyo - Japan) and an Excel 14 microcatheter (Boston Scientific - Galway - Ireland) were inserted, surpassing the stenosis. After placing the micro catheter distal to the injury, the microguide is replaced by a 0.014 CHOICE microguide of 300cm (Boston Scinetific - Galway - Ireland) left distal to the stenosis. The micro catheter is removed and, in a coaxial way, the MAVERICK angioplasty balloon (Boston Scientific - Galway - Ireland) undersized at least 0.5 mm smaller than the adjacent normal vessel diameter and with a variable length from 10mm to 20mm depending on the extent of the injury, is placed in the stenosed segment, always with the concept of slow and progressive enlargement, but never reaching the nominal pressure of the balloon. If angiographic spasm is verified, a continuous infusion of 300 mg of papaverine through the 6F catheter is held.

A NeuroLink® (Guidan Corporation - Indianapolis, IN) coronary stent is positioned coaxially in the stenosed segment and released after a slow and gradual expansion of the balloon. Stent dimensions always obeyed the evaluation of plaque extension, as well as their degree of stenosis, with the use of an undersized stent in the possibility of calcified plaque.

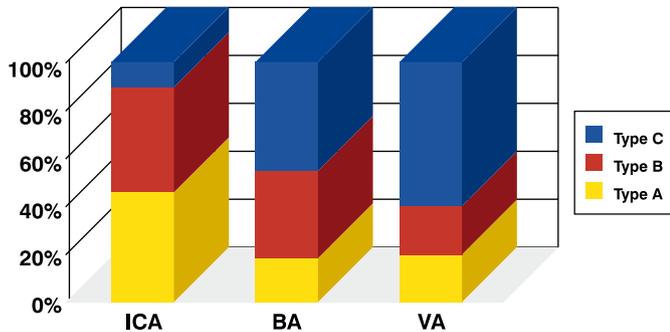
## RESULTS

Using the Kruskal-Wallis test, the degree of stenosis correlated with their location, did not reach significant value with  $p = 0.074$  : the basilar artery showed more severe stenosis and internal carotid showed less severe ones. The correlation of the stenosis grade with MORI classification was significant, with  $p=0.0001$ . Posterior circulation stenosis were more severe with most of MORI B and C cases ( Fig.4). The degree of residual stenosis after the procedure was not significant with  $p=0.43$ . The relative difference in the degree of residual stenosis, correlating with MORI classification, was not significant with  $p = 0.96$ . The evaluation of the kind of used devices and the stenosis grade showed a non-significant result, with  $p=0.78$  (Mann-Witnney test). The average residual stenosis as well as the relative difference in residual stenosis showed no significant result with  $p = 0.12$ .

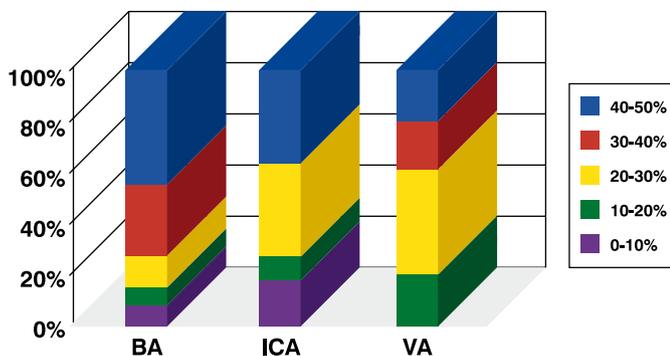
The results show a degree of stenosis before the procedure ranged from 60% to 95% with an average of 83.5%. After the procedure it ranged from 0% to 50% with an average of 33.3%.

The estimate residual stenosis in the basilar artery was between 40% to 50% in half of the cases: in one third of cases it was between 30% to 40%. In the remaining cases residual stenosis was 0% to 30%. In cases of ICA stenosis, 25% the residual stenosis was between 30% : in the remaining 75%, the residual stenosis was less than or equal to 30%. In VA stenosis, 25% had a residual stenosis between 40% to 50%, in 20% the residual stenosis it was 30% to 40% and in 55% the residual stenosis it was between 10% to 30%. The basilar artery showed the largest percentage of residual borderline stenosis between 40% to 50%, followed by ICA and VA (Fig.5).

Two complications (6.6%) occurred in a period of up to 30 days after treatment, with two late reperfusion hemorrhage and permanent neurological deficit. The first case of hemorrhage after stent occurred in a VA stenosis greater than 95% and the other in a stenosis of 95% BA. In two cases of ICA stenosis (5%) there was a technical failure. During clinical and imaging follow-up, at least six months later( average 18.7 months) , only one case showed restenosis greater than 50% (3.3%). All patients had clinical and radiological follow-up with digital or MRi angiography from six months, up to 12 to 15 months, with patients who have up to 120 months of follow-up.

**DISTRIBUTION FOR MORI TYPE AND ARTERY LOCATION**


**Figure 4:** Distribution of the stenosis, according to the Mori classification with Mori C type stenosis, most severe in the posterior circulation.

**RESIDUAL STENOSIS AFTER STENTING**


**Figure 5:** Residual stenosis after angioplasty / stenting, with higher amounts of stenosis between 40-50% in BA and VA.

## DISCUSSION

The clinical treatment of symptomatic intracranial atheromatous disease must be exhausted before any indication for endovascular treatment. Currently it involves the combined use of aspirin, dipyridamole, statins, ticlopidine, clopidogrel, warfarin, and angiotensin-converting enzyme inhibitors. WASID study showed that the annual stroke risk in patients treated with aspirin was 10.4% per year, while with warfarin it was 3.6% but with a significant hemorrhage rate<sup>3</sup>.

ICA is the most common place of stenosis, reaching about 50%

of cases. The first published series showed an annual risk of stroke of 11.6%. Intracranial ICA stenoses greater than 50% are directly related to an increased risk of ischemic stroke. In stenosis of the vertebral basilar system, the stroke rate may reach 14.3% annually and high morbimortality reaching up to 50%<sup>3</sup>. The functional anatomical area related to vertebro-basilar system (brainstem) and ICA which involves large amount of brain tissue, is related to a higher rate of morbimortality in cases of extensive infarction<sup>17</sup>. GESICA multicenter study, with 21 participating centers, evaluated in a prospective way in a period of four years, 102 patients with stenosis of the middle cerebral artery, internal carotid, vertebral and basilar, noting a risk of recurrent ischemic events of 38.2 % in the stenosed artery territory in two years.

According to Poiseuille's Law, flow is directly proportional to the fourth power of the radius artery in a laminar flow system:  $Flow = \Delta P \pi r^4 / 8$ , which means a significant increase in blood flow caused by a small increase in luminal diameter<sup>9</sup>. Another important principle observed was that intracranial arteries are less resistant to expansion when compared to coronary and extracranial arteries, due to the lack of the external elastic lamina as well as the extensive adventitial layer<sup>6</sup>.

Initially the treatment performed with angioplasty and the use of cardiology balloon, showed results with high rates of arterial dissections, as well as restenosis<sup>8</sup>. Since the 1990s the development of expandable stents with small sized balloons allowed its use in intracranial endovascular revascularization, with a high initial success, over 90%. Used initially in the basilar artery, internal carotid and vertebral artery, today there are a series of intracranial or coronary stents<sup>21,24</sup> available. SSVLVIA<sup>30</sup> trial (Stenting of Symptomatic Atheromatous Lesions in the Vertebral or Intracranial Arteries) multicenter study, prospective, nonrandomized, assessed the use of stent mounted in balloon, the NeuroLink stent system (Guildant Corp - Indianapolis - IN), used in stenosis greater than 50%, with initial success in 58/61 of the cases (95%). In the six months follow-up period, the rate of restenosis greater than 50% occurred in 12/37 of the cases (32.4%).

The GESICA<sup>23</sup> multicenter study, in prospective evaluation of symptomatic stenosis equal to or greater than 50%, still showed high morbimortality, with 14.2%, limiting its indication as the first choice treatment of intracranial stenosis, to be reserved to medically refractory treatment cases.

In a Latin American experience, where six centers treated a total of 33 injuries with stent mounted in balloon, all with stenosis greater than 50% (average 68%), all the complication

rate was 6.2%, directly related to small diameter arteries, a stenosis of the MCA and posterior cerebral. The mortality rate was 9.4%<sup>11</sup>.

The effectiveness of the endovascular treatment for intracranial atheromatous disease remains controversial, however, the use of angioplasty alone is not effective with failure in 12.9% of the cases and the need for stenting in the same act<sup>22</sup>.

Complications of the method such as dissections, arterial perforations, thrombus formation during the procedure, as well as the formation of pseudoaneurysm were reduced after the systematization of a series of technical measures such as: general anesthesia, systemic anticoagulation with the use of heparin, subsequent therapy with platelet antiaggregation decreasing the deposition of fibrin and platelets on the endothelium altered by angioplasty, as well as the limitation of time dilation of the angioplasty balloon<sup>6</sup>.

Other complications described in stent use are: subarachnoid haemorrhage, stent migration, occlusion of perforating arteries with segmental ischemic stroke and death<sup>18,25,29</sup>. The presence of perforating arteries in the arterial segment involved by the plaque as in the basilar artery, increases the risk of occlusion of these perforators, the “snow plow” effect, when the plaque is pushed against the ostium during stent implantation<sup>15</sup>. However submaximal dilation can reduce this complication<sup>19</sup>.

Another uncommon complication, the hyperperfusion syndrome, which occurs due to loss of arterial pressure regulation, characterized by unilateral headache, facial and eye pain, convulsions and / or focal neurological deficit, preceding a hematoma or cerebral edema, occurs between 1 to 2% of the cases<sup>29</sup>. The pronounced injuries of the vertebrobasilar system (> 90%) have a high risk of complications and may reach 28%, when added transient ischemia, permanent ischemic stroke and death. The risk of restenosis may vary from 0% to 25% in the vertebrobasilar system, reaching 36% of angioplasties in the anterior circulation in most patients, 61% asymptomatic at six month follow-up<sup>30</sup>.

In our series there were two cases of hyperperfusion, the first in stenosis higher than 95% of the right VA, with absence of contralateral VA and the second a severe stenosis of the basilar artery at 95%, both cases with permanent neurologic deficit. Morbidity rate was 6.6% lower than presented in the literature, which may be related to a series of care that include the indication with stenosis greater than 60%, as well as the choice of material, with the undersized balloon and stent also undersized when needed and the technique with previous angioplasty to stent in very severe stenosis. The use of flexible

systems for navigation in the tortuous intracranial arterial system, as well as the use of undersized systems in order to perform percutaneous transluminal angioplasty in the treatment of intracranial arteries, has been discussed since the early 90s<sup>2</sup>.

The Wingspam intracranial stent has been shown to be effective in the short term results with high technical success rate of around 99% with residual stenosis of 38% after stenting, with a low complication rate of 6.1% in Wingspam Trial<sup>14</sup>: however a high rate of restenosis, reaching 32% in short and medium term evaluations was reported<sup>1,10</sup>.

In the evaluation of stent versus angioplasty, there is a higher rate of residual stenosis after the procedure, as well as late restenosis, in the angioplasty-treated group treated with angioplasty<sup>27</sup>.

A series of “in vitro” models using non-atheromatous arteries has shown that after stent implantation of the stent its entire structure is covered with a thin layer of neointima composed by cell proliferation of the smooth muscle layer, maintaining the permeability of the ostial orifice of the perforating vessels. Some authors who evaluated the tissue response after stents implantation in coronary arteries, suggest that they are initially covered by a thin layer of thrombus and fibrin which is replaced at a late stage by a muscle neointimal proliferation. The success of stent angioplasty depends on a minimum thrombosis and a rapid endothelialization, where the control of stent-induced thrombus should be done with the use of anticoagulant and antiplatelet drugs<sup>20</sup>.

Stenosis of the vertebrobasilar system, treated with stent, may have a high mortality rate according to the characteristics of the plaque according to the MORI classification. However, the treatment of pronounced stenosis of the vertebrobasilar system with stent has shown good results, even more with a moderate rate of complications in cases of severe stenosis above 90%<sup>5</sup>.

Some authors include in the protocol of heparinization and platelet antiaggregation, the routine use of glycoprotein IIb/IIIa (Abxycimab) inhibitor<sup>21</sup>. However, the routine use of glycoprotein IIb/IIIa inhibitor in continuous infusion during the procedure of PTA/stent may be related to an increased rate of hemorrhagic complications, reaching 17%<sup>16</sup>.

The strategy of submaximal dilation followed by stent, from four to six weeks after angioplasty, is also described. After PTA, during this period, neointimal proliferation results in a thin layer of fibrous tissue, which may reduce the risk of plaque embolization and arterial dissection during stent implantation<sup>18</sup>.

Systematic reviews of the literature where the inclusion

criteria were randomized or quasi-randomized studies in intracranial stenosis greater than 50%, perioperative risk of stroke was 7.9% and per-operative mortality risk of 3.4%. The authors concluded that to date there is insufficient evidence to recommend percutaneous transluminal angioplasty with or without stent in the practice of stroke prevention in patients with intracranial arterial stenosis, there is the need for randomized, controlled prospective studies, which can ensure such treatment in preventing stroke in cases of intracranial arterial stenosis<sup>7,12</sup>. The SAMMPRIS trial compared the results of early treatment (<30 days) of high-risk patients with severe intracranial stenosis (70-99%) with aggressive medical therapy plus intracranial angioplasty and stenting (Wingspan stent system) to aggressive medical therapy alone for preventing recurrent stroke, noting an increased risk of stroke in patients treated with stenting<sup>4</sup>.

A retrospective study comparing clinical treatment versus endovascular treatment with stenting in cases of severe stenosis in the Asian population, with follow-up of 3 years, noted that the functional assessment and the risk of late ischemic event was more favorable in patients treated with stenting. However there is an increased risk in cases of stenosis in arterial segments with perforating arteries such as middle cerebral artery and basilar artery, which can be prevented with the option of the use of self-expandable stent<sup>28</sup>.

## CONCLUSION

Intracranial atheromatous disease (ICAD) has significant risk of stroke even under medical treatment. Percutaneous transluminal angioplasty with stenting has been increasingly used at increasingly smaller risks due to technical and material evolution. Studies comparing the complications of conservative treatment and endovascular has been drawn. The risk of late restenosis has shown to be increasingly smaller when stent is used compared to the use of angioplasty alone. However, both the long-term patency and the risk of recurrent stroke in patients treated with stenting remains uncertain.

The analysis of the studied series indicates that the symptomatic intracranial atherosclerotic arterial stenosis, which initially have endovascular treatment with stenting indication are those above 60% and located in the main arterial trunks (basilar

artery, vertebral artery and internal carotid artery), being an effective method, resulting in a low complication rate of 6.6%. The experience shows a very low restenosis rate in this series (1/30), reducing the risk of stroke during a long-term follow-up. A multidisciplinary assessment should always be considered before any therapeutic approach in patients with intracranial atheromatous disease. In the absence of data to support endovascular treatment for intracranial atheromatous disease (ICAD), assisted angioplasty with stent remains a treatment option for patients at high risk of stroke even under drug treatment.

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