REVIEW ARTICLE

Stroke risk in patients with asymptomatic carotid atherosclerosis: should it be treated medically or surgically?

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ABSTRACT

Cerebrovascular disorders remain the leading cause of neurological morbidity and mortality in the world, representing one of the pathological entities responsible for the greatest burden of disease worldwide. Carotid atherosclerosis or stenosis is a potential risk factor for ischemic stroke. The identification and strict follow-up of this condition are essential in the secondary prevention of complications through primary care and the specialized treatment of cardiometabolic risk. However, depending on this risk and/or presence of symptoms, definitive treatment is necessary. Currently, there is controversy as to whether asymptomatic carotid stenosis is better to be treated medically or surgically. Considering the significance of such entity, this review aims to analyze recent evidence on the risk of ischemic stroke in the case of asymptomatic carotid atherosclerosis among adults, as well as the potential benefit of the surgical vs. pharmacological treatment for this condition. For this purpose, a literature search for publications up to 2023 was carried out in PubMed, ScienceDirect, Web of Science and MEDLINE databases. It was shown that there is a significant risk of stroke associated with asymptomatic carotid stenosis (> 10 % approximately), even in patients with active antiplatelet and lipid-lowering therapy. Out of all those who receive medical treatment, around 80 % had a five-year survival rate. However, stenosis progression occurs on average in more than 60 % of the cases and is significant. On the other hand, carotid stenting and endarterectomy are curative interventions. Nevertheless, these procedures involve a higher risk compared to the medical therapy during the peri- and postoperative period, as well as 30 days afterwards, due to the occurrence or recurrence of stroke, acute myocardial infarction or death from any cause. Despite this, the use of endarterectomy has shown superior long-term benefits concerning these same outcomes. Thus, evidence regarding the superiority of surgical treatment compared to pharmacological treatment for asymptomatic carotid atherosclerosis or stenosis is heterogeneous. However, it seems that surgical treatment, specifically endarterectomy, could have a significant impact on the occurrence or recurrence of ipsilateral stroke and death in the long term but with controversial peri- and postoperative outcomes.

Keywords: Stroke; Risk; Carotid Artery Diseases; Surgical Procedures, Operative; Therapeutics (Source: MeSH NLM).

Riesgo de accidente cerebrovascular en pacientes con aterosclerosis carotídea asintomática: ¿se debe tratar médicamente o quirúrgicamente?

RESUMEN

Los desórdenes cerebrovasculares siguen siendo la primera causa de morbilidad y mortalidad neurológica en el mundo, representando una de las entidades patológicas que genera mayor carga de enfermedad a nivel global. La aterosclerosis, o estenosis carotídea, es un potencial factor de riesgo para el ictus isquémico. La identificación y seguimiento estricto de esta condición son esenciales en la prevención secundaria de complicaciones a través de la atención primaria y el manejo especializado del riesgo cardiometabólico. No obstante, dependiendo de este riesgo y/o la presencia de sintomatología, es necesario realizar un manejo definitivo. Actualmente, existe controversia sobre si es mejor tratar la estenosis carotídea asintomática, ya sea médica o quirúrgicamente. Teniendo en cuenta la relevancia de esta entidad, el

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objetivo de esta revisión consiste en analizar la evidencia reciente sobre el riesgo de ictus isquémico en la aterosclerosis carotídea asintomática en adultos, y el potencial beneficio del manejo quirúrgico vs. farmacológico de esta condición. Para esto, se llevó a cabo una búsqueda bibliográfica en las bases de datos PubMed, ScienceDirect, Web of Science y MEDLINE, hasta el año 2023. Se evidenció que el riesgo de ictus asociado a estenosis carotídea asintomática es significativo (>10 %, aproximadamente), incluso en aquellos con terapia antiplaquetaria e hipolipemiante activa. En aquellos con manejo médico, la supervivencia a cinco años es alrededor del 80 %. Sin embargo, la progresión de la estenosis sucede en promedio en más del 60 % de los casos, y es significativa. Por el contrario, el *stent* carotídeo y la endarterectomía son intervenciones resolutivas. Pero existe un riesgo mayor comparado con la terapia médica, el cual se atribuye al periodo peri- y posoperatorio, así como a 30 días de aparición o recurrencia del ictus, infarto agudo de miocardio o muerte por cualquier causa; aunque el uso de la endarterectomía ha demostrado beneficios superiores a largo plazo en cuanto a estos mismos desenlaces. Entonces, la evidencia es heterogénea en cuanto a la superioridad del tratamiento quirúrgico comparado con la terapia farmacológica en el manejo de la aterosclerosis o estenosis carotídea asintomática. Sin embargo, parece ser que el manejo quirúrgico, específicamente la endarterectomía, podría impactar significativamente sobre la aparición o recurrencia del ictus ipsilateral y muerte a largo plazo, pero con resultados controversiales peri- y postoperatorios.

Palabras clave: Accidente Cerebrovascular; Riesgo; Enfermedades de las Arterias Carótidas; Procedimientos Quirúrgicos Operativos; Terapéutica (Fuente: DeCS BIREME).

INTRODUCTION

Cerebrovascular disorders remain the leading cause of neurological morbidity and mortality in the world, representing one of the pathological entities responsible for the greatest disease burden worldwide [1-6]. The high prevalence of cardiovascular factors and established atherosclerotic cardiovascular disease significantly favors this catastrophic outcome [7-10]. In 2019, there were approximately 12 million new cases of ischemic stroke, 101 million prevalent cases, 143 million disability-adjusted life years (DALYs) and 6.5 million deaths for this cause [1]. In the last 30 years, a 70 % increase in incidence has been observed, and it is estimated that this figure will rise at increasingly younger ages [2,3].

Carotid atherosclerosis is a potential risk factor for ischemic stroke [10-14]. It consists in the presence of a fibrolipid plaque, which can be found at different stages (stable, vulnerable, thrombotic and embolized) and, depending on the inflammatory process, the degree of neovascularization and rupture may cause symptoms or not [15]. In 2020, the global prevalence of carotid plaque was 21.1 %, which accounts for 800 million cases, while that of carotid stenosis was 1.5 %, which accounts for approximately 60 million cases [4]. The identification and strict follow-up of this condition are essential in the secondary prevention of complications through primary care and specialized treatment of cardiometabolic risk [16,17]. However, depending on this risk and/or presence of symptoms, definite treatment is necessary.

To date, evidence is discordant as to the efficacy, effectiveness and safety of available treatments for carotid atherosclerosis, particularly if it is asymptomatic [18]. There is an extended debate as to whether it is better to perform a surgical intervention or to prescribe a pharmacological treatment, thereby assessing the surgical risk inherent to the operation [19-23]. Nevertheless, a recent study that compared these interventions in a large cohort evidenced useful results in decision-making to treat severe asymptomatic carotid stenosis [18]. This reveals the need for the detailed analysis of the evidence and outcomes during this condition reported over time. In this context and knowing the high prevalence of asymptomatic carotid atherosclerosis and stenosis, as well as the risk of ischemic stroke and the need to provide evidence for decision-making, this review aims to analyze recent evidence concerning the risk of ischemic stroke in asymptomatic carotid atherosclerosis among adults and the potential benefit of surgical treatment vs. pharmacological treatment of this condition.

SEARCH STRATEGY

A literature search was carried out using terms such as “asymptomatic carotid atherosclerosis” and “stroke,” in addition to synonyms, which were combined with the Boolean operators “AND” and "OR," in PubMed, ScienceDirect, Web of Science and MEDLINE databases. As to the inclusion criteria, any article focused on assessing the risk of ischemic stroke and outcomes in surgical vs. pharmacological treatment of asymptomatic carotid atherosclerosis in adults would be considered, but original studies, systematic reviews and meta-analyses would have priority. Also, the full text of the articles should be available. Concerning the exclusion criteria, those articles published in a language different from Spanish and English would not be included. On the other hand, only articles published up to 2023 were selected. A total of 92 potentially noteworthy articles were identified, and their titles and abstracts were reviewed. Finally, 70 articles were included after a

selection according to the inclusion and exclusion criteria. Estimates and calculations found were expressed in their original measures: frequencies, percentages, confidence intervals (CI), difference of means (DM), relative risk (RR), odds ratio (OR) or hazard ratio (HR).

Stroke risk in asymptomatic carotid atherosclerosis

One of the most significant challenges in treating patients with asymptomatic carotid atherosclerosis or stenosis is the prediction of stroke risk [24-28]. An updated report of evidence, prepared by the United States Preventive Services Task Force through a systematic analysis of the screening process carried out in such country for asymptomatic carotid stenosis demonstrated that there were only two trials—up to 2021—that had assessed the treatments for this condition. It was found that there were no significant differences between surgical and nonsurgical treatments concerning the incidence of stroke or death within 30 days or ipsilateral recurrence [29]. Conrad et al. [30] assessed the natural history of this disease among 115 patients who were followed up for 27 months on average, and it was found that 14 of them developed stroke, particularly 12 months after the examination with carotid Doppler ultrasound. Among the identified predictive factors for stroke, it was found that very severe stenosis (90 % to 99 %; *HR* 3.23; 95 % CI: 1.56-6.76) and chronic renal disease (*HR* 6.25; 95 % CI: 2.05-19.2) were significant. It was not specifically found that the use of statin was a protective factor against stroke or death within five years [30].

Other authors, who focused on the evaluation of the clinical and imaging characteristics and their relationship with the occurrence of late strokes among patients with asymptomatic carotid stenosis, reported that silent strokes diagnosed by tomography or brain magnetic resonance imaging (MRI), stenosis progression, hypoechoic plaques, irregular plaques, spontaneous embolization found by transcranial Doppler, plaque area greater than 80 mm, AHA (American Heart Association) plaque types IV, V or VI, and intraplaque hemorrhage diagnosed by resonance were positively associated with the occurrence of late stroke among these type of patients [31]. The basic concern about this type of subjects—who also have other comorbidities that contribute to the increase of cardiovascular risk and the eventual occurrence of cerebrovascular disorders—is that silent strokes and neurological decline may be confused with the progression of cardiovascular risk and small vessel disease, or Alzheimer's disease and other dementias, associated with causes different from carotid stenosis. Maybe this explains that the neurological decline observed is notably milder in patients undergoing carotid endarterectomy compared to patients undergoing other type of treatments (p = 0.02) [32]. Even an incidence rate of stroke of up to 11.5 % in 24 months has been observed among patients medically treated with antiplatelet therapy and statins [33].

The findings and clinical significance of plaque instability and inflammatory process are correlated with the pathophysiologic descriptions of atherosclerosis and its associated complications. Therefore, an inherent risk should always be the suspected, even in those without significant stenosis [34]. In a cohort of 11,614 carotid arteries with moderate stenosis with an average follow-up of 5.1 ± 2.9 years, 180 cases of ipsilateral strokes—regarding the damaged carotid artery—were observed, and a cumulative incidence of 1.2 % and 2 % was calculated for 5 and 10 years, respectively. However, it should be noted that, out of these cases, 27.8 % of the carotid arteries presented significant stenosis progression [35]. Finally, the CARAS (Carotid Asymptomatic Stenosis) observational study—aimed to prospectively evaluate patients with asymptomatic carotid stenosis up to 2025—revealed its preliminary result, which evidenced that out of 307 patients (average age 81 years, 55 % males) who completed the 12-month follow-up, seven (2.3 %) had some kind of stroke. In addition, it was found that, during this time, 14 % of the plaques had stenotic progression, which was related to the onset of events (*OR* 8.9; 95 % CI: 1.9-41) [36]. In conclusion, it can be pointed out that stroke risk associated with asymptomatic carotid stenosis is significant (approximately >10 %), even in subjects on active antiplatelet and lipid-lowering therapy. There are several predictive factors associated with the incidence of stroke. Nevertheless, the results are heterogeneous and should make patient personal stratification easier.

Evidence about outcomes in the medical treatment of asymptomatic carotid atherosclerosis

In the last 10 years, the studies conducted have allowed knowing the natural history of the disease in patients with asymptomatic carotid atherosclerosis and stenosis to whom medical treatment was prescribed [37-41]. Cheng et al. [37] performed a retrospective analysis of 206 carotid arteries with 70 % to 80 % asymptomatic stenosis. Such analysis revealed that, during an approximate 15-year window period, progression was found in 24 % of such carotids, with an incidence of stroke of 5.3 %. Risk factors reported for stroke without documented progression included atrial fibrillation (*HR* 14.87; 95 % CI: 2.72-81.16) and the use of clopidogrel (*HR* 6.19; 95 % CI: 1.33-28.83), while risk factors for death within five years included end-stage renal disease (*HR* 9.67; 95 % CI: 2.05-45.6), atrial fibrillation (*HR* 7.55; 95 % CI: 2.48-23), prior radiation exposure to the head and neck (*HR* 6.37; 95 % CI: 1.39-29.31) and nonuse of aspirin (*HR* 3.05; 95 % CI: 1.12-8.33). Therefore, the authors of this study concluded that high frequency of stenosis progression but low frequency of stroke were observed [37].

Conrad et al. [38] conducted a study to evaluate the progression of moderate asymptomatic carotid stenosis (50 % to 69 %)

in 794 subjects (900 carotid arteries) with optimal medical treatment (administration of aspirin and statin, thereby reaching LDL levels < 100 mg/dL), compared to the control group. It was evidenced that the five-year survival rate was approximately 82 %, without differences in favor of optimal medical treatment. Though there was evidence that the use of statins was associated as the main protective factor against mortality (*HR* 0.50; 95 % CI: 0.34-0.73), the plaque progression after five years was 61 %, without benefits in the intervention group. Such study found that the plaque progression predictors were chronic renal disease (*HR* 2.1; 95 % CI: 1.2-3.7), use of aspirin (*HR* 1.9; 95 % CI: 1.2-3.0) and calcium channel blockers (*HR* 1.4; 95 % CI: 1.1-1.8). During a six-year follow-up, a rate of ipsilateral neurological symptoms of 11.3 % was found [38]. Thus, the authors demonstrated that the optimal treatment failed to prevent the disease progression. Durham et al. [39] evaluated 366 patients and 468 carotid arteries with evidence of carotid stenosis during 6.6 months on average and observed a rate of cerebrovascular events in 32.1 % of the arteries. They determined that hyperlipidemia was a predictor of events (*HR* 1.5; 95 % CI: 1.0-2.2), while the use of betablockers (*HR* 0.6; 95 % CI: 0.4-0.8), the use of statins or angiotensin inhibitors (*HR* 0.48; 95 % CI: 0.3-0.7) and the use of both statins and angiotensin inhibitors (*HR* 0.14; 95 % CI: 0.08-0.24) were protective factors. The study evidenced that event-free survival within 10 years was higher with the use of both statins and angiotensin inhibitors (82.7 % ± 4.6 %) and that annual health costs were lower with this regime (USD 1,695.40 on average) compared to the use of a single drug (USD 3,916.80 on average) or none (USD 4,126.40 on average) [39]. Consequently, the use of this combination therapy proved to be more beneficial compared to the other therapies.

Hicks et al. [40] also studied the risk of stenosis progression in 258 patients and 282 carotid arteries with moderate asymptomatic atherosclerosis for an average of 2.6 years. They found disease progression in 25.2 % of the carotid arteries, a rate of ipsilateral neurological symptoms of 2.1 % and higher risk among patients with a history of tobacco use (*HR* 1.85; 95 % CI: 0.96-3.55) and on dual antiplatelet therapy (*HR* 1.85; 95 % CI: 1.09-3.15). It should be noted that there were no differences as to mortality compared to the disease progression [40]. However, Kolos et al. [41] conducted a randomized controlled trial comparing medical treatment with or without endarterectomy in 55 patients with severe stenosis, which evidenced lower frequency of events in the endarterectomy group (2 vs. 9), and the incidence of events within three years was significantly higher in the nonendarterectomy group (37.5 % vs. 6.5 %; *HR* 5.06; 95 % CI: 1.53-16.79). Finally, a higher rate of severe or fatal events was found only in the pharmacological treatment group (50 % vs. 12.9 %). Therefore, it was demonstrated that endarterectomy impacted mortality substantially within three years in these cases [41].

A randomized controlled trial (SPACE-2, Stent Protected Angioplasty versus Carotid Endarterectomy) that recently published the results from a five-year intervention comparing endarterectomy vs. stenting vs. medical treatment in subjects with moderate to severe asymptomatic carotid stenosis found that during an approximately five-year follow-up the incidence of stroke or death due to any cause within 30 days as well as stroke within five years was 2.5 %, 4.4 % and 3.1 % in the groups for endarterectomy and medical treatment, stenting and treatment, and only medical treatment, respectively [42]. Thus, the authors concluded that there was no evidence of superiority between treatments in 513 subjects from Austria, Germany and Switzerland [42]. On the other hand, a meta-analysis which assessed the effect of aspirin on asymptomatic carotid stenosis found that five randomized controlled trials conducted with a total of 841 subjects revealed that aspirin did not contribute to the protection against stenosis progression or the incidence of vascular events or death (*RR* 0.73; 95 % CI: 0.41-1.31), compared to control groups. Concerning adverse events, there were no significant differences between aspirin and other agents as to the onset of gastrointestinal bleeding (*RR* 1.04; 95 % CI: 0.07-16.46) [43]. A meta-epidemiological study is currently conducted to evaluate the impact of lipid-lowering drugs on asymptomatic carotid stenosis [44], which could demonstrate the usefulness of combining therapeutic strategies in order to promote different outcomes simultaneously [44].

Nevertheless, evidence has generally shown that medical treatment might be beneficial to avoid the progression but not to prevent stenosis and might not be better than surgical treatment. There is a disparity particularly regarding the benefit of using aspirin and statins. However, these drugs might theoretically contribute to control cardiovascular risk overall and actually provide benefits regarding the reduction of mortality risk within five years.

Evidence about outcomes in the surgical treatment of asymptomatic carotid atherosclerosis

Though pharmacological treatment is initially preferred because of the risk of complication and death inherent to a surgical intervention, the evidence points out that surgical approach could be the best treatment for asymptomatic carotid stenosis [45-50].

Reiff et al. [45] analyzed some preliminary results from the SPACE-2 study—which compared the benefit of medical therapy combined with angioplasty or endarterectomy—and found that there were no significant differences between the use of endarterectomy, carotid stenting and medical treatment as to the incidence of stroke ($p = 0.53$) or mortality from any cause ($p = 0.30$) up to 30 days after the intervention [45]. Nevertheless, this differs from the data reported in previous years, in which a meta-analysis including 10 randomized controlled trials and 8,771

subjects [46] demonstrated that, compared to carotid stenting, endarterectomy reduced the probability of stroke within 30 days by up to 44 % (95 % CI: 0.31-0.98). However, when compared to medical treatment, it was found that endarterectomy increased the probability of stroke within 30 days (*OR* 3.43; 95 % CI: 1.8-6.5), death (*OR* 4.75; 95 % CI: 1.5-14.5) or suffering an acute myocardial infarction (*OR* 9.18; 95 % CI: 1.6-50.5). Despite the foregoing, the probability of suffering an ipsilateral stroke, in the long term, was lower in the endarterectomy group (*OR* 0.46; 95 % CI: 0.36-0.59) [46]. Nonetheless, a systematic review that included nine randomized controlled trials and 3,709 patients [47] and that aimed to compare the benefits of endarterectomy vs. carotid stenting in the treatment of asymptomatic carotid stenosis evidenced that the frequency of stroke or death within 30 days was significantly higher in the stenting group (2.94 % vs. 1.89 %; *OR* 1.57; 95 % CI: 1.01-2.44) as well as in the long term (3.64 % vs. 2.45 %; *OR* 1.51; 95 % CI: 1.02-2.24). However, it did not find any differences as to the incidence of acute myocardial infarction within 30 days between both groups ($p = 0.10$) [47]. This discrepancy may be due to heterogeneity between the groups and the sample size difference as well as technical aspects that are not clarified in detail, as the type of surgical technique used or the type of stenting, or even the degree of stenosis.

This can be demonstrated by the results obtained by Hicks et al. [48], who assessed the results of the records of the Vascular Quality Initiative (VQI), which showed that the raw incidence of stroke or death within 30 days was higher in the stenting group with very severe stenosis (2 % vs. 1.2 %, $p < 0.001$) but not in the group with severe stenosis (1.7 % vs. 1.3 %, $p = 0.17$), compared to endarterectomy. It was also found that the probability of stroke or death within 30 days is 64 % higher in the case of stenting, compared to endarterectomy (95 % CI: 1.26-2.13). This pattern was also found when assessing the outcomes after two years using the stent as to the incidence of stroke and death for both severe and very severe stenosis groups ($p < 0.04$) [48]. Concerning the safety in these two interventions, another meta-analysis—which included five randomized controlled trials conducted with 3,901 patients—demonstrated that the probability of perioperative stroke was lower in the endarterectomy vs. stenting group (*OR* 0.53; 95 % CI: 0.29-0.96) but without differences concerning major stroke (*OR* 0.69; 95 % CI: 0.20-2.35), ipsilateral stroke (*OR* 0.63; 95 % CI: 0.27-1.47), acute myocardial infarction (*OR* 1.75; 95 % CI: 0.84-3.65) or peri- or postoperative death (*OR* 1.49; 95 % CI: 0.26-8.68) [49]. Similar results were obtained for the Asian population, for which the difference in the incidence of major stroke has not been significant in these two interventions [50].

Finally, the most recent study and probably the one having the best quality to date despite being observational, could be that published by Chang et al. [18], who analyzed more than 4,000 arteries with severe/very severe stenosis (70 % to 99 %). They found that the patients who did not undergo any surgical intervention had an annual average incidence rate of stroke of 0.9 % during an approximately 48-month follow-up, thus determining an estimated rate of 4.7 % for ipsilateral stroke within five years [18]. Although it can be generally evidenced that the degree of stenosis, comorbidities, surgical techniques and predictive variables in imaging are associated with the risk and outcome of major event and death, the trend is that surgical treatment might be better than medical treatment, and specifically, endarterectomy would have better results in the long term regarding the occurrence or recurrence of ipsilateral stroke and death. Nevertheless, it seems that there are many more unknown variables involved; therefore, the tailored approach should continue according to the surgeon's expertise, technical and technological tools and the context of the patient's health and disease.

Future perspectives

A research agenda on asymptomatic carotid atherosclerosis and stenosis—particularly focused on the screening techniques—is currently discussed since it was evidenced that there are regions that lack reliable primary registries or data that allow assessing the behavior and risk of cerebrovascular disease associated with this condition in this population, which is potentially preventable [51-57]. It is considered that the exposure time to type 2 diabetes mellitus, which is also associated with old age, could be a predictor for a cerebrovascular event and the target of secondary prevention. Therefore, evidence supports using screening in this population [58].

Also, another discussion topic regarding the use of a new risk score was introduced: PREMY2SE-CEA (PREdiction of long-term MortalitY for patients with severe asYmptomatic de novo carotid stEnosis undergoing Carotid EndArterectomy) tool [59], composed of eight risk factors. It predicts mortality in the long term (*OR* 1.38; 95 % CI: 1.28-1.41; $p < 0.001$) and was validated in the Italian population. However, it has only had the initial validation and should be reproduced in other populations and settings [59]. Generally speaking, research on easier access tools—such as carotid Doppler—should be promoted in low- and medium-income countries. This can be based on innovative genetic proposals with imaging to improve the predictive value of its findings since there remain gaps in the evidence of the potential to extrapolate these tools for extracranial conditions and even it could be extremely useful in the event of intracranial carotid atherosclerosis and stenosis [60]. It should be remembered that the Latin American population has genetic and epigenetic characteristics which are different from those in other regions of the world; therefore, social determinants of health and the health-disease process are different, and the treatment of disease should be adapted to this setting [61-68]. Consequently, studies should be repeated in our region to allow the prompt assessment of the behavior

and performance of these tools and also provide evidence according to the population's needs [69,70]. On the other hand, asymptomatic carotid stenosis is a potential risk factor for ischemic stroke that can be detected on time, thereby preventing a major neurovascular outcome or death.

CONCLUSIONS

The evidence is heterogenous as to the superiority of surgical treatment compared to pharmacological treatment in managing asymptomatic carotid atherosclerosis or stenosis. Nevertheless, it seems that the surgical treatment, specifically endarterectomy, could significantly impact on the occurrence or recurrence of ipsilateral stroke and death in the long term but with controversial peri- and postoperative results. There are no studies on this topic in Latin America; thus, the behavior and outcomes of the approach in this population are unknown.

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