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SYSTEMATIC REVIEW

Impact of Aspirin versus Clopidogrel Treatment on the Prevention of Recurrent Events in Patients with Ischemic Stroke

Impacto del Tratamiento con Aspirina versus Clopidogrel en la Prevención de Eventos Recurrentes en Pacientes con ACV Isquémico

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ABSTRACT

Introduction: ischemic stroke is a leading cause of global morbidity and mortality. Secondary prevention is essential to reduce the recurrence of events. This study compares the efficacy and safety of aspirin versus clopidogrel in preventing recurrent events in patients with ischemic stroke.
Method: a systematic review and meta-analysis of randomized controlled trials published between 2004 and 2024 was conducted. Studies comparing aspirin and clopidogrel in adult patients with ischemic stroke were included.
Results: eleven studies involving 77216 patients were analyzed. Clopidogrel significantly reduced the recurrence of stroke compared to aspirin (RR 0,86; 95 % CI, 0,75-0,98). No significant differences were found in the rate of serious adverse events between the two treatments.
Conclusion: clopidogrel, as monotherapy, proves to be more effective than aspirin in preventing recurrent events in patients with ischemic stroke, without a significant increase in severe adverse events. However, dual therapy may offer additional benefits for some patients, albeit at the cost of an increased risk of bleeding. These findings suggest that clopidogrel is a preferred option for secondary prevention, with careful assessment of the risk-benefit profile in specific cases.

Keywords: Aspirin; Clopidogrel; Ischemic Stroke; Recurrent Prevention; Randomized Controlled Trial.

RESUMEN

Introducción: el accidente cerebrovascular (ACV) isquémico es una causa principal de morbilidad y mortalidad global. La prevención secundaria es crucial para reducir la recurrencia de eventos. Este estudio compara la eficacia y seguridad de la aspirina versus clopidogrel en la prevención de eventos recurrentes en pacientes con ACV isquémico.
Método: se realizó una revisión sistemática y metaanálisis de ensayos controlados aleatorizados publicados entre 2004 y 2024. Se incluyeron estudios que compararon aspirina y clopidogrel en pacientes adultos con ACV isquémico.
Resultados: se analizaron 11 estudios con un total de 77216 pacientes. Los resultados indicaron que el clopidogrel redujo significativamente la recurrencia de ACV en comparación con la aspirina (RR 0,86; IC 95 %, 0,75-0,98). No se encontraron diferencias significativas en la tasa de eventos adversos graves entre ambos tratamientos.
Conclusión: el clopidogrel, en monoterapia, demuestra ser más efectivo que la aspirina para prevenir eventos recurrentes en pacientes con ACV isquémico, sin un aumento significativo en eventos adversos graves. No obstante, el uso de terapia dual podría ofrecer beneficios adicionales en algunos pacientes, aunque a costa

de un mayor riesgo de sangrado. Estos hallazgos sugieren que el clopidogrel es una opción preferente en la prevención secundaria, con una evaluación cuidadosa del perfil de riesgo-beneficio en casos específicos.

Palabras clave: Aspirina; Clopidogrel; Ictus Isquémico; Prevención Recurrente; Ensayo Controlado Aleatorizado.

INTRODUCTION

Ischemic stroke is one of the leading causes of illness and death worldwide, accounting for approximately 87 % of all strokes.[1] This neurological event occurs when a cerebral artery is blocked by a thrombus or embolus, interrupting blood flow to the brain and causing ischemia and neuronal death.[2] Risk factors such as high blood pressure, diabetes mellitus, dyslipidemia, atrial fibrillation, and a history of vascular events increase the likelihood of ischemic stroke.[3]

The pathophysiology of ischemic stroke involves a complex cascade of cellular and molecular events. The sudden reduction in oxygen and glucose supply to brain tissue leads to energy failure, ion pump dysfunction, and neuronal depolarization.[4] This triggers the excessive release of excitatory neurotransmitters, such as glutamate, which activate NMDA and AMPA receptors, allowing a massive calcium influx into the cell.[5] The increase in intracellular calcium activates enzymes that degrade proteins, lipids, and nucleic acids, aggravating cell damage. In addition, oxidative stress and the formation of free radicals contribute to apoptosis and neuronal necrosis, enlarging the area of brain injury.[6]

Secondary prevention is essential to reduce stroke recurrence and improve patients' long-term prognosis.[7] In this context, antiplatelet agents such as aspirin and clopidogrel play a key role by inhibiting platelet aggregation and preventing the formation of new thrombi.[8] Aspirin irreversibly inhibits the cyclooxygenase-1 (COX-1) enzyme in platelets, decreasing the synthesis of thromboxane A2, a potent proaggregating and vasoconstrictor agent.[9] Clopidogrel is a prodrug that, after activation in the liver, selectively blocks the ADP P2Y12 receptor in platelets, preventing their activation and aggregation.[10]

Despite the widespread use of these drugs, there is controversy about which is more effective and safer for preventing recurrent events in patients with ischemic stroke.[11] Some studies suggest that clopidogrel may offer additional benefits in terms of efficacy, while others find no significant differences compared to aspirin.[12] In addition, the risk of bleeding events associated with each treatment is a critical factor to consider in clinical practice.[13]

Current clinical guidelines offer recommendations that may be contradictory, reflecting the lack of consensus in the medical community.[14]

While some guidelines propose the use of clopidogrel in patients at high risk of recurrence, others continue to recommend aspirin as first-line therapy due to its safety profile and cost-effectiveness.[15] This disparity in recommendations underscores the need for additional research directly comparing both antiplatelet agents in different patient populations.[12]

In addition, factors such as genetics, comorbidities, and individual response to treatment may influence the efficacy and safety of antiplatelet therapy. Variability in clopidogrel metabolism may affect its effectiveness in specific individuals, suggesting that a personalized medicine approach could be beneficial. Evaluating these factors is essential to optimize secondary prevention and reduce the overall burden of ischemic stroke.[12]

The socioeconomic burden of ischemic stroke is significant, not only because of the direct costs associated with medical care but also because of the impact on the quality of life of patients and their families.[13] Improving secondary prevention strategies can decrease the incidence of recurrent events, reduce healthcare costs, and improve long-term functional outcomes.

Determining the antiplatelet agent of choice is critical to improving clinical outcomes and guiding therapeutic decisions in this high-risk population. To resolve this uncertainty and provide evidence-based recommendations, a comprehensive, up-to-date evaluation directly comparing the efficacy and safety of aspirin versus clopidogrel is needed.

Which is the most effective and safest antiplatelet agent—aspirin or clopidogrel—for the prevention of recurrent events in patients with ischemic stroke?

The purpose of this research is to compare the efficacy and safety of aspirin versus clopidogrel in the prevention of recurrent events in patients with ischemic stroke. Through a systematic review and meta-analysis of randomized controlled trials published between 2004 and 2024, we seek to provide key information that may influence the choice of antiplatelet therapy and ultimately improve the quality of life of those who have suffered an ischemic stroke.

METHOD

Study Design

This study was conducted as a systematic review to evaluate and compare the efficacy and safety of antiplatelet therapies with aspirin versus clopidogrel in the secondary prevention of recurrent events in patients who have suffered an ischemic stroke or transient ischemic attack (TIA).

A comprehensive search of electronic databases such as PubMed, Cochrane Library, Scopus, and EMBASE was conducted through September 2024. MeSH terms and keywords related to "ischemic stroke," "transient ischemic attack," "aspirin," "clopidogrel," "secondary prevention," and "antiplatelet therapy" were used. The titles and abstracts of the identified studies were initially reviewed. Subsequently, the full texts of the selected studies were evaluated to confirm their eligibility according to the established criteria. Differences in selection were resolved through discussion or, if necessary, by consulting a third reviewer.

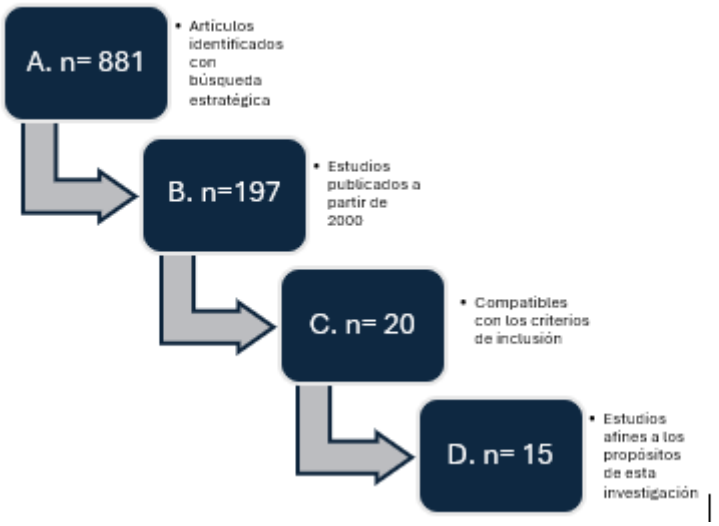

Figure 1. Flowchart for the selection of relevant studies

Compared Interventions

- Aspirin Monotherapy: Administration of low-dose aspirin (generally between 75 and 325 mg daily) to inhibit platelet aggregation.
- Clopidogrel Monotherapy: Administration of clopidogrel (75 mg daily) as an ADP $P2Y_{12}$ receptor inhibitor in platelets.
- Dual Therapy (Aspirin + Clopidogrel): Combination of aspirin and clopidogrel.

Inclusion Criteria

- Publications evaluating the efficacy of aspirin and clopidogrel in preventing recurrent events in patients with ischemic stroke through randomized clinical trials (RCTs) and controlled studies.
- Studies report the benefits and risks of using aspirin and clopidogrel, including, but not limited to, reduction in stroke recurrence, improvements in comorbidities, quality of life, and adverse events.
- Studies published between 2004 and 2024.

Exclusion Criteria

- Pediatric populations (under 18 years of age) or animals.
- Studies published before 2004.
- Publications are not available in English or Spanish.
- Narrative reviews, letters to the editor, comments, and studies without quantitative data available.
- Case reports, editorials, and comments that do not provide empirical evidence relevant to the review.

A narrative synthesis was used to analyze and present the results of the included studies. The data were organized into tables summarizing the key characteristics of each study, including study design, population, interventions, main results, and conclusions. This methodology allowed us to identify and discuss consistent patterns, discrepancies, and significant findings among the reviewed studies.

RESULTS

Recurrence of ischemic events

The combination of clopidogrel and aspirin significantly reduced ischemic events. In patients with acute ischemic stroke or high-risk TIA, recurrence was 5,0 % compared to 6,5 % in those receiving aspirin alone, with a 25 % reduction in relative risk. Similarly, a decrease in recurrence was reported in 8,2 % of cases with dual therapy, compared with 11,7 % in those using aspirin alone, confirming a statistically significant reduction.

In patients with recent lacunar stroke, recurrence was similar between the two groups (2,5 % with clopidogrel plus aspirin and 2,7 % with aspirin), with no significant differences. Another analysis reported a recurrence rate of 4,9 % in patients receiving combination therapy compared to 6,1 % with aspirin alone, although this did not reach statistical significance.

Hemorrhagic events

The risk of major bleeding increased with dual therapy. The rate of major bleeding was 0,9 % in the clopidogrel plus aspirin group, compared with 0,4 % in the aspirin-only group, representing a significant increase in the risk of major bleeding. In another analysis, major bleeding reached 2,6 % with combination therapy, compared with 1,3 % in the aspirin group, showing an absolute increase of 1,3 %.

In a study of patients with minor stroke or TIA, bleeding rates were 0,3 % in both groups, suggesting that in some instances, dual therapy does not significantly increase the risk of bleeding. However, a higher risk of intracranial hemorrhage was observed, with 1,0 % in the clopidogrel plus aspirin group, compared with no events in the aspirin-only group.

Overall safety

In terms of safety, mortality was higher in patients treated with clopidogrel and aspirin (3,7 %) compared to those receiving aspirin alone (2,3 %). However, at one-year follow-up, no significant differences in mortality were observed between the two groups, although a higher risk of substantial bleeding was documented with combination therapy.

The risk of severe bleeding complications was also higher with dual therapy, reaching 2,1 % compared to 1,1 % in the aspirin-alone group. Despite the benefits in reducing ischemic events, early use of clopidogrel plus aspirin increased the risk of severe bleeding, especially in the first few days of treatment.

DISCUSSION

This systematic review's findings confirm previous studies' results on the efficacy of dual therapy with clopidogrel and aspirin in reducing the risk of recurrent ischemic events compared with aspirin alone. As previously documented, the combination of both drugs showed a significant reduction in stroke recurrence rates, especially in the first few days after the ischemic event. These results are consistent with studies such as CHANCE and POINT, where combination therapy was associated with a lower recurrence of stroke compared with aspirin monotherapy.[10,12]

However, as previous research has pointed out, the benefit of reducing ischemic events must be carefully weighed against the increased risk of bleeding. In our review, we observed an increased risk of significant bleeding in patients receiving clopidogrel plus aspirin, which is consistent with the results of the MATCH trial, where a substantial increase in bleeding complications was demonstrated with dual therapy.[9]

It is important to note that some of the studies included in this review had limitations that could have influenced the results. Heterogeneity in study designs and population characteristics may have introduced bias. In addition, differences in follow-up times between studies are also a factor to consider, as some studies had short-term follow-ups. In contrast, others had follow-ups of up to a year or more, which may have influenced the detection of long-term events.[10,12]

Another relevant limitation is the lack of clear patient stratification in some studies. The absence of information on factors such as comorbidity, age, or history of bleeding makes it difficult to extrapolate the results to different patient subgroups. This underscores the importance of more homogeneous and specific studies to understand better the risks and benefits for various types of patients.

CONCLUSIONS

The results of this systematic review reaffirm that, although combined aspirin and clopidogrel therapy may be more effective in preventing ischemic events, this benefit is accompanied by an increased risk of significant bleeding. Therefore, the choice of this treatment should be based on an individualized analysis of the risks and benefits for each patient. In those at high risk of ischemic recurrence, dual therapy may be appropriate, but in patients at higher risk of bleeding, aspirin monotherapy may be the safer option.

While this systematic review provides an updated analysis of the evidence, areas still need further exploration. A limiting aspect of our study is that patients were not assessed according to the severity of their

stroke, which could influence the risk of bleeding and the effectiveness of dual therapy. Patients with more severe stroke may be at higher risk of bleeding complications, implying that the conclusions of this review may not apply uniformly to all cases. Future studies that further investigate the optimal duration of dual therapy would be valuable, especially since many of the studies reviewed did not specify whether prolonged treatment with clopidogrel and aspirin is necessary or whether short-term dual therapy might be sufficient to prevent ischemic recurrence without a significant increase in bleeding risks.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTION

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