



Antiplatelet therapy after gastrointestinal bleeding, decision-making in a complex situation in clinical practice

Terapia antiagregante posterior a hemorragia gastrointestinal, toma de decisiones en una situación compleja de la práctica clínica

Thérapie antiplaquettaire après hémorragie gastro-intestinale, prise de décision en situation complexe en pratique clinique

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ABSTRACT

Introduction: gastrointestinal bleeding emerges as one of the most frequent complications associated with the use of antiplatelet therapy due to cardiovascular diseases. **Objective:** to analyze the growing evidence related to the management of antiplatelet therapy after gastrointestinal bleeding. **Methods:** The methodology used for the elaboration of this article was through the consultation of databases, such as: Google Scholar, PubMed, Cochrane and SciELO. The search was performed using the following words: antiplatelet, hemorrhage, gastrointestinal, basic research, clinical, animal models of human diseases, basic scientific research, clinical studies, mechanisms, pathophysiology, and translational studies. The search inclusion criteria were: information from the last 5 years, in Spanish or English, and whether they were review articles, meta-analyses, or systematic reviews. After that, 300 articles were obtained, of which those that did not contain valuable and updated information that responded to the objective of the present review were excluded. After the exclusion, 35 articles that met the proposed requirements were obtained. **Conclusions:** gastrointestinal bleeding is a complication of antiplatelet therapy that can increase the risk of death, so the risk must be estimated in each of the patients and the continuation must be managed both acutely and after the bleeding, in order to avoid recurrences and to avoid thrombotic risk.

Keywords: antiplatelet therapy, gastrointestinal bleeding, risk, decision making

RESUMEN

Introducción: la hemorragia gastrointestinal surge como una de las complicaciones más frecuentes asociadas al uso de la terapia antiagregante debido a enfermedades cardiovasculares. **Objetivo:** analizar la creciente evidencia relacionada con el manejo de la terapia antiagregante, posterior a hemorragia gastrointestinal. **Métodos:** La metodología utilizada para la elaboración de este artículo fue por medio de la consulta de bases de datos, tales como lo son: Google Scholar, PubMed, Cochrane y SciELO. La búsqueda se realizó utilizándose las siguientes palabras: antiagregante, hemorragia, gastrointestinal, investigación básica, clínica, modelos animales de enfermedades humanas, investigación científica básica, estudios clínicos, mecanismos, fisiopatología, estudios traslacionales. Los criterios de inclusión de la búsqueda fueron: información de los últimos 5 años, en idioma español o inglés y que fueran artículos de revisión, metaanálisis o revisiones sistemáticas. Posterior a eso, se obtuvieron 300 artículos, de los cuales se excluyeron aquellos que no contenían información valiosa y actualizada que respondiera al objetivo de la presente revisión. Posterior a la exclusión, se obtuvieron 35 artículos que cumplen con los requisitos propuestos. **Conclusiones:** la hemorragia gastrointestinal es una complicación de la terapia antiagregante que puede aumentar el riesgo de muerte por lo que debe estimarse el riesgo en cada uno de los pacientes y se debe manejar la continuación tanto de manera aguda como posterior al sangrado, con el fin de evitar recurrencias y evitar el riesgo trombótico.

Palabras clave: terapia antiagregante, hemorragia gastrointestinal, riesgo, toma de decisiones

RÉSUMÉ

Introduction: les saignements gastro-intestinaux apparaissent comme l'une des complications les plus fréquentes associées à l'utilisation d'un traitement antiplaquettaire en raison de maladies cardiovasculaires. **Objectif:** analyser les preuves croissantes liées à la prise en charge du traitement antiplaquettaire après une hémorragie gastro-intestinale. **Méthodes:** La méthodologie utilisée pour l'élaboration de cet article est passée par la consultation de bases de données, telles que: Google Scholar, PubMed, Cochrane et SciELO. La recherche a été effectuée en utilisant les

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*mots suivants: antiplaquettaire, hémorragie, gastro-intestinal, recherche fondamentale, clinique, modèles animaux de maladies humaines, recherche scientifique fondamentale, études cliniques, mécanismes, physiopathologie, études translationnelles. Les critères d'inclusion de la recherche étaient: les informations des 5 dernières années, en espagnol ou en anglais, et s'il s'agissait d'articles de revue, de méta-analyses ou de revues systématique. Après cela, 300 articles ont été obtenus, dont ceux qui ne contenaient pas d'informations précieuses et actualisées répondant à l'objectif de la présente revue ont été exclus. Après l'exclusion, 35 articles répondant aux exigences proposées ont été obtenus. **Conclusions:** l'hémorragie gastro-intestinale est une complication du traitement antiplaquettaire qui peut augmenter le risque de décès, le risque doit donc être estimé chez chacun des patients et la poursuite doit être gérée à la fois en aigu et après l'hémorragie, afin d'éviter les récurrences et d'éviter le risque thrombotique.*

Mots-clés: traitement antiplaquettaire, saignement gastro-intestinal, risque, prise de decisión.

INTRODUCTION

Antiplatelet therapy is currently one of the most important pharmacological measures, both in primary and secondary prevention of cardiovascular diseases. The benefits in cardiovascular outcomes are indisputable. However, the use of these antiplatelet agents increases the risk of bleeding, especially those of gastrointestinal origin. ⁽¹⁾

Randomized clinical trials have shown that the highest risk of bleeding (44.6%) is given in inhibitors of GP IIa/IIIb compared with a low dose of aspirin (3.6%). On the other hand, studies have shown that after antiplatelet therapy, the incidence of gastrointestinal bleeding is approximately 11.9% and this is associated with an increased risk of mortality due to cardiovascular events. ⁽²⁾

Despite being a frequent complication, there is no specific evidence to guide us regarding the mode of intervention for this clinical condition. Hence, the purpose of this study is to analyze the growing evidence related to antiplatelet management after a gastrointestinal bleeding event.

MÉTODO

The methodology used for the elaboration of this article was through the consultation of databases, such as: Google Scholar, PubMed, Cochrane and SciELO. The search was carried out using the following words: "antiplatelet, hemorrhage, gastrointestinal, basic, clinical research, animal models of human diseases, basic scientific research, clinical studies, mechanisms, pathophysiology, translational studies". The search inclusion criteria were: information from the last 5 years, in Spanish or English, and that they were review articles, meta-analyses, or systematic reviews.

After that, 300 articles were obtained, of which those that did not contain valuable and updated information that responded to the objective of the present review. After the exclusion, 35 articles that met the requirements were obtained.

ANALYSIS AND INTEGRATION OF INFORMATION

Assessment of the risk of bleeding associated with antiplatelet therapy

In order to avoid or reduce the probability of gastrointestinal bleeding in patients with antiplatelet therapy, it is essential to apply tools that allow predicting this outcome. This with the aim of guiding decision-making regarding the type of therapy, and its duration after a coronary event. Among the scores currently used, the following stand out.

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CRUSADE (Can Rapid risk stratification of Unstable angina patients suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines)

Most useful score in the prediction of intrahospital hemorrhage in the context of patients with non-ST segment elevation acute myocardial infarction (AMI). But also validated for supra ST cases. For its application, it takes into account variables such as heart rate, systolic blood pressure, hematocrit, creatinine clearance, sex, signs of heart failure, and history of arterial disease or diabetes mellitus. In this way, the score ranges from 1-100 points, considered as very low risk, scores ≤ 20 ; low-risk scores of 21-30; moderate risk scores of 31-40; high-risk scores of 41-50; and very high-risk scores >50 .⁽³⁾

PRECISE-DAPT (Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy)

Predicts out-of-hospital bleeding risk for patients treated with dual antiplatelet therapy (ASA + P2Y12 inhibitor) after percutaneous coronary intervention (PCI) with stent implantation. It includes 5 variables: age, hemoglobin levels, leukocytes, creatinine clearance, and history of previous bleeding. Based on the result of this, it is possible to compare the ischemic and hemorrhagic risk of the patients, to determine the duration of the double therapy antiplatelet.^(4,5)

Thus, patients with a PRECISE-DAPT score >25 do not benefit from prolonging antiplatelet therapy, since this is associated with the same ischemic risk, but with a greater risk of bleeding. However, it should be borne in mind that patients with a PRECISE-DAPT score <25 and being managed with short-term dual antiplatelet therapy (6 months) are associated with a higher ischemic risk and a similar risk of bleeding compared with long-term therapy (12 months).⁽⁴⁾

Endoscopic bleeding risk assessment

Blatchford scale should be applied in order to determine the risk of complications in order to decide the place of management and consider or not endoscopy. Therefore, if there is a score >2 , the patient should be treated in an intrahospital setting; and if it is >6 , it presents a high risk of complications, which requires endoscopy urgently.⁽⁶⁾

Once the endoscopy has been performed, based on the observed findings, the Forrest scale can be applied. According to this, the groups at high risk of recurrence are group Ia: jet hemorrhage with a 90% risk of recurrence; group Ib: drooling hemorrhage with a 10-33% risk of recurrence; group IIa: visible vessel with a 50% risk of recurrence; group IIb: adhered clot with a 25-30% risk of recurrence. On the other hand, the groups with a low risk of recurrence are group IIc: hematin points with a risk of 7-10% of recurrence; group III: lesion with a clean base, 3-5% risk of recurrence.⁽⁷⁾

However, depending on the risk groups, management can be determined. Thus, low-risk groups (IIc and III) do not benefit from endoscopic treatment, since it does not impact rebleeding. Conversely, evidence of recent bleeding seen in groups IA, IB, IIA, and IIB is associated with an increased 30-day risk of rebleeding. For this reason, they should receive endoscopic therapy (adrenaline + other mechanical, thermal, or sclerosing therapies) to achieve hemostasis and prevent rebleeding. It has been shown that these patients must be hospitalized for at least 72 hours, already a great part of the recurrences HE presents in this limit of time.^(7,8)

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How to manage patients with gastrointestinal bleeding and antiplatelet therapy?

The type of antiplatelet therapy that the patient receives must be taken into account, since the risk of bleeding depends on it. As previously mentioned, therapy with GP IIa/IIIb inhibitors is associated to a greater extent with bleeding compared with aspirin. Likewise, multiple clinical trials have shown that dual antiplatelet drugs are associated with a bleeding risk of 0.6-4.8%, compared to 0.6-3.8% with aspirin monotherapy. For this reason, it is necessary to individualize the type of therapy that the patient receives and the management that he will have both during active bleeding and after it. ⁽⁹⁾

Within the control of bleeding in patients receiving antiplatelet therapy, platelet transfusion has been considered. However, a study was carried out on patients with gastrointestinal bleeding who were managed with antiplatelet drugs and without thrombocytopenia-associated platelet transfusion with a higher risk of mortality without modifying the risk of bleeding. ⁽¹⁰⁾

Management of Gastrointestinal (GI) Bleeding in Patients Using Aspirin (ASA) Monotherapy

In patients being managed with low doses of ASA, it has been seen that its interruption was largely associated with higher mortality rates. On the other hand, the continuation of this is associated with a greater recurrence of bleeding (50%). For this reason, the European Society of Gastrointestinal Endoscopy recommended that therapy should be continued after endoscopic evaluation of the source of bleeding, as long as it has a Forrest classification with a low risk of recurrence (IIc or III). On the contrary, Forrest's classification indicates a high risk of recurrence (Ia, Ib, IIa, IIb) it is recommended to stop aspirin for 3-7 days, and after that continue it, as long as the patient is hemodynamically stable. ⁽¹¹⁾

Management of gastrointestinal bleeding in patients with double antiplatelet therapy

Decisions made regarding the management of bleeding depend on its severity. Thus, it is recommended to continue dual therapy if Forrest is found to be a low risk on endoscopy. However, the duration of this should be considered and in cases where the patient receives ticagrelor/Prasugrel, switch to clopidogrel. ⁽¹²⁻¹⁴⁾

When there is moderate bleeding defined as loss of >2 mmol/L of hemoglobin, it is recommended to discontinue dual antiplatelet therapy and switch to monotherapy; in the context of upper gastrointestinal bleeding, it should be aspirin or ticagrelor/ prasugrel since it has been seen that clopidogrel administered together with proton pump inhibitors (PPIs) causes multiple interactions due to the fact that they share the same metabolism through the cytochrome pathway CYP2C19. ⁽¹⁵⁻²⁹⁾

In cases of severe bleeding defined as loss >3 mmol/L of hemoglobin, the same considerations apply as in moderate bleeding, but with the condition that all antiplatelet therapy be discontinued if the bleeding persists. In both cases, it is recommended to re-establish dual antiplatelet therapy at least 3-5 days after the bleeding resolves. ⁽¹⁷⁻²¹⁾

The importance of good bleeding control is that the 30-day mortality rate is 20.5% in patients with bleeding, compared with 2.4% in patients without bleeding. For this reason, the thrombotic and bleeding risk must be evaluated in patients in whom antiplatelet therapy should be indicated, in order to make decisions supported by scientific evidence regarding the type of therapy and its

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duration. In order to achieve the purpose of thrombotic control and decrease cardiovascular outcomes but without increasing the risk of bleeding. (23-26)

The role of proton pump inhibitors (PPIs)

The use of PPIs in conjunction with antiplatelet therapy is not yet defined. But what is clear is that these are the number 1 prevention of gastrointestinal bleeding. The reason why PPIs are not widely used is because they are metabolized by the same pathway as clopidogrel, CYP2C19, so it is believed that their concomitant use may decrease the antithrombotic action of clopidogrel. (14-34)

However, in studies such as Clopidogrel with or without omeprazole in coronary artery disease (COGENT), omeprazole was administered to patients at high cardiovascular risk and this was not significantly associated with an increase in cardiovascular outcomes but rather decreased the risk of gastrointestinal bleeding. However, what must be taken into account is the specific population that would benefit from the administration of PPIs. For this reason, it is essential that bleeding risk scores be applied when starting antiplatelet therapy. Patients who are at high risk of bleeding benefit from the administration of PPIs. (14-34)

Another recommendation to take into account is the use of PPIs such as rabeprazole or pantoprazole that have no effect on CYP2C19 in patients receiving clopidogrel, so as not to run the risk of diminishing its antithrombotic action. For these reasons, therapy with proton pump inhibitors would be recommended in patients on antiplatelet therapy who develop gastrointestinal bleeding and who are at high risk of recurrence; this should be extended for the same time as antiplatelet therapy. (16-20)

In conclusion, the great importance of antiplatelet therapy in the primary and secondary prevention of cardiovascular events is undeniable. Even to the point of becoming the fundamental pillar of management. However, despite their great clinical utility in reducing ischemic events, they greatly increase the risk of bleeding. To avoid this complication, it is necessary to apply tools to assess the risk of each of the patients who are managed with antiplatelet therapy, in order to make the best decisions regarding the appropriate choice of therapy, maintaining a certain balance between ischemic risk and hemorrhagic.

On the other hand, individualizing the patient regarding the antiplatelet therapy that he should receive and the duration that it should last, is crucial to reduce the bleeding risk; Considering the use of proton pump inhibitors in patients with a high risk of bleeding reduces this complication, which increases mortality in patients.

Even so, there is not enough evidence, and the available evidence has not yet been able to specify the management of antiplatelet therapy after gastrointestinal bleeding, so research must continue and clinical practice guidelines should be developed at the national level; so that you can have a protocol for each of the specific cases of patients, their comorbidities and risk factors for suffering this complication, which can increase the mortality rate associated with cardiovascular events, which by itself is already one of the leading causes of death worldwide.

Abbreviations: PPI: proton pump inhibitors, ASA: acetylsalicylic acid, AMI: acute myocardial infarction.

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CONFLICTS OF INTEREST

No conflicts of interest are declared.

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