Should Hip Fracture Surgery be delayed in Patients Receiving Clopidogrel?

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Introduction

Medicine is the science and art of taking decisions in situations of uncertainty, weighing up the risks and benefits and searching for the best option for the patient at all times. To aid clinical reasoning and to standardize criteria, guidelines, publications and professional experience are all extremely valuable. However, there are cases in which our present state of knowledge is insufficient and a high degree of uncertainty remains.

One such case is that of hip fracture patients taking antiplatelet drugs, especially clopidogrel [1,2]. In these patients the risk of bleeding in the case of rapid surgical intervention should be assessed and set against the risk of thromboembolism if the operation is postponed until the action of the drug has ceased [3-7].

Hip fractures are a common pathology among the elderly. It is estimated that worldwide there are 1.6 million fractures per year [8]. Most patients suffer from multiple pathologies, among which cardiovascular diseases are the most prevalent. The standard treatment for repair of a fracture with neuraxial anesthesia is surgery [6,9,10].

Clinical guidelines recommend the suspension of clopidogrel for seven days prior to elective surgery, and replace it acetylsalicylic acid at low doses. While the administration of low molecular weight heparin is recommended as prophylaxis against venous thromboembolism. In the case of semi-urgent operations such as hip fracture, individualized assessment of the risks and benefits of postponing surgery is advised [11,12].

In this mini review we discuss the management of patients with hip fracture receiving treatment with clopidogrel, and provide some recommendations.

Platelet Physiology: Half-Life and Action of the P2Y12 Receptor

Platelets are constantly being produced and destroyed continuously. The number of platelets ranges between 150,000 and 400,000 per ml and their half-life is seven to ten days. Between 10% and 15% of the platelet population is renewed every day. In the presence of vascular abnormalities, platelet aggregation is essential in order to prevent bleeding. The P2Y12 receptor plays a central role in the process of platelet aggregation. This receptor is activated by adenosine diphosphate (ADP) and acts through the G protein complex, contributing via a range of mechanisms to the formation and stabilization of a thrombus [13].

Clopidogrel: Metabolism, Mechanism of Action and Indications

Despite the difficulty of interpreting the results in the literature, it appears that currently between 5% and 9% of patients with hip fracture are taking clopidogrel [14-17].

Clopidogrel is absorbed via the intestine and metabolized in the liver cells to convert it in active form. This process involves several enzymes, including those in the cytochrome P450 pathway. Clopidogrel covalently binds to the structure of the platelet P2Y12 receptor, which is inactivated throughout the platelet's lifetime [18]. The recovery of platelet activity after discontinuation of clopidogrel treatment is gradual and requires platelet renewal. According to Metzler et al. [19], 53% of patients recover platelet function within three days of treatment withdrawal, and 85% of patients within five days.

The absorption and metabolism of clopidogrel are subject to genetic factors, and so the drug's bioavailability and activity vary widely. In addition, age, certain pathologies and the use of certain drugs which are metabolized by the same enzyme pathway further increase the biological variation [20,21].

The laboratory tests that are currently available to measure platelet function in response to antiplatelet agents are not sufficiently sensitive for routine use in clinical practice.

Clopidogrel is prescribed for the prevention of cardiac, cerebrovascular and peripheral vascular disorders. Its action can only be reversed with platelet transfusion, and its withdrawal increases the risk of thromboembolism [1,22].

Risks Associated with Clopidogrel Treatment and with its Discontinuation

The main risks of hip fracture in patients with chronic treatment with clopidogrel are surgical bleeding and complications caused by neuraxial anesthesia, such as spinal hematoma [23,24]. The current guidelines of ASRA (American Society of Regional Anesthesia) [12], contraindicate the use of neuraxial anesthesia in patients treated with clopidogrel, and recommend withdrawal of the agent five days prior to the blockade. No randomized controlled studies have evaluated the risk of bleeding due to continuation of clopidogrel treatment during the perioperative management of patients undergoing hip fracture. Some studies in which surgery was performed under general anesthesia [17,25] did not find an increase in bleeding, postoperative complications or mortality in the first 48-72 hours in patients treated with clopidogrel. For this reason, the authors argue against delaying surgery in this group of patients.
Hip fracture causes a physiological situation of pain and stress which triggers a systemic response. One consequence is an alteration of the balance between the vascular endothelium, the platelets and the blood coagulation system, leading to thrombophilia [26].

In this situation, the withdrawal of antiplatelet drugs increases the risk of diseases associated with thromboembolism such as stroke, venous thrombosis, cerebral vascular accident and pulmonary thromboembolism.

Current literature reports recognize these risks but the study samples are small and the results inconclusive. Several studies have demonstrated that the risk of thromboembolism is more serious than the risk of bleeding complications [2,14-17,25, 27].

Table 1 shows data from recently published studies, evaluating the main risks associated with the withdrawal or discontinuity of treatment with Clopidogrel in patients with hip fracture.

Table 1: Risks associated with the withdrawal or discontinuity of treatment with Clopidogrel in patients with hip fracture

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Type of study</th>
<th>Withdrawal of clopidogrel</th>
<th>Risk of thromboembolia</th>
<th>Risk of bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gagli et al. [22]</td>
<td>2011</td>
<td>Systematic review</td>
<td>Yes</td>
<td>Yes</td>
<td>-----</td>
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<tr>
<td>Chechik et al. [3]</td>
<td>2011</td>
<td>Prospective</td>
<td>No</td>
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<td>Yes</td>
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<tr>
<td>Collyer et al. [14]</td>
<td>2011</td>
<td>Retrospective</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Collinge et al. [17]</td>
<td>2012</td>
<td>Retrospective</td>
<td>No</td>
<td>----</td>
<td>No</td>
</tr>
<tr>
<td>Al Khudairy et al. [27]</td>
<td>2013</td>
<td>Prospective</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Hossain et al. [25]</td>
<td>2013</td>
<td>Retrospective</td>
<td>No</td>
<td>----</td>
<td>No</td>
</tr>
<tr>
<td>Reguant et al. [16]</td>
<td>2013</td>
<td>Retrospective</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Table 2: Effects of surgical delay on severe postoperative complications and mortality in patients with hip fracture, provided by literature

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Type of Study</th>
<th>Clopidogrel Treatment</th>
<th>Increase of complications</th>
<th>Increase of mortality</th>
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</thead>
<tbody>
<tr>
<td>Hart et al. [24]</td>
<td>2007</td>
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<td>Yes</td>
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<tr>
<td>Shiga et al. [30]</td>
<td>2008</td>
<td>Meta-analysis</td>
<td>----</td>
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<td>Johansen et al. [4]</td>
<td>2008</td>
<td>Prospective</td>
<td>Yes</td>
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<td>Maheshwari et al. [23]</td>
<td>2011</td>
<td>Retrospective</td>
<td>Yes</td>
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<tr>
<td>Simunovic et al. [8]</td>
<td>2011</td>
<td>Meta-analysis</td>
<td>----</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Collyer et al. [14]</td>
<td>2011</td>
<td>Retrospective</td>
<td>Yes</td>
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<tr>
<td>Moja et al. [29]</td>
<td>2012</td>
<td>Meta-analysis</td>
<td>----</td>
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</tbody>
</table>

What is Already Known on this Topic?

1. The basic concepts of this revision are summarized below:
2. Approximately 10% of patients with hip fracture are treated with clopidogrel
3. Clopidogrel inhibits platelet activation and aggregation, the effect lasting from 7 to 10 days.
4. The laboratory tests currently available are not sensitive enough to measure platelet function in response to clopidogrel
5. The main anesthesia technique used in hip fracture surgery is neuraxial anesthesia.
6. The main risks of hip fracture in patients with chronic treatment with clopidogrel are surgical bleeding and spinal haematoma derived from the neuraxial anesthesia, due to which clopidogrel treatment is suspended and the surgery postponed.
7. The current guidelines advise to postpone the use of neuraxial technique for 5 days as a safety margin.
8. The discontinuity of clopidogrel treatment during the perioperative management of the patient increases the risk of thromboembolic alterations.
9. Surgical delay increases the risk of severe postoperative complications

What Would we Recommend?

Based on the currently available knowledge, we advocate personalizing the surgical and anesthetic management of patients with hip fracture and particularly those under treatment with clopidogrel.

In agreement with some authors [28,34] we believe that surgical delay is justified only in patients who require medical stabilization. Treatment with clopidogrel and the need to perform neuraxial anesthesia should not be the only criteria for delaying surgery. In fact the reviews by Parker et al. [35], and Luger et al. [36], did not find compelling evidence that neuraxial anesthesia performs better than general anesthesia.

Therefore, we believe that assessment of the risks and benefits of surgery under general anesthesia (except if contraindicated) in the first 48 hours should be part of our normal anesthetic practice, in order to reduce the risk of postoperative complications due to surgical delay.

Nevertheless, recommendations from experts in the matter should be provided, drawn up by a work group from a Scientific Society.

Further prospective studies and randomized clinical trials are needed to provide conclusive evidence of the beneficial effects of prompt surgery in patients treated with clopidogrel.

References


