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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 is surgical repair with neuraxial anesthesia [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.

Author	Year	Type of study	Withdrawal of clopidogrel	Risk of thromboembolia	Risk of bleeding
Gaglia et al. [22]	2011	Systematic review	Yes	Yes	------
Chechik et al. [3]	2011	Prospective	No	------	Yes
Collyer et al. [14]	2011	Retrospective	Yes	Yes	No
Collinge et al. [17]	2012	Retrospective	No	------	No
Al Khudairy et al. [27]	2013	Prospective	Yes	Yes	No
Hossain et al. [25]	2013	Retrospective	No	------	No
Reguant et al. [16]	2013	Retrospective	Yes	Yes	No

Table 1: Risks associated with the treatment and withdrawal of Clopidogrel in patients awaiting surgery for hip fracture, provided by literature

Risk Associated with Delay of Surgery

Hip fracture is associated with a high morbidity and mortality. Age, sex and underlying pathologies are well-known prognostic factors that are non-modifiable at the time of admission. On the other hand, it is possible to improve certain aspects of patient stabilization and preparation [6,10,28,29].

At present there is sufficient scientific evidence of an association between surgical delay, increased postoperative complications and prolonged hospital stay. The impact of delay on mortality remains a matter of debate [6,29,30]. In our 2008 study16, postponing surgery by four days in patients treated with clopidogrel was not associated with increases in transfusion rate, mortality or hospital stay, but a significant rise in postoperative respiratory complications was recorded as well as a tendency towards an increased risk of serious cardiovascular events. The most common postoperative complication was acute respiratory infection; as Simunovic et al. [6] states, this was probably due to the patients being bedridden before surgery.

According to previous reports, delays longer than 5 to 13 days [29,31] are associated with increased mortality, but in shorter, standard delays (1 to 4 days) the literature is inconclusive, although short waiting times are recommended [5,15,23,29,32]. Many of these studies do not specify the strategy applied, even though it is becoming increasingly clear that a multidisciplinary approach reduces mortality and morbidity [8,28,33]. The current data suggest that in patients with hip fracture the best option is multidisciplinary treatment and prompt surgery.

Table 2 shows some results published by different authors in the last years, on the effects of surgery delay on severe postoperative complications and mortality in patients operated from hip fracture. Some of these studies have evaluated the effects of surgical delay specifically within the group of patients treated with clopidogrel.

Author	Year	Type of Study	Clopidogrel Treatment	Increase of complications	Increase of mortality
Harty et al. [24]	2007	Retrospective	Yes	-------	Yes
Shiga et al. [30]	2008	Meta-analysis	-------	Yes	Yes
Johansen et al. [4]	2008	Prospective	Yes	Yes	-------
Maheshwari et al. [23]	2011	Retrospective	Yes	Yes	Yes
Simunovic et al. [6]	2011	Meta-analysis	-------	Yes	Yes
Collyer et al. [14]	2011	Retrospective	Yes	Yes	-------
Moja et al. [29]	2012	Meta-analysis	-------	Yes	Yes

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

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

1. 1. Baron TH, Kamath PS, McBane RD (2013) Management of antithrombotic therapy inpatients undergoing invasive procedures. N Engl J Med 368: 2113-2124.
2. Wordsworth DR, Halsey T, Griffiths R, Parker MJ (2013) Clopidogrel has no effect on mortality from hip fracture. Injury 44: 743-746.
3. Chechik O, Thein R, Fichman G, Haim A, Tov TB, et al. (2011) The effect of clopidogrel and aspirin on blood loss in hip fracture surgery. Injury 42: 1277-1282.
4. Johansen A, White J, Turk A (2008) Clopidogrel therapy--implications for hip fracture surgery. Injury 39: 1188-1190.
5. Dineen PF, Curtin RJ, Harty JA (2010) A review of the use of common antiplatelet agents in orthopaedic practice. J Bone Joint Surg Br 92: 1186-1191.
6. Simunovic N, Devereaux PJ, Sprague S, Guyatt GH, Schemitsch E, et al. (2010) Effect of early surgery after hip fracture on mortality and complications: systematic review and meta-analysis. CMAJ 182: 1609-1616.
7. Lefaivre KA, Macadam SA, Davidson DJ, Gandhi R, Chan H, et al. (2009) Length of stay, mortality, morbidity and delay to surgery in hip fractures. J Bone Joint Surg Br 91: 922-927.
8. Hung WW, Egol KA, Zuckerman JD, Siu AL (2012) Hip fracture management: tailoring care for the older patient. JAMA 307: 2185-2194.
9. Reguant F1, Bosch J, Montesinos J, Arnau A, Ruiz C, et al. (2012) [Prognostic factors for mortality in elderly patients with hip fracture]. Rev Esp Anestesiol Reanim 59: 289-298.
10. Roche JJ, Wenn RT, Sahota O, Moran CG (2005) Effect of comorbidities and postoperative complications on mortality after hip fracture in elderly people: prospective observational cohort study. BMJ 331: 1374.
11. Sierra P, Gomez-Luque A, Castillo J, Llau JV (2011) Practice guideline for the preoperative management of platelet aggregation antagonists in non-cardiac surgery. Sociedad Espanola de Anestesiologia y Reanimacion. Rev Esp Anestesiol Reanim 58 Suppl 1:1-16.
12. Horlocker TT (2011) Regional anaesthesia in the patient receiving antithrombotic and antiplatelet therapy. Br J Anaesth 107 Suppl 1: i96-106.
13. Dorsam RT, Kunapuli SP (2004) Central role of the P2Y12 receptor in platelet activation. J Clin Invest 113: 340-345.
14. Collyer TC, Reynolds HC, Truyens E, Kilshaw L, Corcoran T (2011) Perioperative management of clopidogrel therapy: the effects on in-hospital cardiac morbidity in older patients with hip fractures. Br J Anaesth 107: 911-915.
15. Feely MA, Mabry TM, Lohse CM, Sems SA, Mauck KF (2013) Safety of clopidogrel in hip fracture surgery. Mayo Clin Proc 88: 149-156.
16. Reguant F, Martínez E, Gil B, Prieto JC, Del Milagro Jiménez L, et al. (2013) [Hip fracture, antiplatelet drugs treatment and postoperative complications]. Rev Esp Anestesiol Reanim 60: 504-510.
17. Collinge CA, Kelly KC, Little B, Weaver T, Schuster RD (2012) The effects of clopidogrel (Plavix) and other oral anticoagulants on early hip fracture surgery. J Orthop Trauma 26: 568-573.
18. Cattaneo M (2010) New P2Y(12) inhibitors. Circulation 121: 171-179.
19. Metzler H, Prüller F, Münch A, Primus G, Kainz J, et al. (2010) Premature preoperative discontinuation of antiplatelet drug therapy in cardiovascular risk patients: a preliminary study on the role of P2Y12 receptor monitoring. Eur J Anaesthesiol 27: 138-145.
20. Sangkuhl K, Klein TE, Altman RB (2010) Clopidogrel pathway. Pharmacogenet Genomics 20: 463-465.
21. Freedman JE, Iafrati HF. (2010) Use of genetics and transcriptomics in the diagnosis and treatment of coronary artery disease. Rev Esp Cardiol 63:1123-1126.
22. Gaglia MA Jr, Waksman R (2011) Systematic review of thienopyridine discontinuation and its impact upon clinical outcomes. Eur Heart J 32: 2358-2364.
23. Maheshwari R, Acharya M, Monda M, Pandey R (2011) Factors influencing mortality in patients on antiplatelet agents presenting with proximal femoral fractures. J Orthop Surg (Hong Kong) 19: 314-316.
24. Harty JA, McKenna P, Moloney D, D'Souza L, Masterson E (2007) Anti-platelet agents and surgical delay in elderly patients with hip fractures. J Orthop Surg (Hong Kong) 15: 270-272.
25. Hossain F, Rambani R, Ribee H, Koch L (2013) Is discontinuation of clopidogrel necessary for intracapsular hip fracture surgery? Analysis of 102 hemiarthroplasties. J Orthop Traumatol 14: 171-177.
26. Hietala P, Strandberg M, Strandberg N, Gullichsen E, Airaksinen KE (2013) Perioperative myocardial infarctions are common and often unrecognized in patients undergoing hip fracture surgery. J Trauma Acute Care Surg 74: 1087-1091.
27. Al Khudairy A, Al-Hadeedi O, Sayana MK, Galvin R, Quinlan JF (2013) Withholding clopidogrel for 3 to 6 versus 7 days or more before surgery in hip fracture patients. J Orthop Surg (Hong Kong) 21: 146-150.
28. Association of Anaesthetists of Great Britain and Ireland, Griffiths R, Alper J, Beckingsale A, Goldhill D, et al. (2012) Management of proximal femoral fractures 2011: Association of Anaesthetists of Great Britain and Ireland. Anaesthesia 67: 85-98.
29. Moja L, Piatti A, Pecoraro V, Ricci C, Virgili G, et al. (2012) Timing matters in hip fracture surgery: patients operated within 48 hours have better outcomes. A meta-analysis and meta-regression of over 190,000 patients. PLoS One 7: e46175.
30. Shiga T, Wajima Z, Ohe Y (2008) Is operative delay associated with increased mortality of hip fracture patients? Systematic review, meta-analysis, and meta-regression. Can J Anaesth 55: 146-154.
31. Shoda N, Yasunaga H, Horiguchi H, Matsuda S, Ohe K, et al. (2012) Risk factors affecting inhospital mortality after hip fracture: retrospective analysis using the Japanese Diagnosis Procedure Combination Database. BMJ 4: 2: 10.1136/bmjopen-2011-000416.
32. Daugaard CL, Jørgensen HL, Riis T, Lauritzen JB, Duus BR, et al. (2012) Is mortality after hip fracture associated with surgical delay or admission during weekends and public holidays? A retrospective study of 38,020 patients. Acta Orthop 83: 609-613.

33. Grigoryan KV, Javedan H, Rudolph JL (2014) Orthogeriatric care models and outcomes in hip fracture patients: a systematic review and meta-analysis. J Orthop Trauma 28: e49-55.

34. McBrien ME, Heyburn G, Lappin E, McGuirk S, McBrien JL, et al. (2013) Multidisciplinary guideline for hip fracture patients taking clopidogrel. Anaesthesia 68: 116-118.

35. Parker MJ, Urwin SC, Handoll HH, Griffiths R (2000) General versus spinal/epidural anaesthesia for surgery for hip fractures in adults. Cochrane Database Syst Rev 2: CD000521.

36. Luger TJ, Kammerlander C, Gosch M, Luger MF, Kammerlander-Knauer U, et al. (2010) Neuroaxial versus general anaesthesia in geriatric patients for hip fracture surgery: does it matter? Osteoporos Int 21: S555-572.