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Should we add antiplatelet agents to current deep venous thrombosis treatments? A Cochrane Review summary with commentary

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Abstract.
BACKGROUND: Venous thromboembolism (VTE) is an important complication in rehabilitation practice despite preventive measures. The management can be complicated because patients may have co-existing cardiovascular comorbidities.
OBJECTIVE: To assess the effects of antiplatelet agents in addition to current best medical practice (BMP) compared to current BMP (with or without placebo) for the treatment of deep venous thrombosis (DVT).
METHODS: A summary of the Cochrane Review by Flumignan et al. (2022), with comments from a rehabilitation perspective.
RESULTS: The review included six studies with 1625 eligible participants, with data up to 37.2 months of follow-up. When used after standard initial treatment with anticoagulants, antiplatelet agents such as aspirin in addition to BMP, may reduce recurrence of DVT or pulmonary embolism, when compared to BMP plus placebo in a chronic DVT setting and there may be a lower risk for post-thrombotic syndrome in patients with acute DVT. There is no clear difference in side effects, major bleeding, or pulmonary embolism (PE) with the use of antiplatelet agents.
CONCLUSION: Adding antiplatelet agents to standard anticoagulation treatment in patients with VTE could provide benefit without increasing risks in selected patient groups. However, high quality studies with a long-term follow up are needed, including patients in rehabilitation settings.

Keywords: Platelet aggregation inhibitors, venous thrombosis, pulmonary embolism, postthrombotic syndrome, hemorrhage, rehabilitation, fractures, bone, immobilisation

The aim of this commentary is to discuss from a rehabilitation perspective the Cochrane Review "Antiplatelet agents for the treatment of deep venous thrombosis" (Flumignan et al., 2022) by Flumignan CDQ, Nakano LCU, Baptista-Silva JCC and Flumignan RLG[1], published by the Cochrane Vas-

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[1]This summary is based on a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2022, Issue 7, Art. No.: CD012369, DOI: 10.1002/14651858.CD012369.pub2 (see www.cochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.

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1. Background

Deep vein thrombosis (DVT) is a blood clot in a deep vein, usually in the lower extremities. On breaking loose it can cause pulmonary embolism (PE). It is a common complication in rehabilitation practice as some of the main causes are: trauma or bone fracture; surgery of the abdomen, hip or leg; bed rest and other forms of immobilization; cancer; COVID-19. Incidence and prevalence are still relatively high, despite prevention with low-molecular-weight heparins, in particular after spinal cord injury, stroke or traumatic brain injury where prophylaxis can be an issue in case of intracerebral hemorrhage. Moreover, cardiac surgery patients, who represent the main group enrolled in cardiac rehabilitation programs, are at twice the risk of developing postoperative DVT as compared with vascular surgery patients and at thrice the risk as compared with general surgery patients (Ho et al., 2015). However, an increased risk of bleeding and cardiac tamponade remains a major concern for patients who have undergone cardiac surgery. The current best medical practice (BMP) for treating DVT includes mainly anticoagulation and compression stockings, but antiplatelet agents may be useful when used in addition to BMP.

Antiplatelet agents for the treatment of deep venous thrombosis

(Flumignan CDQ, Nakano LCU, Baptista-Silva JCC & Flumignan RLG, 2022)

2. Objective

The aim of this Cochrane Review was to assess the effects of antiplatelet agents (AA) in addition to current BMP compared to current BMP (with or without placebo) for the treatment of DVT.

*The views expressed in the summary with commentary are those of the Cochrane Corner authors (different than the original Cochrane Review authors) and do not represent the Cochrane Library or Wiley.

3. What was studied and methods

The population addressed in this review was persons of both sexes and of any age as long as they were diagnosed with both symptomatic and asymptomatic DVT (acute or chronic) by a medical specialist on clinical assessment and further investigation (duplex ultrasound, multislice computed tomography or angiography).

The intervention studied was AA plus BMP. BMP was considered as anticoagulation, compression stockings and clinical care, such as physical exercises, skin hydration etc. The intervention was compared to BMP alone or to BMP plus placebo. The same interventions and comparisons were considered in participants with acute and chronic DVT. The acute phase was defined as up to 21 days from onset of symptoms and the chronic phase after 21 days. The primary outcomes studied were: recurrent VTE, major bleeding, and PE. Secondary outcomes included: mortality, post thrombotic syndrome (PTS), adverse events, quality of life, and duration of hospitalization.

4. Results

The review included six studies (with 1625 participants), that provided data for three different comparisons. The review shows that:

AA plus BMP versus BMP alone (1 study) did not result in more deaths and no cases of major bleeding were reported in patients with acute DVT, while very low certainty evidence showed that AA plus BMP resulted in a lower risk of PTS (RR 0.74 (0.61 to 0.91)).

AA plus BMP versus BMP alone (1 study) did not result in major bleeding, mortality, or adverse events during 3 years of follow-up in patients with chronic DVT while there was very low certainty for an effect estimate for recurrent VTE in favour of AA plus BMP (RR 0.12 (0.05 to 0.34)). There was no information on PE and PTS.

A meta-analysis on AA plus BMP versus BMP plus placebo (4 studies) in patients with chronic DVT showed low certainty evidence for a lower risk of recurrent VTE for the AA group (RR 0.65 (0.43 to 0.96)). There was no clear difference for major bleeding, PE fatal/non-fatal outcome, all-cause mortality, or adverse effects (moderate certainty evidence). PTS was not assessed.

5. Conclusions

The authors concluded that AA in addition to BMP may reduce recurrent VTE when compared to BMP plus placebo in (chronic DVT setting, low certainty evidence), while moderate evidence shows no clear difference in adverse events, major bleeding, and PE when AA are used. No conclusions could be drawn for AA in addition to BMP when compared to BMP alone (acute and chronic DVT setting, very low certainty evidence).

5.1. Implications for practice in (neuro)rehabilitation

Patients with acute neurological health conditions such as stroke, traumatic brain injury or spinal cord injury are often immobilized for a prolonged time. Despite preventive measures, VTE remains a serious complication in rehabilitation practice. Also, considering that patients often have long-term risk factors such as immobility or cardiovascular comorbidities, the risk for recurrence persists. For patients with DVT/PE with stable cardiovascular disease, the American Society of Hematology 2020 guidelines suggest suspending aspirin therapy when initiating anticoagulation and state that: "the combination of anticoagulation plus aspirin increases the risk of bleeding without clear evidence of benefit for patients with stable cardiovascular disease" (Ortel et al., 2020). On the other hand, recent evidence suggested that a prothrombotic state owing to multiple mechanisms is common after cardiac surgery from day 1 up to 30 days involving the rehabilitation setting and the use of low-dose antiplatelet agents alone would not be sufficient in preventing VTE, suggesting, without strong evidence of increased risk of bleeding, initiating low-dose unfractionated or low-molecular-weight heparins as soon as possible after cardiac surgery (Ho et al., 2015).

The results from this CSR (Flumignan et al., 2022) do not seem to demonstrate a higher risk of major bleeding or death in patients with acute or chronic DVT, when adding AA to BMP, while the risk of recurrence of DVT and/or PE may be decreased in patients with chronic DVT, and in patients with acute DVT it may decrease the risk for PTS. More studies with long-term follow up are needed, in particular in patients within the neurological, but also other rehabilitation fields such as cardiorespiratory or orthopaedic but adding antiplatelet agents to standard anticoagulation treatment could provide benefit without increasing risks in selected patient groups.

Conflict of interest

The authors declare no conflicts of interest.

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