Cochrane Corner: The use of anticoagulants in patients hospitalised with COVID-19

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In this Cochrane Corner, we highlight the main findings of a Cochrane Review by Flumignan *et al.* entitled 'Anticoagulants for people hospitalised with COVID-19' and discuss the implications of these findings for research and practice in South Africa. In particular, we underscore the need for additional, high-quality, randomised controlled trials comparing different intensities of anticoagulation in patients with COVID-19 illness. Individuals in the intensive care unit and those hospitalised with another illness who are incidentally found to be infected with SARS-CoV-2 should still only be treated with prophylactic-dose low-molecular-weight heparin.

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Contribution of the study
This Cochrane Corner summarises findings in a recent systematic review on the use of anticoagulation in people hospitalised with COVID-19, and provides insights on the implications of these findings for implementation by clinicians in South Africa. It highlights the need for clinicians to balance the benefits and harms of providing an anticoagulant, while considering the patients underlying risk for bleeding and thromboembolism

We summarise a Cochrane review that evaluated the efficacy and safety of anticoagulation in patients admitted to hospital with COVID-19.[1]

Pulmonary effects of COVID-19 are common in hospitalised patients, possibly related to the high rates of inflammation, immobilisation and diffuse intravascular coagulation, thus predisposing patients to both arterial and venous thrombosis.[2,3] Venous and arterial thromboembolic complications affect around 16% of patients hospitalised with COVID-19 and approximately 31% - 49% of patients with COVID-19 in intensive care units (ICUs), with the majority of patients (90%) being diagnosed with venous thromboembolism.[4-6]

In South Africa, over 4 million people have contracted COVID-19 since the beginning of the pandemic in 2020. Of those, there have been over 100 000 COVID-19-related deaths.[7] In this context, it is important to stay abreast of the latest research evidence regarding anticoagulation for people hospitalised with COVID-19.

Objectives

This review evaluated the efficacy and safety of anticoagulants v. placebo, active comparator, or no intervention in patients admitted to hospital with COVID-19.

Intervention and methods

Parallel or cluster-randomised controlled trials (RCTs), quasi-RCTs and cohort studies were eligible for inclusion. Participants for inclusion were those eligible for anticoagulation while hospitalised with COVID-19. There was no restriction on disease severity. Participants with a history of venous thromboembolism were also included. Direct anticoagulants (both factor Xa inhibitors and direct thrombin inhibitors, e.g. bivalirudin), vitamin K antagonists and heparinoids (unfractionated heparin, low-molecular-weight heparin (LMWH) and pentasaccharides) were the considered pharmacological interventions. Studies that compared different formulations, doses or schedules or the same intervention were included.

Studies that compared an anticoagulant with placebo or no treatment; a different anticoagulant; a different formulation, dose or schedule of the same anticoagulant; other pharmacological interventions (such as antiplatelet agents); or non-pharmacological interventions were included. **Primary outcomes**: all-cause mortality, and necessity for additional respiratory support (defined by review authors as 'oxygen by noninvasive ventilators or high-flow intubation and mechanical ventilation or extracorporeal membrane oxygenation'). **Secondary outcomes**: COVID-19-specific mortality, deep-vein thrombosis, pulmonary embolism, major bleeding, adverse events, hospitalisation time (days) and changes in quality of life.

A comprehensive search for studies (regardless of publication status or language) was conducted in the Cochrane Central Register of Controlled Trials (CENTRAL), Medline, Embase, LILACS Virtual Health Library and IBECS Virtual Health Library to identify eligible studies up to 14 April 2021. Other resources, including ongoing trials, preprints and reference lists were also searched. Data were managed and synthesised in RevMan 5. Risk of bias (RoB) was assessed through the RoB tool for RCTs and the ROBINS-I tool for non-randomised studies (NRS). A data collection form was used for study characteristics and outcome data. The authors planned to use a fixed-

effect model for meta-analysis if included studies were homogeneous, or a random-effects model if substantial heterogeneity or clinical differences were identified.

Results

The search yielded 7 329 records for screening – 257 full-text articles were screened for eligibility. Seven studies comprising four RCTs and three non-randomised studies with 16 185 participants, of whom at least 9 403 received anticoagulants, were included in the quantitative synthesis. The RCTs compared lower v. higher doses of anticoagulant while the NRS compared anticoagulation v. no anticoagulation. In this Cochrane Corner, we discuss the effects of higher- v. lower-dose anticoagulant dosing up to 30 days' follow-up. Results for longer-term follow-up and anticoagulant v. placebo can be accessed in the review.[1]

Higher-dose v. lower-dose anticoagulants (short term)

The present review found that there was little to no difference in all-cause mortality in higher dose compared with lower-dose for up to 30 days (relative risk (RR) 1.03, 95% confidence interval (CI) 0.92 - 1.16, four RCTs, 4 489 participants, high-certainty evidence). Sensitivity analysis did not markedly change the effect estimate. In terms of the use of higher-dose v. lower-dose necessitating additional respiratory support up to 30 days, the evidence was very uncertain (RR 0.52, 95% CI 0.12 - 2.47, three studies, 3 407 participants, very-low-certainty evidence). The sensitivity analysis only including trials at low risk of bias substantially changed the effect estimate (RR 0.16, 95% CI 0.02 - 1.35).

There was little to no difference in the incidence of deep-vein thrombosis in higher- compared with lower-dose anticoagulants up to 30 days (RR 1.08, 95% CI 0.57 - 2.03, I^2 = 0%, four studies, 3 422 participants, low-certainty evidence). Sensitivity analysis did not markedly change the effect estimate. Higher-dose anticoagulants might reduce pulmonary embolism for up to 30 days (RR 0.46, 95% CI 0.31 - 0.70, four studies, 4 360 participants, moderate-certainty evidence). Sensitivity analysis including studies only with low risk of bias changed the effect estimate (RR 0.50, 95% CI 0.23 - 1.10). In terms of major bleeding, higher-dose anticoagulants likely increased the risk slightly compared with low-dose, up to 30 days (RR 1.78, 95% CI 1.13 - 2.80, four studies, 4 400 participants, moderate-certainty evidence). Sensitivity analysis changed the effect estimate (RR 2.13, 95% CI 0.92 - 4.90). Subgroup differences suggested that severity of the condition did not have any effect on major bleeding.

Higher-dose anticoagulants increased minor bleeding, compared with lower-dose (RR 3.28, 95% CI 1.75 - 6.14, three studies, 1 196 participants, high certainty of evidence). Subgroup tests suggested that condition severity did not have a modifying effect on minor bleeding, and sensitivity analysis including only trials at low risk of bias did not markedly change the effect estimate. There may be little to no difference in the incidence of stroke, major adverse limb events, myocardial infarction, atrial fibrillation, thrombocytopenia and length of hospitalisation in higher-dose anticoagulation compared with lower-dose. There were no data available for quality of life and mortality owing to COVID-19 outcomes.

Conclusions

The review authors concluded that using higher-dose anticoagulants compared with lower-dose anticoagulants results in little to no difference in all-cause mortality, and an increase in minor bleeding in people hospitalised with COVID-19 for up to 30 days. Furthermore, there may be a slightly increased risk for major bleeding with higher-dose anticoagulants, and a possible reduction in the incidence of pulmonary embolism, with little to no difference in length of hospitalisation, deep-vein thrombosis, myocardial infarction, atrial fibrillation, thrombocytopenia and major adverse limb events. The evidence around whether higher-dose v. lower-dose anticoagulation changes the need for additional respiratory support during hospitalisation is unclear.

Implications for practice

Acute COVID-19 pneumonia is a hypercoagulable state where the thrombotic risk is influenced by many factors including the host response and severity of illness, the infecting viral variant and any underlying predisposing medical conditions.[8-11] The course of hospitalised patients is complicated by a high incidence of venous thromboembolism, and anticoagulation with unfractionated or LMWH is appropriate. Recommendations for dose intensity, however, are dynamic and have evolved over the course of the pandemic as data have informed practice. At Groote Schuur Hospital, as in many hospitals in the rest of South Africa, the initial strategy of prescribing therapeutic-intensity anticoagulation in all patients in the first wave (particularly those requiring ICU-level of care such as high-flow nasal cannula oxygen therapy (HFNO) or mechanical ventilation) changed as new evidence (some synthesised in this Cochrane review) became available, suggesting that prophylactic-intensity anticoagulation was more appropriate, particularly in patients on higher levels of respiratory support where therapeutic-intensity anticoagulation did not confer outcome benefit and bleeding complications were higher. The National Essential Medicines List (NEML) Ministerial Advisory Committee (MAC) on COVID-19 Therapeutics reviewed the evidence of benefits, harms, costs and feasibility and recommend the use of prophylactic rather than therapeutic doses, unless specifically indicated for the management of thrombosis.[12]

However, nuances remain. Meta-analyses such as this Cochrane review have not been able to convincingly differentiate whether subgroups of patients may benefit from therapeutic-intensity anticoagulation, and the need to prescribe anticoagulation in hospitalised patients with COVID-19 pneumonia still requires an individualised thrombotic and bleeding risk assessment. Guideline recommendations on this issue have shifted dynamically over the course of the pandemic, and are not consistent: the National Institutes of Health (NIH) advises therapeutic-dose LMWH in selected medical inpatients who are not critically ill and who have an elevated D-dimer (and in whom the bleeding risk is deemed low),[13] whereas updated guidelines from the American Society of Hematology suggest prophylactic-intensity anticoagulation only.[14] The strategy of risk stratification by level of breakdown products of fibrinolysis (D-dimer) may be useful to identify the subgroup of patients with thrombo-inflammation who are at higher risk. However, these recommendations are based on very-low-certainty evidence, underscoring the need for additional, high-quality, randomised controlled trials comparing different intensities of anticoagulation in patients with COVID-19 illness. Individuals in the ICU and those hospitalised with another illness who are incidentally found to be infected with SARS-CoV-2 should still only be treated with prophylactic-dose LMWH.

Declaration. None.

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Conflict of interest. TK was a member of the National Essential Medicines List COVID-19 Ministerial Advisory Committee.

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