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COVID-19 and venous thromboembolism – prophylaxis and treatment

KLINISK OVERSIKT

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As the pandemic has been unfolding, reports have emerged of a relatively high incidence of coagulopathy and thromboembolic events in connection with COVID-19 infections. Raised awareness surrounding this issue, and appropriate antithrombotic prophylaxis and treatment, are therefore important for this group of patients.

The COVID-19 pandemic has dominated the medical debate in recent months, and has impacted all aspects of society (1). SARS-CoV-2 is a virus of the Corona group which primarily attacks the respiratory epithelium and can result in acute respiratory distress syndrome. In extreme cases, the outcome may be fatal (2). Recent reports have also shown that thromboembolic events are frequent in COVID-19 patients and contribute to increased mortality and morbidity (3). This has also been registered in Norway (4). Arterial thromboembolism is serious, but is much rarer among COVID-19 patients than venous thromboembolism (5). This article provides a brief overview of the association between COVID-19 and venous thromboembolic disease. Given our brief experience of COVID-19, few large-scale clinical studies have been conducted. This article is therefore based on non-systematic literature reviews, recently published recommendations and guidelines, initial experience and discussions among the medical professionals who are treating this group of patients. Based on available knowledge at this stage of the pandemic, we can now provide general prophylaxis and treatment recommendations, with a focus on venous thromboembolic events.

Pathophysiology

We have known for a long time that there is an association between the activation of an inflammatory response and the activation of the coagulation system. This is often referred to as thrombo-inflammation or immunothrombosis (6, 7), and patients with an infectious disease will therefore have an elevated risk of thromboembolic events (7). Increased production of proinflammatory multi-effect cytokines is probably an important link (6, 7). The inflammatory effects of cytokines also cause activation of and damage to endothelial cells, which further strengthens procoagulatory mechanisms (6, 8). The extensive inflammation seen in patients with COVID-19 infection is reflected in high levels of inflammatory markers such as CRP, fibrinogen and various cytokines – interleukin 6 appears to be particularly important (9). SARS-CoV-2 does not itself appear to have direct procoagulatory effects, but more recent data suggest that the virus does not only attack the respiratory epithelium, but can also attack the endothelium, especially in the lungs (10). The reason is probably that SARS-CoV-2 uses a receptor for angiotensin-converting enzyme 2 (ACE2) as a gateway to the cells (11). This receptor is found on the epithelium of the respiratory tract and the gastrointestinal tract, as well as in the endothelium. This is additional to the factors that increase the risk of severe COVID-19 disease as well as venous thromboembolism in at-risk patients, the most important of which appear to be age, obesity and kidney disease (12, 13). Finally, there are factors such as immobilisation due to disease or hospitalisation and central venous catheters, which in themselves increase the thromboembolic tendency.

Incidence, diagnostics and risk stratification

It is difficult based on existing data to estimate reliable incidence figures for venous thromboembolism in cases of COVID-19 infection. However, the risk of events appears to increase with the severity of the disease and with other coexisting predisposing factors (14–18). Furthermore, it also seems to be clear that the incidence of thrombotic events is higher for COVID-19 infections than for other viral infectious diseases (5, 18). Epidemiological data are largely available only from hospitalised patients, and we have no indication of the real incidence of venous thromboembolism among all COVID-19 patients, including ambulant patients and elderly care home residents. A cohort study from a large Dutch hospital showed that the cumulative incidence rates of venous thromboembolism after 7, 14 and 21 days of hospitalisation were 16 %, 33 % and 41 % respectively (16). It is also worth noting that thromboembolic complications have been reported in patients who are already receiving prophylactic anticoagulation (5, 14, 18). Studies have also indicated that biochemical markers can be used as diagnostic and prognostic markers – especially elevated D-dimer levels (19, 20). If there are biochemical signs of coagulopathy, greater clinical attention should be given to a potential coexisting thromboembolism. Several studies have also shown a clear association between developing coagulopathy and mortality risk (19, 21). Some COVID-19 patients develop disseminated intravascular coagulation (DIC) a few days into the disease, and these patients clearly have a poorer prognosis (22, 23). We must stress that the increased mortality may well be due to a more generalised inflammation (including the development of a cytokine storm) rather than the effect of coagulation (9, 24). It is also worth noting that COVID-19 patients generally appear to have a low risk of haemorrhaging (3).

Pulmonary embolism can be difficult to diagnose. Pulmonary emboli are easily missed, since severe COVID-19 disease in itself results in hypoxaemia and respiratory failure (17). The thrombotic tendency and thromboembolic events may occur at a relatively late stage of the disease (4).

The diagnostic procedures do not in principle differ from any other diagnosis of pulmonary embolism, for which a CT scan under pulmonary embolism protocol is the standard. However, this may be harder to achieve with COVID-19 patients, as it may be difficult to move those who are most severely affected, and the heightened risk of transmission will add to the complications. In some cases, treatment should therefore be initiated on the basis of a strong suspicion, such as changed haemodynamics and oxygenation, and echocardiography signs that the right side of the heart is under acute stress. Several studies have tested the use of coagulation parameters as potential prognostic and diagnostic markers. Given that D-dimer values are often elevated due to general inflammation, it is difficult to use this test specifically to diagnose pulmonary embolism, but it has been pointed out that a clear increase of values should generally give cause to suspect coexisting thromboembolism in patients with COVID-19 (3, 20).

Prophylaxis and treatment

Given our short experience of COVID-19, general recommendations have been based on initial reports and knowledge acquired to date (3, 21, 23). International guidelines have now appeared which provide a more systematic summary of recommended prophylaxis and treatment of thromboembolic complications in cases of COVID-19 (25). On this basis, Table 1 outlines our proposals for how to manage such patients. Thromboprophylaxis is not normally recommended for ambulant patients who receive treatment for relatively mild symptoms of COVID-19. Ambulant patients who are at a higher risk of thromboembolic events, for instance due to a history of thrombosis, obesity (BMI > 30) and active cancer disease, can be considered for prophylaxis with low-molecular-weight heparin on an individual basis. All hospitalised patients with COVID-19 should be assessed for standard prophylaxis with low-molecular-weight heparin if there are no contraindications, such as a known tendency to haemorrhage or a clear thrombocytopenia (thrombocytes $< 25 \cdot 10^9$/l).

Table 1

The authors' proposals for prophylaxis and anticoagulation in cases of COVID-19 disease, updated in May 2020. The recommendations are generally based on international, national and local anticoagulation guidelines and discussions among Norwegian medical experts (3, 4, 21, 23, 25).

Status	Proposed anticoagulation treatment
Prophylaxis for ambulant patients	Not generally indicated, but a prophylactic dose of low-molecular-weight heparin may be considered for patients with a history of venous thrombosis, active cancer disease or obesity (BMI > 30 kg/m^2).
Prophylaxis for hospitalised patients	Standard prophylactic dose of low-molecular-weight heparin for all patients unless there is a significantly elevated risk of haemorrhage.
Prophylaxis for hospitalised patients in intensive care	Increased prophylactic dose of low-molecular-weight heparin (50 % of therapeutic dose or double the prophylactic dose).
Continuation for patients already on anticoagulant drugs (atrial fibrillation, history of venous thrombosis, mechanical heart valve)	Continue the patient's current anticoagulation medication; consider changing to therapeutic dose of low-molecular-weight heparin.
Treatment in cases of suspected venous thromboembolism	Therapeutic dose of low-molecular-weight heparin until diagnosis is verified.
Treatment in cases of verified venous thromboembolism	Therapeutic dose of low-molecular-weight heparin, consider changing to peroral treatment on discharge. Treatment to continue for at least three months.

The data are less unequivocal when it comes to increasing the prophylactic dose. International reports have shown a high incidence of venous thrombosis even if standard prophylaxis is administered (14, 18). This suggests that the thromboprophylaxis should be increased for patients with severe COVID-19 disease, particularly patients who are treated in an intensive care unit, including those on a ventilator (3, 18, 23). It is difficult to estimate the correct dose, but one common approach is to administer 50 % of the therapeutic dose or double the standard thromboprophylactic dose (3, 4, 21, 23, 25). Whichever of the two approaches is adopted, the resultant dose tends to be roughly the same. Verified coagulopathy, defined as elevated D-dimer values, is a factor which further indicates increased prophylaxis (20). When pulmonary embolism or deep vein thrombosis is determined, a therapeutic dose of low-molecular-weight heparin should be administered. The total treatment period should be at least three months from the time of discharge when the patient has full mobilisation, unless other factors suggest a longer treatment period. Changing to peroral treatment should be considered on discharge. For patients who are already on anticoagulants when COVID-19 infection is determined, the treatment should continue. We should be alert to any potential interaction between anticoagulation and experimental treatments for COVID-19 infection, if this is relevant (23). Changing to parenteral treatment should be considered if peroral treatment is impossible, or in order to ensure stable anticoagulation in cases of gastrointestinal symptoms, which can be relatively common in cases of COVID-19 infection. When changing from peroral to parenteral treatment, therapeutic doses of low-molecular-weight heparin should be considered.

Conclusion

COVID-19 disease appears to be associated with a particularly high risk of venous thromboembolic complications, especially in severe cases. There are still no unequivocal data for what constitutes appropriate prophylaxis and treatment, and for the time being recommendations are largely based on short patient series and initial experiences. Nevertheless, it appears to be clear that liberal use of thromboprophylaxis is

recommendable, and it is probable that the same applies for increased prophylaxis in certain patients. Norwegian doctors who treat this patient group should be aware of these issues.

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