Editorial

Risk stratification for SARS-CoV-2-related venous thromboembolic events: time for a new paradigm?

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SARS CoV-2 viral infection leading to COVID-19 has been identified as causing substantial peri-operative complications due to pulmonary and coagulation pathologies. Early studies suggested a postoperative mortality rate of 15–24% [1–3], much higher than the global case fatality rate of 2.2% due to COVID-19 seen more generally [4, 5]. The risk factors and cause of death associated with this excess mortality have, until recently, not been clear; the recent study by the COVIDSurg and GlobalSurg collaboratives found an association between 30-day mortality with pulmonary complications and venous thromboembolism (VTE) [6].

The COVIDSurg and GlobalSurg collaboratives conducted a prospective observational study in October 2020 of patients > 18 y undergoing emergency or elective surgery. The degree of coordination and number of patients enrolled is impressive. In total, 128,013 patients in 1630 hospitals from 115 countries were enrolled. They observed a 50–90% increased risk of VTE in patients with a peri-operative (7 days before to 30 days after surgery) or recent (1–6 weeks before surgery) SARS-CoV-2 infection after multivariable analysis. Concerningly, those patients who did develop VTE had a five-fold greater risk of mortality.

Effect of venous thromboembolism

Venous thromboembolism is a leading cause of preventable death in hospitals in high-income countries [7]. The use of decision-making prompts within electronic health records is now common in many countries and have helped standardise protocols for VTE prophylaxis. [8]. Nevertheless, the observed increased VTE risk in surgical patients with recent SARS-CoV-2 infection heralds a new set of complexities relating to timing and risk stratification of surgery. Of note, the observed increased risk from SARS-CoV-2 infection relates primarily to patients undergoing elective surgery where some planning of the timing of surgery is possible.

The authors speculate that the greater effect of SARS-CoV-2 infection in increasing risk in elective rather than emergency surgery patients is possibly because emergency surgery is already much higher risk for VTE. Using data from the National Surgical Quality Improvement Program database from the years 2005 to 2016 of over 600,000 patients, Ross et al. [9] found the risk of VTE following emergency surgery was double that of patients undergoing elective surgery (1.9% vs. 0.8%, OR = 2.4). If there is a 'ceiling effect' of VTE risk in patients undergoing emergency surgery, we might expect a smaller increased risk of VTE in patients with SARS-CoV-2 infection undergoing emergency vs. elective surgery. Data presented in this article confirm this [6]. In patients undergoing emergency surgery, those with peri-operative SARS-CoV-2 infection have only a slight increase in VTE risk compared with those without (OR = 1.26). However, on univariate analysis, patients undergoing elective surgery with peri-operative, recent or

previous SARS-CoV-2 infection show a significantly higher rate of VTE compared with patients without such history (OR = 2.10, 2.93, and 1.51, respectively).

Prophylaxis

Although the authors state this was a planned sub-study and analysis from data collected in October 2020, no observational study of VTE is complete without the significant confounder of whether VTE prophylaxis was employed. Although VTE prophylactic regimes may vary, simply including a binary 'yes/no' variable for its use would have increased the study's strength considerably. Given the known higher risks of emergency surgery and greater likelihood of uncontrolled comorbid conditions, it is likely that these patients were given a more aggressive regime of anticoagulation than the elective surgery patients based on existing protocols and electronic health record decision-making tools. It is, therefore, unclear to what extent we can draw conclusions about the true differential increase in the risk of elective vs. emergency surgery. The authors appropriately state this limitation in their Summary and Discussion.

Increased coagulation risk with SARS-CoV-2 infection is thought to be due to an inflammatory cytokine response, predominantly an over-expression of tissue factor stimulated by the pathogen. In contrast, emergency surgery is likely associated with a multitude of different mechanisms that may be unrelated to tissue factor expression [9]. Tissue factor expression is invariably a significant contributor to procoagulant risk particularly in traumatic injuries or where there is extensive damage to the vascular endothelium. The authors may be correct in assuming this mechanism has a 'ceiling effect' but it is not possible to tell without understanding the prophylactic regimes employed.

Markers of the extent of the inflammatory reaction caused by COVID-19 are known to be associated with increased mortality. A meta-analysis of studies in ICUs in 2020 correlated rises in D-dimer, neutrophil count and ferritin levels and a reduction in platelet and lymphocyte counts with the risk of death [10]. While the specifics of the cause of death were not analysed, it is likely that these were also associated with VTE as organ damage from fatal SARS-CoV-2 infection observed post-mortem almost invariably includes evidence of pulmonary thrombosis. In a random sample of 10 post-mortem exams performed on patients who died from COVID-19, all had evidence of pulmonary thrombosis despite no clinical signs of VTE and all having had VTE prophylaxis [11]. Furthermore, another post-mortem study found evidence of deep venous thrombosis in over half of the patients that were not evident clinically, with a third having pulmonary embolism as the direct cause of death [12]. The presence of apparently universal small to medium pulmonary vessel thrombosis in fatal COVID-19 infections has been suggested to be due to endothelial damage due to the diffuse alveolar damage [13]. Additionally, most patients also exhibit haemorrhage and infarction of the lung parenchyma. In short, the lung disease caused by SARS-CoV-2 infection is of both the alveoli and the pulmonary vasculature. The thrombotic disease occurs peripherally as thromboembolic insult, in addition to direct injury to the pulmonary vasculature [11]. While the COVIDSurg data observed clinically apparent VTE, the frequent subclinical peripheral venous thromboses and ubiquitous pulmonary vascular effects were not measured. It is not known to what degree these may be prevented and mitigated by prophylaxis.

Risk management

The COVIDSurg/GlobalSurg collaboration study raises valid questions about how we must now manage this increased VTE risk. Apart from following existing recommendations to delay surgery for 7 weeks post-infection (i.e. beyond the high-risk period) wherever possible [14], the need to modify our existing VTE prophylaxis protocols for this at-increased-risk population must also be examined. Changes will not be without risk; as with any anticoagulation regime, there is a balance between prevention of thrombotic complications and the potential for bleeding. Any changes to the current VTE prophylaxis guidelines will need to consider the risks of each of these events including the nature of the surgery and risks posed by additional procedures such a neuraxial blocks.

Many health services have introduced routine pre-operative testing to risk stratify those with SARS-CoV-2 infections and to prevent spread within the hospital. Even this approach might not be enough if a postoperative SARS-CoV-2 infection within 30 days can also cause such devastating complications. If the virus is at high levels within the community, should we be taking a precautionary approach to increased VTE risk in any case and treat all post-surgical patients with more aggressive prophylaxis? Another option may be to use a daily viral testing schedule with rapid tests and titrate the VTE prophylaxis to the potential risk. Although not without a financial and human resources burden, such an aggressive approach to infection detection may strike a balance between VTE prevention and bleeding risk by tailoring prophylaxis to individual patient risk.

This rigorous approach to assessment, risk stratification and escalation of thromboprophylaxis has already been

successfully implemented in the ICU. In a cohort study of 188 patients, Atallah et al. demonstrated a reduction of VTE events using a high-intensity, tailored approach to prophylaxis based on D-dimer levels and imaging studies [15]. This approach to longitudinal, daily observation of D-dimer levels triggering imaging and escalation of anticoagulant doses as required is unlikely to be successful outside the ICU due to the resources and acceptability of testing for those patients having relatively minor procedures. Nevertheless, an approach to tailoring therapy to risk is likely to be successful [16]. Guidance might be found in other settings such as for cancer surgery where a risk stratification score has been successfully applied in reducing the incidence of VTE in this cohort without increasing the risk of bleeding [17]. We believe that tailoring of VTE prophylaxis to the risk profile of the surgery and the patient should now be routine. Low-risk interventions such as thromboembolic deterrent stockings and sequential calf compression devices should be used for all but the most minor of procedures while there is community spread of SARS-CoV-2. There must also be a low threshold for commencing prophylaxis with pharmacological drugs and escalation to more aggressive prophylaxis if there is a suspicion of SARS-CoV-2 infection, or if screening questionnaires and testing for viral fragments or inflammatory markers suggest disease is present.

Limitations

The current study did not include those aged <18 y. This disqualified 13,650 patients from the original database of 141,809 patients. The authors include good justification for this decision; it is not currently clear if this increased risk of VTE extends to paediatric patients as children have a much lower baseline risk and incidence of peri-operative VTE. Using data from the National Surgical Quality Improvement Program database from the years 2012 to 2015 of 267,299 patients aged <18 y, Ahn et al. [18] found overall peri-operative VTE incidence to be 0.12%, with ambulatory surgery being associated with an even lower incidence (0.012%). Risk factors included neonatal and adolescent patients, and those with pre-existing coagulation, malignancy, diabetes or ambulatory challenges. While children have a low risk of VTE, it is not yet known if SARS-CoV-2 infection increases it to the level where prophylaxis might be needed for major surgery.

Data in this study were collected in October 2020, before widespread vaccine availability. Currently, 65% of the UK population is fully vaccinated, with an additional 7% being partially vaccinated [19] (data updated 13 September 2021). Of note, SARS-CoV-2 vaccination is rarely associated with prothrombotic events via a very different mechanism to that induced by the viral infection itself [20]. Vaccine-induced thrombotic thrombocytopenia is not relevant to the peri-operative period or the need for additional prophylaxis. Nevertheless, the widespread uptake of immunisation since the COVIDSurg/GlobalSurg study would make a repeat of the study extremely difficult and add yet another complicating factor to an already impossible Gordian knot. The risk of peri-operative VTE caused by breakthrough infections of immunised patients is also unknown. Presumably, breakthrough infections produce a lesser inflammatory response and therefore lower-risk of thrombotic tendency. It would be very useful to repeat this study protocol given the fundamental change in the immunisation status of both general and peri-operative populations in many countries.

In addition to questions arising from potential VTE risk profile changes due to vaccination, further research needs to identify which markers, in addition to viral testing, will be useful in predicting morbidity and mortality from VTE and pulmonary vascular thrombosis. Implementing these tailored approaches will likely be challenging. A process of shared decision-making will be needed between the surgeon, anaesthesia provider and patient, similar to negotiation of timing of surgery as outlined in the consensus guidelines [21]. Introduction of these tailored approaches would also need to be assessed to ensure they are successful in reducing the risk of VTE while not increasing the risk of postoperative bleeding.

It is known that other viral illnesses cause a similar prothrombotic effect but it is not obvious to what degree this is problematic. SARS-CoV-2 may be typical or atypical in elevating the risks of VTE. In the future, there may be targeted therapies for the prevention of VTE related to tissue factor over-expression. These medications would hopefully minimise the risk of VTE without overly increasing the risk of haemorrhage. Until then, a risk stratification approach and tailoring of prophylactic measures depending on evidence or risk of SARS-CoV-2 infection has the potential to avoid preventable postoperative deaths.

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