Efficacy and Safety of Prophylactic

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Efficacy and Safety of Prophylactic-Dose Anticoagulation Therapy with Intermediate-Therapeutic Doses in Covid-19 Patients

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Abstract

Introduction: Coronavirus Disease-19 (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARSCoV-2) was declared a worldwide pandemic on March 11, 2020 and globally, on April 29, 2022, there were 510,270,667 confirmed COVID-19 cases, including 6,233,526 deaths, reported to WHO. As of April 2022, the Government of the Republic of Indonesia has reported 4,249,323 confirmed cases of COVID-19. There have been 143,592 COVID-19-related deaths reported and 4,096,194 patients have recovered from the disease. COVID-19 is associated with a high risk of venous thromboembolism (VTE), however, to date, optimal prophylactic anticoagulant therapy remains uncertain and may depend on the severity of COVID-19.

Objective: The aim of this study was to determine the difference in efficacy and safety in administering prophylactic doses with intermediate/therapeutic doses in confirmed COVID-19 patients.

Results: This study used 6 studies that met the inclusion of differences in efficacy and safety in administering prophylactic doses with intermediate/therapeutic doses in confirmed COVID-19 patients.

Conclusion: From 6 studies, there were 2 studies comparing anticoagulant prophylactic doses with intermediate doses and 4 studies comparing anticoagualnt prophylactic doses with therapeutic doses. In all studies, there were no significant differences in thromboembolic events or all-cause mortality in COVID-19 patients. The incidence of bleeding at the intermediate and therapeutic doses increased compared to the prophylactic dose, but the difference was not significant.

Keywords: COVID-19, thromboprophylaxis, anticoagulants, thrombosis, bleeding

Introduction

SARS-CoV-2 not only causes viral pneumonia, but also affects the cardiovascular system. Many cardiovascular complications from COVID-19, one of which is venous thromboembolism (VTE). The overall frequency of VTE in all patients, ICU and non-ICU, was 12.8% (95% confidence interval [CI]: 11.103-14,605), 24.1% (95% CI: 20,070-28,280),

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and 7.7.% (95%). CI: 5,956–9,700), respectively. PE occurred in 8.5% (95% CI: 6,911-10,208), and proximal DVT occurred in 8.2% (95% CI: 6,675-9,874) of all hospitalized patients. The relative risk for VTE associated with ICU admission was 2.99 (95% CI: 2.301–3.887, p < 0.001).[1]

In a systematic review conducted by Kollias et al. mentioned that the overall prevalence of PE/DVT in hospitalized patients with COVID-19 tested was approximately 30%, while heterogeneity was observed.[2] The prevalence of VTE is high, even in patients receiving thrombosis prophylaxis and appears to be higher in studies with <50% of patients receiving anticoagulants.[2] The risk of death is higher in patients with COVID-19 with VTE compared to patients without VTE.[2]

Anticoagulants in prophylactic doses are routinely used in hospitalized patients with COVID-19 without contraindications according to guidelines, because they are associated with a survivability benefit.[3] The combined incidence of VTE was approximately 50% lower in patients receiving standard-dose pharmacologic thrombosis prophylaxis than in patients not receiving pharmacologic thrombosis prophylaxis. However, the optimum dose of anticoagulant that should be given is still unclear, the question arises whether a higher dose should be given. Aspects of efficacy and safety in terms of bleeding rate are important to be taken into consideration in selecting anticoagulant doses in COVID-19 patients. Compared with standard dose prophylaxis, intermediate and therapeutic doses of anticoagulation were associated with lower VTE rates and higher bleeding rates, although the differences did not reach statistical significance.[4]

From the results of observational studies that have been carried out, the results show that, patients with acute respiratory failure requiring intubation due to SARS-CoV-2 infection did not show a difference in all-cause mortality up to 28 days when empirically treated with therapeutic doses of anticoagulants compared with prophylactic doses. among those with D-dimer levels greater than 2 g/mL.[5]

To determine the optimum dose, further research using randomized controlled trials was conducted. Many randomized controlled trials were in progress at the time of the observational studies, and those studies were completed at the time of this review. Therefore, the investigators conducted a systematic review of randomized controlled trials of studies comparing high-intensity (medium or therapeutic doses) versus standard doses (prophylactic doses) with respect to outcomes in hospitalized patients with COVID-19.

Materials and Methods

Search Strategy

A systematic search of PubMed and *Science Direct* databases was performed until October 4th, 2021 using the following search algorithm: COVID-19 AND (*anticoagulant* OR *prophylaxis* OR *thromboprophylaxis*) AND (*thrombosis* OR *coagulopathy* OR *thrombus* OR "*venous thromboembolism*") until October 4th 2021.

Study Selection

The study selection was performed independently by two investigators (D.R.K and A.S.). Eligible studies were randomized controlled trial study with a population of adults (aged 18 years) hospitalized with SARS-CoV-2 infection, confirmed by standardized tests or clinical criteria, in English language including ≥10 patients. Studies must be reporting pharmacological thromboprophylaxis strategies and thrombotic and/or bleeding events at each dose level. Secondary research (comments, letters, and reviews) and/or observational research and case report were excluded.

Data Extraction

Two investigators (D.R.K. and A.S.) extracted and tabulated, independently, data concerning study design, main characteristics of included populations, and that regarding the primary (thrombotic events, all-cause mortality, and bleeding) and secondary outcomes.

Risk of Bias Assesment

The risk of bias was assessed in terms of selection of patients, exposure measurement, confounding factors identification, outcome measurement, methodology, and analysis, independently, by two investigators (D.R.K. and A.S). Checklists for

randomized controlled trials from cochrane.[6] RCTs that scores as low at bias at all domains, included as low bias.

Statistical Analysis

In this study, data related to the risk ratio of the dependent variable outcomes were also collected including the value of the 95% confidence level interval and the significance value of p. If the data has not been included in the study under study and there is data that allows the calculation of the risk ratio to be carried out, the MedCalc electronic calculator (MedCalc Software Ltd, Belgium) is used.

Result

From the two databases, 3893 articles were obtained in the initial search with details of PubMed NCBI 1886 articles, and Science Direct as many as 2207 articles. Then from the 3893 articles, after eliminating duplicated articles, 3400 articles were left. Then the Search Back article by reading the title and abstract, obtained as many as 3288 articles whose titles and abstracts did not match so that there were 112 articles left. After the articles were based on the inclusion and exclusion criteria, the final results obtained 6 study articles that met the inclusion criteria and could be included in this systematic study[7,8,9,10,11,12] A diagram of the data management process can be seen in Chapter IV on Research Materials and Methods, which uses the Preffered Reporting Items for Systematic Review and MetaAnalysis (PRISMA) method to select the studies in this research. The result of this systematic review is presented in **table 1**.

Table 1. Main characteristics of included studies that compared intermediate or therapeutic versus prophylactic dose of thromboprophylaxis in terms of outcomes in hospitalized COVID-19 patients and their relative risk [95% CI] and p value.

Study	N	I/P Or T/P	Type Of Anticoagulation	Thrombosis Event (RR [95% CI], p value)	Overall Mortality (RR [95% CI], p value)	Bleeding (RR [95% CI], p value)	
						Major Bleeding	Minor Bleeding
Bikdeli	562	276/286	LMWH	9 v 10 (0,93 [0,38 - 2,26] p=0,88)	127 v 123 (1,07 [0,89 - 1,29], p=0,47)	19 v 10 (1,97 [0,93 - 4,16], p= 0,08)	17 v 10 (1,76 [0,82 - 3,78], p=0,15)
Perepu	173	87/86	LMWH	7 v 6 (1,15 [0,40 - 3,29], p=0,79)	13 v 18 (0,71 [0,37 - 1,37], p=0,31)	2 v 2 (0,99 [0,14 - 6,86], p=0,99)	6 v 6 (0,99 [0,33 - 2,95], p=0,98)
Lopes	615	311/304	LMWH/DOAC	23 v 30 (0,75 [0,45 - 1,26], p=0,32)	35 v 23 (1,49 [0,90 - 2,46], p=0,13)	26 v 7 (3,64 [1,61 - 8,27], p=0,001)	36 v 9 (3,92 [1,92 - 8,00], p=<0,0001)
ATTACC Investigators; ACTIV-4a Investigators; REMAP-CAP Investigators	2226	530/559	LMWH	13 v 22 (0,52 [0,27 - 1,03], p=0,063)	86 v 86 (0,89 [0,67 - 1,18], p=0,41)	22 v 9 (2,17 [1,00 - 4,69], p=0,045)	–
REMAP-CAP Investigators; ACTIV-4a Investigators; ATTACC Investigators	1089	1180/1046	LMWH	34 v 58 (0,62 [0,41 - 0,93], p=0,0204)	199 v 200 (1,05 [0,90 - 1,23], p=0,53)	20 v 13 (1,63 [0,82 - 3,25], p=0,16)	–
Lemos	20	10//10	LMWH/UFH	2 v 2 (1,00 [0,17 - 5,77], p=1)	1 v 3 (0,33 [0,04 - 2,69], p=0,3)	–	2 v 0 (5,00 [0,27 - 92,67], p=0,28)

Discussion

The use of prophylactic doses is recommended in the guidelines to be given to all patients without contraindications.[3] However, the use of higher doses, empirically in selected patients is given to patients at high risk of coagulopathy such as in severe COVID-19 patients admitted to the ICU. The use of higher doses (intermediates-therapeutic) is expected in these patients to improve clinical conditions and increase life expectancy. This systematic review was conducted to provide a summary of several randomized controlled trials in comparative studies of prophylactic doses with intermediate-therapeutic doses in confirmed COVID-19 hospitalized patients.

The mechanism of coagulopathy in COVID-19 patients is still unclear. However, several mechanisms can explain which include RAAS dysregulation and immune system dysregulation that can occur in several pathways as described in Chapter 2. The use of LMWH anticoagulants was found to be good for improving coagulation in COVID-19 patients. As in other sepsis the risk of bleeding in COVID-19 patients is low[13], so bleeding can be observed as a side effect of the anticoagulants given.

The therapeutic-intermediate dose was found not to reduce the occurrence of thrombosis in COVID-19 patients, but to increase the risk of bleeding, although both were not significant. However, therapeutic-intermediate doses can improve the patient's clinical condition such as gas exchange.

Conclusion

Intermediate and therapeutic doses of anticoagulants were no more effective in reducing the incidence of thrombosis in COVID-19 patients compared to prophylactic doses. The incidence of bleeding in the administration of intermediate and therapeutic doses of anticoagulant increased compared to the prophylactic dose.

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Conflict of Interest: There is no conflict of interest

Ethical Clearance: Ethical clearance is not required in conducting systematic review

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