Review Article

Interventional Cardiology

Clinical considerations for aspirin use in hospitalized COVID-19 patients

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Abstract

The novel Coronavirus Disease 2019 (COVID-19) pandemic has yielded significant morbidity and mortality worldwide, with thromboembolic complications that can progress to severe multi-organ dysfunction. Aspirin is a promising therapeutic option for reducing COVID-19 related thrombosis and in-hospital mortality. Given the available data, aspirin use in hospitalized COVID-19 patients is associated with decreased in-hospital mortality, especially among the elderly or those with pre-existing coronary artery disease. However, there is necessity for more data regarding the dosage, timing, and duration of therapy. This review assimilates the existing data on the association between aspirin use in hospitalized COVID-19 patients and in-hospital mortality. Overall, most recent observational studies, randomized controlled trials, and meta-analyses suggest that aspirin administration confers a protective effect in hospitalized moderate-severe COVID-19 patients. Further data will be necessary to determine the ideal dosage and time frame for administration of this medication in this clinical context.

Keywords: Aspirin; COVID-19; Thromboembolism; Hospitalization

Abbreviations: ASA: Acetylsalicylic Acid Aspirin; CI: Confidence Interval; COVID-19: Coronavirus disease 2019; COX: Cyclooxygenase Enzyme; HR: Hazard Ratio; OR: Odds Ratio; RR: Risk Ratio; RCT: Randomized Controlled Trial

Introduction

Since its discovery in November 2019, the Coronavirus disease 2019 (COVID-19) pandemic and its associated morbidity and mortality have led to a worldwide unprecedented healthcare emergency. During the height of the pandemic, in-hospital mortality associated with COVID-19 patients reached as high as 11.1% [1]. While mild respiratory disease occurs in most COVID-19 patients, those requiring hospitalization suffer from moderate-severe disease with adverse impact on different organ systems [1]. Thromboembolic events in COVID-19 are particularly devastating. Clinical questions remain regarding therapeutic options to prevent this outcome. Aspirin has been suggested as a potential agent in decreasing thromboembolic events related to moderate-severe COVID-19.

Pathophysiology of COVID-19 thromboembolism and pharmacology of aspirin

On top of its hallmark pulmonary effects, a key increase in thromboembolic events in hospitalized COVID-19 patients has been well documented in literature, thought to be a manifestation of transient hyper coagulability secondary to an exaggerated and severe inflammatory response [2]. A commonly proposed etiology for this COVID-19 related hypercoagulability is dysregulated complement system activation combined

with systemic platelet recruitment and sequestration [3]. Indeed, the development of thromboembolic phenomena often serves as a marker for severe COVID-19 infection and is associated with progression to multi-organ failure and increased patient mortality [4].

Acetylsalicylic Acid Aspirin (ASA), is well known for its use in patients with coronary artery disease for prevention of myocardial infarction or ischemic stroke. ASA is a potent Cyclooxygenase enzyme (COX) inhibitor that may lower thromboembolic events due to its robust platelet inhibition as well as its systemic anti-inflammatory and anti-thrombogenic effects [5]. In low doses, ASA exhibits anti-thrombotic properties by irreversibly binding COX-1, leading to a downstream reduction in thromboxane A2 and reduction of platelet activation and aggregation. In intermediate and high doses, ASA exhibits anti-inflammatory effects *via* inhibition of COX-2 and its downstream prostaglandin production. There is evidence that ASA may affect even more cellular signaling pathways leading to its strength as an anti-inflammatory medication [5]. As a medication, ASA is widely available, relatively cheap, and effectively inhibits platelet function and prostaglandin synthesis.

Given the pathophysiology of COVID-19 thromboembolic disease and the pharmacology of ASA, ASA is often hypothesized to be an ideal therapeutic agent, hence its recent popularity as a research topic. However, expert opinion still offers conflicting data and recommendations regarding routine ASA use in COVID-19 hospitalized patients [6]. The role of ASA in COVID-19 patients and associated clinical considerations are to be reviewed.

Clinical Considerations for Aspirin Usage

Evidence for reduction in thromboembolic events

The use of ASA and other antiplatelet medications has been documented to decrease thromboembolic events in hospitalized patients [7]. In the moderate to severe COVID-19 hospitalized patient population, where there exists evidence of a 2.4-fold increase in rate of thrombotic events and a 5.5-fold increase in pulmonary embolism, antiplatelet therapy appears a promising option [8]. The CATAMARAN (COVID-19 Analysis to Assess the Mortality Impact of Antiplatelet Regimens at North American Centers) study, an observational cohort with 17,000 hospitalized moderate to severe COVID-19 patients, found the rate of pulmonary embolism to be 27% lower in patients receiving antiplatelet agents such as ASA or clopidogrel (2.2% vs 3.0%) [9]. A larger study by Chow and colleagues, CRUSH-COVID (Collaborative Registry to Understand the Sequelae of Harm in COVID-19), examined 112,000 moderate COVID-19 patients receiving ASA or no anti-platelet medication. CRUSH-COVID reported a 29% reduction in pulmonary embolism in the ASA group compared to non-ASA patients (1.0% vs 1.4%; OR, 0.71; CI (0.56-0.90); P=0.004) [10]. These studies suggest ASA therapy confers a protective effect against pulmonary embolism in hospitalized COVID-19 patients.

Despite a decrease in pulmonary emboli, the CRUSH-COVID study and following studies showed no reduction in the incidence of cerebrovascular accident or deep vein thrombosis between ASA and control groups [9,10]. It remains unclear why there exists a substantial difference between the reduction of pulmonary embolism and the lack of other thromboembolic events for patients receiving ASA therapy. However, the clinical implication of ASA therapy decreasing pulmonary embolism remains supported and related directly to in-hospital mortality reduction [11].

Evidence for in-hospital mortality reduction

ASA use is associated with a reduction of in-hospital mortality. This reduction of in-hospital mortality indicates an effective clinical outcome secondary to decreasing thromboembolic events and supports aspirin usage in hospitalized COVID-19 patients. As a primary example, the CRUSH-COVID study by Chow et al. reported a statistically significant reduction in risk (OR, 0.71; CI (0.56-0.90); P=0.004) in a cohort of 112,000 patients [10]. This association is supported by the meta-analysis by Baral et al. of 136,000 hospitalized COVID-19 patients, pooling data from ten observational studies and one randomized controlled trial and demonstrating a 16% reduction in in-hospital mortality in the aspirin use groups versus the non-aspirin use groups though with significant heterogeneity [12].

While the RECOVERY Randomized Controlled Trial (RCT) did not find a reduction in mortality with ASA use, there existed a modest (4%) increase in alive discharge rate for its 15,000 patient cohort [13]. This RCT examined several therapies simultaneously; approximately 90% of patients enrolled in the RECOVERY RCT were receiving concomitant corticosteroids and low molecular weight heparin throughout the study. This may limit the applicability of data regarding ASA, as the major effects of ASA may be minimized for patients receiving other anti-inflammatory and anti-coagulant medications. In contrast, the retrospective study of 3000 patients performed by Meizlish and colleagues assessed both heparin and aspirin use as separate variables, finding a significant decrease in both the incidence of in-hospital mortality for individuals receiving in-hospital aspirin (HR 0.522; (CI 0.336–0.812); P=0.004) and Heparin (HR 0.518 (CI 0.308-0.872), P=0.13) [14]. This suggests that both therapies may have beneficial effect, but it may be difficult to determine which medication is the most beneficial when administered at the same time [13-16].

Timing of initiation and duration of therapy

Studies suggest that initiation prior to hospitalization or by first day of hospitalization confers a protective effect for in-hospital mortality [17]. It follows that the potential benefit of antithrombotic agents such as ASA is diminished if thrombi have developed prior to ASA initiation [13]. Srinivasin et al. reason that the RECOVERY RCT may have found no association between ASA use and mortality due to the data limitation to patients receiving ASA therapy only after hospitalization, thus likely including some patients potentially outside of the ideal therapeutic window [18]. Alternatively, the CRUSH-COVID study found a decrease in in-hospital mortality when initiating aspirin at least within the first 24 hours of admission, including patients with pre-hospital and in-hospital exposure [10]. Of note, the authors of the CRUSH-COVID study suggest that patients receiving ASA prior to hospitalization may have higher incidence of chronic disease, thus impacting their mortality [10]. Regardless, from this study, there exists a significant reduction of in-hospital mortality from ASA use, especially when initiated within the first 24 hours of admission.

Duration of ASA therapy has yet to be specifically compared and determined. Treatment duration of aspirin within hospitalized patients varied amongst multiple randomized control trials. From Liu and colleagues, antiplatelet therapy has been shown to significantly lower 30- and 60-day mortality in as little as five days of treatment with low-dose aspirin in a Propensity-score matched case-control analysis (log-rank Chi-Squared=5.45, P=0.021; log-rank Chi-Squared=4.78, P=0.031, respectively) [19]. Still, there is insufficient evidence from other studies to corroborate duration for ASA therapy. More studies will be required to determine the ideal period of treatment initiation and duration.

Aspirin dosage

No studies have yet determined the optimal dosage of ASA in COVID-19 patients. From the previously mentioned studies, ASA dosages vary widely and contribute to heterogeneity of data. Even more confounding, some studies do not report the dosage for their ASA participants or instead give qualitative metrics such as "low" or "intermediate" dose. Ma and colleagues, in analyzing the RECOVERY RCT, the CRUSH-COVID study, and 16 other robust studies, suggest that low dose ASA (defined as 75-100 mg/day) may be associated with relative anti-platelet effects whereas higher doses (defined as 150 mg/day or more) are associated with more anti-inflammatory effects [20,21]. This meta-analysis finds a statistically significant association with low doses of ASA and decreased in-hospital mortality (RR 0.64; CI (0.48–0.85); P<0.01), but does not find the same correlation at intermediate (RR 0.96; CI (0.89–1.04); P=0.3), or unknown doses (RR 0.87; CI (0.65–1.16); P=0.34) [20]. Interestingly, RECOVERY RCT does indeed describe intermediate (150 mg/daily) doses of ASA, offering another explanation for the absent correlation of ASA and decreased in-hospital mortality for its cohort [13]. These findings insinuate a protective effect of low dose ASA greater than that of higher doses of ASA. Ultimately, more randomized controlled trials will be necessary to ascertain the ideal dosage of ASA for COVID-19 mortality reduction.

Comorbidities for special populations

Low dose ASA is used worldwide for its effective prevention of myocardial infarction and ischemic cerebrovascular accident. Of those patients prescribed ASA for daily use, there tend to be more severe comorbidities such as hypertension, diabetes, and congestive heart failure. An early study from Yuan and colleagues in March 2020 recommended continuation of low dose aspirin in the inpatient setting for COVID-19 patients receiving aspirin for pre-existing coronary artery disease [22]. While Yuan and researchers studied 200 patients and could find no all-cause mortality reduction between ASA and non-ASA groups, there was similarly no evidence to recommend cessation of ASA during hospitalization. In contrast, Chow et al. performed subgroup analysis on 116,000 COVID-19 patients with pre-existing comorbidities, finding the association between ASA use and decreased mortality to be stronger in those with 1 or more comorbidities compared with baseline [16]. Additionally, Aghajani et al. performed an initial bivariate analysis that suggested a higher rate of in-hospital mortality of the ASA group versus non-ASA group, however after adjusting data for pre-existing comorbidities and condition at time of admission, ASA use was found to be protective [15].

It is important to mention that patient age has been mentioned primarily as a confounding variable for many prior studies, however, age as an independent risk factor for COVID-19 mortality has been described thoroughly [3]. Age was also included as a subgroup for analysis by Chow et al. these researchers found that the benefits of ASA were most significant for those older than 60 years old (F=10.8, P=0.001) [16]. Indeed, the absolute risk reduction conferred by ASA is likely greater among older adults, as COVID-19 has been shown to have higher rates of mortality with increasing age. While more studies will be required for full examination of these benefits, these findings suggest that ASA should be used for COVID-19 patients with significant comorbidities and age greater than 60 years.

Risk of hemorrhagic complication

The risk of hemorrhagic complications, defined as GI bleeding or hemorrhagic stroke, of ASA therapy is well documented in literature; for hospitalized COVID-19 patients, however, this risk is incompletely understood [23]. While the RECOVERY RCT found a significant increase in hemorrhagic events (1.6% vs 1.0%, absolute increase 0.6%) for ASA recipients, this correlation

remains limited to studies using higher doses (150 mg or above) of ASA [12,18,21]. Studies using lower doses (<100 mg/day) of ASA such as studies by Santoro et al., the CRUSH-COVID study, and other studies by Chow et al. found no difference in major bleeding events between ASA recipients and non-recipients [10,16,17]. Whereas minimal risk of bleeding complications exists with low doses of ASA, this risk may be exaggerated for high dose ASA use [23]. The risk-benefit ratio of in-hospital mortality reduction vs hemorrhagic complication risk of ASA usage should is weighed for individual patients prior to its administration shown in the Table 1.

Table 1: Characteristics and designs of selected studies.

First author	Year	Location	Study method	Patients enrolled	Primary outcome	Aspirin dose	Aspiration initiation	Duration of therapy	Hemorrhagic risk
Recovery collaborative group [12]	2021	Nepal, United Kingdom, and Indonesia	Randomized control trail	14,892	All-cause mortality	150 mg daily	Admission	Discharge	1.6% vs. 1.0% increase; Absolute increase 0.6%
Chow, et al. [9]	2020	United States of America	Cohort	17,347 propensity score-matched	In-hospital mortality	N/A	Admission	N/A	No difference in groups (P=0.1-0.38)
Meizlishet, et al. [13]	2021	United States of America	Cohort	1,956 propensity score-matched	In-hospital mortality	81 mg daily	Admission	Discharge	N/A
Chow, et al. [10]	2020	United States of America	Cohort	412	Mechanical ventilation risk, ICU admission, and In-hospital mortality	81 mg daily	Within 24 hours of admission or 7 days proir to admission	Discharge	No difference (P=0.69)
Santoro, et al. [17]	2020	Spain, Italy, Ecuador, Cuba, Germany, China, Canada	Cohort	7824	In-hospital mortality	N/A	Admission	Discharge	No difference (P=0.43)
Chow, et al. [16]	2020	United States of America	Cohort	1,12,269	In-hospital mortality	81 mg median	Admission	5-day median	No difference (P=0.054)
Liu, et al. [19]	2021	China	Case-control	232 propensity score-matched	30-days and 60-days mortality	100 mg daily	Admission	5-day minimum	N/A

Discussion and Conclusion

Thromboembolic events remain a major cause of death in hospitalized COVID-19 patients. Aspirin, with its anti-inflammatory and anti-thrombogenic properties, may have a role in reducing this risk. However, existing data is largely limited to retrospective observational data, making it hard to draw robust conclusions. While questions remain regarding timing, dosage, and duration of therapy for ASA in hospitalized COVID-19 patients, data suggests its use confers a protective effect against thromboembolic outcomes. This benefit extends to decreased in-hospital mortality for hospitalized COVID-19 patients. Patients older than 60 years or who have significant comorbidities appear to have the biggest benefit from ASA therapy. For the significant number of patients currently on outpatient low-dose ASA therapy, there does not appear to be a conferred harm with continuing this medication in the inpatient setting. Despite data suggesting low dose ASA does not increase bleeding, there remains a concern for the risk-benefit ratio in patients who may be in danger of severe hemorrhage or require higher doses of ASA. More data from randomized controlled trials will be needed to better characterize the role of aspirin in hospitalized COVID-19 patients.

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Ethics Statement

Not applicable.

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