2016

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Anticoagulation following gastrointestinal bleeding: assessing harms and benefits

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ABSTRACT   A critical appraisal and clinical application of Sengupta N, Feuerstein JD, Patwardhan VR, et al. The risks of thromboembolism vs. recurrent gastrointestinal bleeding after interruption of systemic anticoagulation in hospitalized in patients with gastrointestinal bleeding: a prospective study. *Am. J. Gastroenterol*. 2014;110:328-335. doi: 10.1038/ajg.2014.398

Keywords: gastrointestinal bleed, gastrointestinal hemorrhage, pulmonary embolism, anticoagulation, thromboembolism, thromboembolic disease, GI, PE

Clinical Context

A 73-year old male presented to the ED with altered mental status and severe anemia. The patient had a positive fecal occult blood test and was having melanic stools throughout admission. His hemoglobin was unstable, dropping as low as 5.6 during the hospitalization, and he required several units of packed red blood cells (pRBCs). An underlying pulmonary embolism (PE) several days after admission complicated the hospital course. The PE, in light of the recent gastrointestinal bleed (GI) bleed, led to controversy over whether to anticoagulate the patient. The patient was placed on heparin drip twice, on separate occasions, each leading to its discontinuation due to repeat decreases in hemoglobin. When the patient was eventually stabilized, upper endoscopy showed LA class B esophagitis, friable mucosa in the esophagus and stomach, and dark, old blood clots. Colonoscopy was deferred due to the fluctuating condition of the patient. Ultimately, his condition improved. At the time of discharge, the challenging decision remained, regarding whether to anticoagulate or not in light of the GI bleed and subsequent PE.

Clinical Question
Should a patient be anticoagulated as an outpatient for a PE following a recent comorbid GI bleed?

Research Article
Sengupta N, Feuerstein JD, Patwardhan VR, et al. The risks of thromboembolism vs. recurrent gastrointestinal bleeding after interruption of systemic anticoagulation in hospitalized in patients with gastrointestinal bleeding: a prospective study. *Am. J. Gastroenterol*. 2014;110:328-335. doi: 10.1038/ajg.2014.398

Literature Review
An extensive literature search began with articles found in PubMed and Google Scholar, using several combinations of keywords, including "anticoagulation," "gastrointestinal bleeding," "gastrointestinal hemorrhage," "pulmonary embolism," "thromboembolism,"

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and "thromboembolic disease." Publications were limited to the last five years. It became apparent that, although the clinical question at hand was important, there exists very little direct research addressing it. Most research on restarting anticoagulation and GI bleeds included patients who were already on anticoagulation prior to the study; however, this patient was on no current home medications. Also, these studies looked into patients' future risk of thromboembolic events and didn't include those with concurrent DVT/PE's. Although this patient may not have directly fit the criteria for these studies, there are learning points that can be extrapolated and applied to his care.

There have been a few recent retrospective studies in which the utility of restarting anticoagulation after a GI bleed has been investigated[1,2]. In a study by Witt et al., 442 patients with warfarin-associated GI bleeds were included. They found restarting warfarin at hospital discharge following a GI bleed was associated with decreased risk of thrombosis and death without significant increase in recurrent GI bleed[1]. However, due to its retrospective nature, it was limited by data collection through administrative databases. This means that it could not address many of the other clinical features that contribute to the ultimate clinical decision made by the physician. On further literature review, a recent prospective observational cohort study by Sengupta et al. also investigated similar outcomes 90 days after discharge[3]. Due to its prospective nature, this article was able to paint a clearer picture by identifying the source of the bleed and other contributing clinical features.

Critical Appraisal

The article by Sengupta et. al is a single center, prospective observational cohort study of 197 patients who developed GI bleed while on systemic anticoagulation[3]. It falls under 2C evidence for therapy in accordance with the Oxford Centre for Evidence Based Medicine. A heterogeneous group was included in the study. The patients were divided into two groups: those started on anticoagulation at discharge (61% of the cohort), and those who were not. It is important to note that this is not a randomized trial and that the physician directly caring for these patients made a decision on whether a patient was restarted on anticoagulation. This nonrandom assignment of patients causes concern for selection bias, one of the biggest threats to the validity of the study. There is no amount of post-hoc statistical analysis that can achieve the validity of a randomized trial; however in lieu of randomization, the researchers used consecutive patients, a proxy sampling method that adds strength to the study design. Statistically, there was no difference between the groups at discharge in terms of hospital management, etiology of bleeding, and comorbid risk factors except for the following: those on anticoagulation were more likely to have a prosthetic valve, prior stroke or transient ischemic attack, or prior history of GI bleed, while those not started on anticoagulation were more likely to have history of active malignancy. This was accounted for by incorporating the Charlson comorbidity index score into the statistical analysis. Only 12% of the cohort at the time of 90-day follow-up was lost, with no significant difference between the two groups, also strengthening the study. Lastly, it is important to keep in mind that investigators themselves contacted patients, potentially introducing measurement bias.

Analysis of the data showed a significantly lower risk of thromboembolism in those resumed on anticoagulation (hazard ratio [HR]=0.121, 95% confidence interval [CI]=0.006-0.812). There is potential for confounding bias since those with active malignancy were more likely to have a thrombotic episode and also less likely to be anti-coagulated; however, this association was accounted for, and the increased risk of thromboembolism and anticoagulation remained significant. It is also a reasonable possibility that those who did not start anticoagulation at discharge were sicker and at greater risk of adverse events, but as previously mentioned these confounding factors were accounted for by the Charlson comorbidity index.

The study showed an increased risk of recurrent GI bleed in those restarted on anticoagulation (HR=2.17, 95% CI=0.861-6.67). That said, this was not found to be statistically significant (P=0.10). The authors noted that the primary outcome was thromboembolism, and that the study likely may have been underpowered to determine the association with GI bleed[3]. A larger patient population would have strengthened the study. Because there was no statistical difference between groups for either recurrent thromboembolism or re-bleeding, it is misleading to calculate NNH or NNT. The potential outcomes of a thromboembolism may be of greater consequence than GI bleed. For instance, only 36% (8/22) of those with GI bleeds in the anticoagulated group had a hemoglobin drop of >1 g/dl and only 14% (3/22) required endoscopic, surgical, or radiologic intervention. Taking this into consideration, the HR for thromboembolism after discontinuing anticoagulation was much higher than that of the HR for GI bleed and resuming anticoagulation. This suggests that even if there was a significant relationship with increased GI bleed and resuming anticoagulation, the benefits of resuming anticoagulation may outweigh the risks.

Clinical Application

It is important to note that there are a few differences between the patient in question and those studied. His GI bleed was not related to anticoagulation since he was on no medications prior to hospitalization. Also, several days into his hospitalization he was found to have a PE. This is an unusual set of complications, and both need to be factored into decision-making. The fact that he had a PE signifies that he was already at higher risk for a secondary thromboembolic event. The GI bleed significantly dropped his hemoglobin and required him to receive several units of pRBCs. One might be concerned about his rough hospital course, but several of the patients included in the appraised article also required transfusions and Medical Intensive Care Unit support[3].

Ultimately, the team and the patient agreed on starting warfarin one-week status post discharge with close follow-up. There were a few factors that played into this decision. First, he was at increased risk for recurrent thromboembolic disease in light of his recent PE. The decision was further strengthened by upper endoscopy showing no active bleed and stabilization of his hemoglobin. As for choosing warfarin, it shows a lesser incidence of GI bleeds compared to new oral anticoagulants. Lastly, there is not much guidance on when exactly anticoagulation should be started if it is initially withheld. The study by Sengupta et al. suggests that it should be no later than two weeks after discharge. Although this was not the focus of their study, they noticed that most thromboembolic events occurred after the two-week mark while most bleeds occurred within the first two weeks[3]. These findings ultimately factored into our decision to start warfarin one week after discharge.

Take Home Points:
1.) Giving an anticoagulant shortly after a GI bleed seems counterintuitive; however, the study by Sengupta et al. suggests the risk is less than the risk of thromboembolic disease upon stopping anticoagulation.
2.) The optimal time at which anticoagulation should be restarted likely falls within two weeks after discharge.
3.) Medical decisions are often not clear-cut. In this case, the patient had concurrent bleed and PE. There is little literature on this since it occurs infrequently. Although the patient may not have been a candidate for the cohort study appraised, the findings are potentially helpful in management. It is important to consider all the benefits and risks for each patient. Ultimately, research findings cannot replace the clinical judgment of the physician.

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