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The transfusion threshold for upper gastrointestinal bleeding is a hemoglobin of 7.0 g/dl or less

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ABSTRACT A critical appraisal and clinical application of Villanueva C, Colomo A, Bosch A, Concepcion M, Hernandez-Gea V, Aracil C. Transfusion strategies for acute upper gastrointestinal bleeding. *New Eng J Med*. 2013;368(1):11-21. doi: 10.1056/NEJMoa1211801.

Keywords: *gastrointestinal bleeding, transfusion, transfusion threshold*

Clinical Context

The patient is a 70 year old man with a past medical history of hypertension, hyperlipidemia, peripheral vascular disease, abdominal aortic aneurysm repair, and coronary artery disease. He presented to the Emergency Department complaining of a two-day history of dark stool associated with dizziness, tremulousness, bilateral facial dysesthesia, and generalized weakness. He stated, “My sleep has been bad and I’ve been fatigued and weak before this, but now it seems worse.” Upon presentation, the patient’s vital signs were stable. Fecal occult blood testing was positive, patient was transferred to the general medicine floor, Plavix and aspirin were held, and gastroenterology was consulted.

After admission, the patient was boarded to undergo an endogastroduodenoscopy but that night his hemoglobin fell from 9.1 g/dL to 7.1 g/dL. At admission, he understood that blood transfusion might be necessary during his hospital stay. He stated, “I understand; I’ll take a transfusion if it will help me.” He was transfused with two units packed red blood cells and one unit of platelets. Subsequent to transfusion his hemoglobin level rebounded to 9.5 g/dL. Following transfusion, his symptoms, while still present, had improved.

He lives at home with his wife and anxiety over his recent health concerns was affecting his personal life and day to day activities. He was feeling overwhelmed and nervous about his admission. He had a 70 pack-year smoking history, but stated he quit “a year ago”. He used to drink about a pint of liquor every day but he quit four weeks

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ago. He saw his primary care physician 10 days prior to admission complaining of difficulty falling asleep and staying asleep and depressed mood. His PCP prescribed melatonin to help him sleep and sertraline for depression, but patient said he hadn't experienced any relief with either.

The patient had the abdominal aortic aneurysm repair two months prior and had been following with the vascular surgeon. On rounds, our team told him that he was losing blood and that we would try to find the site of blood loss during this hospitalization. At this point, the patient said, "I hope my artery repair isn't leaking." The team reassured him that it was unlikely that his prior surgery was causing any of his current signs or symptoms. We informed him that the dark color of his stools led us to believe that his bleeding in his GI tract.

Our attending asked, "Did you counsel him about the risks of harm and risks of benefit from transfusion with a hemoglobin of 7.1?"

Clinical Question

For patients with a recent upper gastrointestinal (GI) bleed, is it appropriate to transfuse a patient who has a hemoglobin of 7.1 g/dl ?

Research Article

Villanueva C, Colomo A, Bosch A, Concepcion M, Hernandez-Gea V, Aracil C. Transfusion strategies for acute upper gastrointestinal bleeding. *New Eng J Med*. 2013;368(1):11-21. doi: 10.1056/NEJMoa1211801

Related Literature

The search started in Google Scholar using the following search term: "For gastrointestinal bleeding when is transfusion appropriate?" The first two citations revealed an article thought to be relevant to our patient[1] and a guideline.[2] These two citations were reviewed on PubMed. The "similar articles" recommendations were reviewed for new studies, as well as the "cited by systematic reviews" list. A Cochrane review was found[3], and the systematic review results were read. A PubMed search was also done with search terms (transfus*[tiab] AND "threshold") AND (gastrointestinal OR "gi bleed"). After this process, ultimately three total randomized, controlled trials were identified that studied outcomes of transfusion in patients with acute GI bleeding.[1,4,5] The TRIGGER trial was a pragmatic open-label, cluster randomized feasibility trial that sought to confirm the Villanueva trial, published two years earlier.[5] The outcomes measured were specific to feasibility and not designed to be direct evidence related to the question. The Blair trial was a pilot study, which investigated different transfusion thresholds.[4] Mortality was investigated as a secondary outcome and showed a trend towards reduced mortality in patients with less transfusion. Due to the exploratory nature of the study, only 50 subjects were studied. The strongest design with the largest sample size was the Villanueva trial, so it was chosen for review.[1]

Critical Appraisal

All three randomized trials are consistent in demonstrating equivalence or benefit with restrictive transfusion strategies and because this has also been shown in other clinical settings the strength of recommendation taxonomy for this body of literature is A. For the paper reviewed the strength of recommendation taxonomy is level 1.[6]

This study was a nonblinded randomized controlled trial at a single institution comparing restrictive versus liberal transfusion protocols in the setting of acute upper GI bleed. Restrictive transfusion was defined as a transfusion at hemoglobin of 7 g/dl or less with target goal of 7-9 post transfusion versus liberal transfusion which is defined as transfusion at hemoglobin of 9 g/dl with a target goal of 9-11. There was no commercial sponsorship for the study.

Patients greater than eighteen years old who had melena, hematemesis, or both were eligible to participate. There were multiple exclusion criteria including but not limited to: patient declining blood transfusion, acute bleeding emergencies, unstable cardiac

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conditions, or recent surgery. Patients with lower GI bleeding were not eligible. Patients who were completely stable based on ROCKALL score also were not included.[7] Based on these inclusion and exclusion criteria, the patient described in the clinical scenario is similar to the patients in the study.

Randomization occurred immediately after admission using computer-generated random numbers with block size of 4, stratified for presence or absence of cirrhosis. The research paper did not describe how eligible patients were identified, creating a potential selection bias.

Doctors could exclude individual patients based on clinical judgment alone, creating a potential source of selection bias by decreasing the number of participants who are potentially medically unstable.

Because this is an open label trial, the largest potential bias could be greater efforts to monitor and treat patients in what might've been considered a higher risk category. Although the authors described re-bleeding (45 patients in restrictive group and 71 patients in liberal transfusion group), they do not specify whether they maintain the same cut off for transfusion on the second bleed compared to the first bleed.

All-cause mortality within the first 45 days was the primary outcome measure. Twenty-three people in the restrictive transfusion strategy (N=444) died. Forty-one people in the liberal transfusion strategy (N=445) died. Number needed to treat was 25 for restrictive protocol compared to liberal protocol over the first forty-five days to prevent one death. The hazard ratio for death favored restrictive therapy, 0.55 [95% CI 0.33-0.92, p=0.02. Only 3.5% of patients withdrew from the study and the analysis was done with an intention to treat protocol.

Clinical Application

With regards to our patient, his primary concern rested with the source and control of his bleeding. This was especially evident with his concern for abdominal aneurysmal rupture for which he knew the prognosis would be poor. At esophagogatroduodonoscopy, he was found to have mild gastritis and minimal peptic disease. The patient was pleased with the relatively benign diagnosis, but we encouraged him to continue to deal with his other life stresses.

Applying the chosen study to our patient, we wondered if he would have done just as well without the transfusions. Our clinical scenario mirrors many aspects of the study appraised. However, the study was not designed to stratify the rate of blood loss, as the argument could be made that a more rapidly decreasing hemoglobin may warrant a blood transfusion even when hemoglobin levels return above the suggested restrictive threshold. Thus, the benefit of applying a restrictive hemoglobin level threshold for transfusion of 7.0 mg/dL may indeed be evident for patients with mild to moderate upper gastrointestinal bleeding, whereas using this approach in patient with more severe bleeding (perhaps evidenced by more rapidly decreasing serum hemoglobin levels) may result in a delay of life saving treatment.

Alternatively, the harm of transfusing blood products to patients with higher more "liberal" hemoglobin levels is multifactorial, including subjecting the patient to potential transfusion reactions, blood product infections, and unnecessary healthcare spending. Our patient did in fact meet inclusion criteria for this study and we believed that he was a good candidate for a restrictive transfusion threshold.

Lessons learned:

1. Through this experience our team has come to the agreement that there is indeed a large disparity in knowledge with respect to the risk versus benefits of a liberal versus a restrictive blood transfusion strategy.

2. Patients continue to be transfused "liberally" despite evidence that this may be in fact be harmful to the patient and less effective than the alternative more restrictive approach. This was reinforced when two different Intensive Care Unit intensivists used differing thresholds for similar patients on two sequential days.

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3. As with most aspects of medicine, our understanding of appropriate treatment strategies for different disease states continues to expand; it is our professional duty and obligation to propagate this information amongst us for the benefit of the patient.

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