Is undertransfusion a problem in modern clinical practice?

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BACKGROUND: Significant progress has been made in reducing inappropriate transfusion of blood products. However, there is also a need to monitor for their underutilization in patients who would benefit from transfusion. This study aimed to develop a method to monitor for undertransfusion and conduct a preliminary examination of whether it is a problem in modern clinical practice.

STUDY DESIGN AND METHODS: All patients with a hemoglobin (Hb) concentration below 6 g/dL or platelet (PLT) count of fewer than 10×10^9/L were identified during a 1-month period in an academic medical center in the United Kingdom. Patients who were transfused within 72 hours of the low reading were excluded from further analysis. For all other patients, records were examined against predefined criteria to ascertain whether the reason for nonadministration of transfusion was justified.

RESULTS: During the study period there were 63 eligible Hb readings and 130 eligible PLT counts in 93 patients. Of these, 36 patients were not transfused within 72 hours of the low reading. The majority of nonadministration (n = 28) was justified by either an additional Hb or an additional PLT count on repeat sampling being above the transfusion threshold or the transfusion being medically inappropriate. No documentation was found to indicate that any cases of nonadministration of blood were unjustified.

CONCLUSION: This study did not find that patients with low Hb readings or PLT counts were inappropriately undertransfused. However, systems similar to those described in this study should be developed to monitor for inappropriate undertransfusion as well as continuing efforts to monitor for and reduce inappropriate overtransfusion.

The medical community is increasingly aware of risks associated with blood transfusion, and numerous steps have been taken to try to reduce the amount of blood products administered to patients inappropriately.[1] Part of the recent "Choosing Wisely" campaign highlights five priorities for reducing blood product usage.[2] However, when used in their correct context, blood products have the power to save lives and reduce morbidity. As was first suggested in 1992[3,4] and again more recently,[5] there is also a need to monitor whether blood products are being underutilized in patients who would benefit from transfusion. The UK hemovigilance scheme, the Serious Hazards of Transfusion (SHOT), mentions the need for monitoring undertransfusion but reports up to now have been focussed on underdosing of fresh-frozen plasma.[6]

There is a paucity of studies of undertransfusion, with only two previous studies reported to our knowledge. The first by Mair and colleagues[7] evaluated all patients at a single center in Florida that had a hemoglobin (Hb) concentration below 7 g/dL or platelet (PLT) count of fewer than 10×10^9/L over a 3-month period. Of the 55 patients identified, all but eight had received a transfusion, and of those eight all had appropriate reasons for nonadministration of transfusion.

Saxena and coworkers[8] monitored for undertransfusion over a 14-month period at the Los Angeles County–University of Southern California Medical Center by identifying all patients with a Hb concentration below

ABBREVIATION: ITP = idiopathic thrombocytopenic purpura.

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5 g/dL or PLT count of fewer than 10×10^9/L. Of patients with these very low readings, they identified 148 cases in which a transfusion was not given. Of these, only one patient with thrombocytopenia and one patient with anemia were judged as inappropriately undertransfused; the remainder had appropriate reasons for nonadministration of transfusion.

Does this mean that undertransfusion is unlikely to occur in modern clinical practice? There were several limitations to these studies. Both were single-center studies. The study by Saxena and colleagues[8] used a particularly strict cutoff for low Hb that could have missed other cases in which transfusion was underutilized. Furthermore, these studies were published in 1996 and 2001, respectively, and it is feasible that heightened efforts to curtail overtransfusion have increased the risk of undertransfusion.

While other studies have sought to develop and refine sophisticated systems to monitor for overtransfusion,[9] little methodologic development has occurred for underutilization monitoring. This study therefore sought to further develop a method for monitoring undertransfusion and to report the incidence of undertransfusion over three UK hospital sites in the setting of a large academic medical center.

MATERIALS AND METHODS

The Oxford University Hospitals NHS Trust is a multisite academic medical center that provides a full range of routine and complex clinical services to a large surrounding region including Oxfordshire and neighboring counties. It includes several intensive care units, specialist surgical services including cardiac surgery and organ transplantation, a children's center, an obstetric unit, and a regional hematology and cancer center. The central hematology and transfusion laboratory provides hematology testing and blood products for three of the four hospitals, the exception being a regional hospital 25 miles distant from the main hospital sites. The study was registered with the oncology and hematology departments, approved by the academic center's Caldicott guardian (a senior clinician responsible for protecting the confidentiality of patient and service-user information and enabling appropriate information sharing), and lead clinicians for patients requiring notes review were informed.

All patients with a Hb level below 6 g/dL or PLT count of fewer than 10×10^9/L measured during the month of March 2014 were retrospectively identified using the hospital laboratory information system. The BloodTrack system (Haemonetics Corp., Braintree, MA) records all blood transfusions at Oxford University Hospitals[10] and was used to ascertain whether patients had received red blood cell (RBC) or PLT transfusions in the period after their corresponding low Hb or PLT count reading; this records the exact time of the administration of transfusion through the use of bedside handheld computers linked to the blood bank information system. Any transfusions given up to 72 hours after the low reading were recorded.

Patients who had received a transfusion within 24 hours of a low reading were excluded from further analysis. A separate group of those with delayed transfusions (defined as between 24 and 72 hr after a low reading) were also excluded from further analysis.

For patients with low readings that were not followed by a corresponding transfusion within 72 hours, medical records were sought to ascertain the reason that a transfusion was not administered. Predefined justifications for nonadministration of transfusion were adapted from a previous study[8] as follows:

1. The clinician considered that a transfusion was medically inappropriate and an effective alternative treatment was available (e.g., for iron or vitamin deficiency anemia, autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura [ITP]).
2. The patient's condition did not correlate clinically with the reported Hb concentration or PLT count, and the clinician repeated the count and found that it was above the relevant transfusion threshold.
3. There was no effective alternative treatment for the cause of anemia or thrombocytopenia. However, immediate transfusion therapy was not medically indicated for treatment by the stable nature of the patient's clinical condition.
4. The patient was being treated palliatively as part of end of life care.
5. The patient refused transfusion (for religious or other reasons).
6. There was a delay in transfusion due to awaiting special units (e.g., HLA-matched PLT concentrates).

Three methods were used to ascertain the reason for nonadministration of transfusion. First, if the patient had a Hb level higher than 8 g/dL or a PLT count of more than 150×10^9/L within 24 hours of the low reading, it was assumed that the initial reading was erroneous and the reason for nonadministration of transfusion was recorded as Category 2. Category 2 also included episodes where a repeat count within 24 hours found that the Hb or PLT count was now above the relevant transfusion threshold but was still subnormal, and these episodes required notes review to ascertain that this contributed to clinical reasoning. Second, electronic patient records were identified to search for additional clinical information to justify nonadministration of transfusion, for example, cause of anemia or thrombocytopenia more appropriately treated without transfusion.

Finally, for patients for whom electronic steps failed to identify a reason for nonadministration of transfusion, full paper records were acquired and analyzed. If a low Hb

TABLE 1. Number of episodes of low readings followed by timely transfusion (within 24 hr), delayed transfusion (24-72 hr), or no transfusion

Outcome measure	Reading of Hb < 6 g/dL	Reading of PLT count < 10×10^9/L	Total
Episodes of low readings followed by transfusion within 24 hr	38	81	119
Episodes of low readings followed by delayed transfusion between 24 and 72 hr	5	20	25
Episodes of low readings not followed by transfusion within 72 hr	20	29	49
Total	63	130	193

TABLE 2. Justification for withholding transfusion in patients who were not transfused after low Hb or PLT count readings

Outcome measure	Patients with Hb < 6 g/dL	Patients with PLT count < 10×10^9/L	Total
Notes not available	1	0	1
Patient's condition did not correlate clinically with the reported PLT or Hb reading, and the clinician repeated the count and found that it was above the relevant transfusion threshold	9	6	15
Clinicians felt that transfusion was medically inappropriate and an effective alternative treatment was available (e.g., iron or vitamin deficiency anemia, AIHA, or ITP)	4	9	13
There was no effective alternative treatment for the cause of anemia or thrombocytopenia. However, immediate transfusion therapy was not medically indicated for treatment by the stable nature of the patient's clinical condition	0	1	1
Patient was being treated palliatively as part of end-of-life care	3	2	5
Patient refused transfusion (for religious or other reasons)	0	1	1
Delay due to awaiting special units (e.g., HLA-matched)	0	0	0
Total	17	19	36

AIHA = autoimmune hemolytic anemia.

or PLT count reading was measured in the community, the patient's primary care physician was contacted to ascertain the reason for nonadministration of transfusion. Where two potential justifications were present, the justification most likely to have contributed to the decision not to transfuse was recorded. One author (SH) assessed each patient record for whether a justification was present and discussed any uncertainties with the senior author (MM).

RESULTS

During the study period, there were 193 episodes of low readings (63 with Hb < 6 g/dL, 130 with a PLT count $<10 \times 10^9$/L; Table 1). These 193 episodes occurred in 93 patients. In total, 57 of the 93 patients received a corresponding transfusion within 72 hours of all of their episodes of low readings. The remaining 36 patients had at least one episode of a low reading that was not followed by transfusion within 72 hours of the episode (corresponding to 49 individual episodes).

Of these 36 patients, 17 had low Hb readings and 19 had low PLT counts not followed by transfusions. No patients had a combination of low Hb readings and low PLT counts not followed by transfusion. For 21 patients, a justification for nonadministration of transfusion could be ascertained from electronic records, but the remaining 15 required analysis of paper notes or contact with the patient's primary care physician. One patient's paper notes were not available and so a justification could not be found. The results of notes review can be seen in Table 2.

The most common justification for withholding transfusion was that the patient's condition did not correlate clinically with the low reading and the clinician sent a repeat sample. In the majority of episodes, the initial sample was clearly erroneous, such as a Hb of 3.1 g/dL preceding a repeat sample of 9.9 g/dL with no intervening transfusion. Other differences were subtler, such as an initial PLT count of 8×10^9/L followed by a repeat sample of 12×10^9/L.

Patients for whom transfusion was deemed to be medically inappropriate received effective alternative treatment in all but one episode (such as erythropoietin for anemia of renal failure or steroids for ITP). The one episode in which an alternative effective treatment was not available was a patient with myelodysplastic syndrome who had chronic thrombocytopenia and was not bleeding, and prophylactic PLT transfusion was not considered to be appropriate. One patient with myelodysplastic syndrome refused additional PLT transfusions on the grounds of not wanting to come into hospital.

DISCUSSION

A significant number of patients with low Hb readings or PLT counts do not receive transfusions. In our 1-month

study in a large academic medical center, 25.4% of Hb readings below 6 g/dL or PLT counts below 10×10^9/L were not followed by transfusion. However, all that we were able to fully investigate (35/36) had a clear justification for nonadministration of transfusion. In the episodes of low Hb readings, the most frequent reason was where a low reading did not correlate with the patient's clinical condition and a repeat sample either found that the Hb had normalized or was above the transfusion threshold, whereas in the episodes of low PLT counts the most frequent justification was that transfusion was medically inappropriate (most commonly due to ITP).

It is reassuring that we not only found no evidence of transfusions being inappropriately withheld, but also that clinicians are not transfusing inappropriately even when blood test results are very low. In one instance a child with a Hb reading of 3.7 g/dL with low ferritin and transferrin saturation appropriately received oral iron supplementation, dietician input, and pediatric follow-up without any transfusion. However, even within this population with very low Hb readings or PLT counts, there was evidence of inappropriate transfusion. An elderly patient with a Hb level of 4.7 g/dL due to folate deficiency received a blood transfusion despite early improvement on folic acid replacement.

There were a substantial number of episodes (25/193; 13.0%) in this study where patients were transfused between 24 and 72 hours from their low Hb or PLT count reading. This is a population that deserves further investigation but was excluded in this study, as the factors driving transfusion delay are likely to be different to those leading to transfusion being withheld.

A central aim of this study was to develop a practical process to monitor for undertransfusion. The necessary components are threefold. First, the ability to search laboratory records for critically low Hb and PLT count values within a given time frame. Second, a reliable database of transfusion records to ascertain which low readings were followed by transfusion; this step is helped hugely by accurate recording of the time of transfusion ideally using an electronic bedside process. Third, clear predefined categories that justify the withholding of transfusion such as those used in this study. Additionally, an electronic patient record system that records key diagnoses, clinical reasoning, and treatment decisions reduces the need for laboriously searching paper notes when assessing whether transfusion decisions are appropriate.

There are several limitations of this study. Our inclusion criteria only identified one of several populations who are potentially undertransfused. Future work could examine those who received a subtherapeutic transfusion (such as clinically unstable patients with a Hb level of 4 g/dL receiving only 1 unit of RBCs). Other important populations would include those at increased risks of harm from anemia or thrombocytopenia, such as patients with acute ischemia and a low-normal Hb or patients with moderate thrombocytopenia undergoing neurosurgical procedures. In addition, our study did not analyze patients with abnormal coagulation variables who were potentially undertransfused with plasma components.

Ascertaining the rationale for withholding transfusion was limited to what could be seen in paper and electronic medical notes. This was particularly limiting when more than one potential justification was identified. This limitation could be reduced by prospective studies in which reasons for withholding transfusion could be clarified with teams in real time.

Despite these limitations, this study is an important reminder that monitoring processes should be established for undertransfusion as well as overtransfusion.[5] What the transfusion community is aiming for is not less blood usage in isolation, but appropriate transfusion decisions that combine an up-to-date evidence base of transfusion and alternatives to transfusion, the full clinical context of individual patients, and each patient's own values.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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