Things We Do for No Reason™: Routinely Prescribing Transfusion Premedication to Prevent Acute Transfusion Reactions

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Inspired by the ABIM Foundation's Choosing Wisely® campaign, the "Things We Do for No Reason™" series reviews practices that have become common parts of hospital care but which may provide little value to our patients. Practices reviewed in the TWDFNR series do not represent "black and white" conclusions or clinical practice standards, but are meant as a starting place for research and active discussions among hospitalists and patients. We invite you to be part of that discussion.

CLINICAL SCENARIO

A 68-year-old woman with a known history of myelodysplastic syndrome is admitted for fatigue and shortness of breath on exertion. Her hemoglobin concentration decreased from 9.1 g/dL to 6.5 g/dL. Her physical examination is unremarkable except for mild tachycardia with a heart rate of 105. She is scheduled to receive her first red blood cell (RBC) transfusion. The hospitalist orders premedication with acetaminophen and/or diphenhydramine to prevent an acute transfusion reaction.

BACKGROUND

The most frequent complications of blood transfusion are allergic transfusion reactions (ATRs) and febrile nonhemolytic transfusion reactions (FNHTRs), with a combined incidence of approximately 1%-4% per transfusion.[1] ATRs may range in severity from mild urticaria to life-threatening anaphylaxis. FNHTRs manifest as a fever (oral temperature greater than or equal to 38 °C/100.4 °F and an increase of at least 1 °C/1.8° F from pretransfusion values) or chills/rigors. With approximately 17 million blood transfusions, including RBCs, plasma, platelet, and cryoprecipitate components, administered annually in the United States, often to those with severe illnesses, ATRs and FNHTRs confer a substantial public health burden. Currently, the prevalence of premedication to prevent acute transfusion reactions in the United States and Canada is variable, ranging from 1.6% in one Canadian institution to as high as 80% in one large US hospital.[2,3]

WHY YOU MIGHT THINK PREMEDICATION IS HELPFUL TO PREVENT TRANSFUSION REACTIONS

FNHTRs are thought to be caused by cytokines elaborated by donor leukocytes that remain in blood products and/or by recipient antibodies reacting with donor leukocytes.[1] While the clinical course is self-limited, these reactions can cause patients significant distress. The rationale behind acetaminophen premedication is to blunt the febrile response.

ATRs are usually mild, but anaphylaxis (which may include respiratory compromise, hypotension, and even death) can occur. They are caused by recipient histamine release in response to exposure to donor plasma proteins.[1] This provides the theoretical rationale for antihistamine (eg, diphenhydramine) premedication as a prevention strategy.

Data on pretransfusion medication originate from the mid-20th century. In 1952, Ferris et al. published results showing a significant decrease in both febrile and ATRs when blood bottles were injected with an antihistamine.[4] This was followed, in 1956, by Winter and Taplin's further demonstration that both febrile and allergic reactions were significantly reduced when patients received units of blood injected with both oral acetylsalicylic acid and an antihistamine (chlorprophenpyridamine).[5] These trials notably lacked appropriate controls and blinding, and numerous transfusion practice changes have taken place during the subsequent decades.

WHY PREMEDICATION TO PREVENT TRANSFUSION REACTION IS NOT HELPFUL

In the past 20 years, three double-blind randomized controlled trials published show that premedication with a combination of acetaminophen and an antihistamine (either diphenhydramine or chlorpheniramine) does not reduce the risk of ATR and FNHTR. The first study, published in 2002, randomized 51 patients with hematologic malignancies receiving prestorage-irradiated, leukocyte-reduced, single-donor apheresis platelets to premedication with either acetaminophen and diphenhydramine or placebo.[6] Patients with a history of either ATR or FNHTR were included, but patients with a history of hemolytic transfusion reaction were excluded.[6] The study found that premedication did not significantly lower the incidence of these transfusion reactions (15.4%) as compared with placebo (15.2%; $P = .94$).[6]

In a larger study published in 2008, Kennedy et al randomized 315 patients with hematologic malignancies receiving RBC or platelet transfusion to either pretransfusion acetaminophen and diphenhydramine or placebo.[7] Patients with a documented history of an ATR or FNHTR were excluded, which may have con-

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tributed to the lower incidence compared with the aforementioned earlier clinical trial. There was no significant difference in the overall rate of transfusion reactions between the two groups (1.44 per 100 transfusions vs 1.51 per 100 transfusions, $P = .433$). When the rates of ATRs and FNHTRs were analyzed separately, there was no significant difference between the treatment and control groups for either reaction type ($P = .899$ and $P = .084$, respectively). There was a trend toward a reduction in FNHTRs, but the authors calculated that we would need to premedicate approximately 344 transfusions to prevent one febrile reaction.[7]

A more recent study published in 2018 evaluated 147 Thai children and adolescents with thalassemia receiving leukoreduced blood products.[8] Researchers randomized them to either premedication with acetaminophen and chlorpheniramine or placebo.[8] The incidences of FNHTR were not statistically significantly different: 6.9% in the intervention group, compared with 9.5% in the placebo group ($P = .565$).[8] These three studies constitute the best currently available evidence and suggest that pretransfusion antihistamines and/or antipyretics are not effective.

Beyond a lack of proven benefit, the use of premedication is not without risk. Diphenhydramine, the most commonly used antihistamine for premedication, can cause cognitive impairment, sedation, and delirium.[9] Such adverse effects are potentially heightened in the elderly and seriously ill populations where transfusion commonly occurs. Acetaminophen, although generally safe, can result in hepatotoxicity in patients who are fasting, regularly consume alcohol, or have underlying liver disease. Since there is both a lack of clinical benefit and potential for harm, avoid premedication.

WHAT YOU SHOULD DO INSTEAD

Rather than pretreating the patient, consider modifying the blood product selected for transfusion. Administering platelet and/or RBC components with certain modifications (a product-centered approach) is effective at reducing mild transfusion reactions.[10] A well-known product-centered modification method includes prestorage leukoreduction of RBC and platelet components to remove donor leukocytes to a level $<5 \times 10^6$ per unit. This intervention reduces the incidence of FNHTRs by approximately 50%.[11] A recent large, national survey demonstrated 90% of institutions (2,712/3,032) use universal leukoreduction.[12] This widely employed and effective prevention strategy has likely helped reduce FNHTRs nationwide, so there are now fewer to prevent.[12]

Irradiation is another common modification of blood components used to prevent transfusion-associated graft-vs-host-disease (TA-GVHD) for recipients with significantly compromised cellular immunity. TA-GVHD is a rare but nearly universally fatal delayed complication of transfusion. Note that irradiation does not prevent FNHTRs or ATRs.

Under the premise that platelet-related allergic reactions are the result of recipient reaction to donor plasma proteins, reducing the plasma volume administered should decrease the coadministration of allergy-inducing plasma proteins.[1] Reducing plasma volume can be achieved by two means: using a platelet additive solution that replaces two-thirds of the plasma content in a platelet unit or plasma removal by centrifugation. These two strategies decrease the plasma volume from 300 mL to ~100 mL per unit transfused, which effectively reduces the incidence of platelet-associated ATRs by 50%.[10] For patients with recurrent severe ATRs, blood banks can wash RBC and platelet components, virtually removing all plasma proteins from the units.[13] Epinephrine should be available at the bedside for patients with a history of severe ATRs.

Volume reduction and washing do negatively affect the quality of the unit: platelets activate during the process, and transfusions result in a 20%-30% reduction in posttransfusion platelet counts.[14] In addition, product manipulation takes significant blood bank processing time and results in an open system with greater risk of bacterial contamination, leading to a significantly shortened product expiration (24 hours for washed RBCs and 4 hours for washed or volume-reduced platelets).[1] Reserve volume reduction and washing for patients with a history of multiple recurrent or severe ATRs, respectively. Platelet additive solution results in a reduction in posttransfusion count but does not require additional manipulation. Platelet additive solution products may not be available at many centers but could be used selectively (similar to volume reduction) depending on availability and cost.

Avoiding unnecessary transfusions is an essential strategy to prevent ATRs and FNHTRs. Evidence-based patient blood management (PBM), now considered the standard of care, is defined as optimizing anemia and hemostasis in patients with the goal of restricting blood transfusions. Evidence supporting restrictive transfusion strategies continues to accumulate, and numerous hospital systems have implemented PBM programs resulting in a significant nationwide reduction in transfusions since 2008. An effective PBM program reduces unnecessary transfusions and subsequent transfusion reactions.

Finally, appropriate close monitoring of patients undergoing blood transfusion and after completion of a transfusion is highly important. Paying close attention to signs and symptoms can alert the transfusing team to a developing adverse reaction and should prompt immediate cessation of an ongoing transfusion, the critical first step when a transfusion reaction is suspected. Hospitalists may need to take additional actions to treat the patient (eg, antihistamines *after* an ATR manifests or a diuretic in the setting of transfusion-associated circulatory overload). Report suspected transfusion reactions to the transfusion service. Failing to report a suspected transfusion reaction can lead to catastrophic consequences that can even be fatal.[15]

RECOMMENDATIONS

- Do not prescribe an antihistamine or acetaminophen prior to transfusion.
- Reduce the risk of FNHTRs in all transfusion recipients with universal prestorage leukoreduction.
- For individuals with multiple recurrent ATRs to platelets, employ platelet additive solution or platelet volume reduction.
- Reserve washing RBC and platelet components for patients with a history of severe ATRs. Make sure epinephrine is at the patient's bedside.

- Curb unnecessary blood transfusions to reduce avoidable transfusion reactions.
- Monitor patients undergoing transfusion closely.

CONCLUSION

In our clinical scenario, there is no indication for premedication with acetaminophen and/or an antihistamine. Routine premedication is a low-value practice. Our RBC and platelet components are leukoreduced to prevent FNHTRs (and lower the risk of human leukocyte antigen alloimmunization and cytomegalovirus transmission). For individuals with multiple recurrent ATRs to platelets, we recommend platelet additive solution–stored or volume-reduced platelet components to lower the risk of future reactions. For patients with a history of severe ATRs, some blood banks may be able to provide washed components. Make sure epinephrine is at the patient's bedside. Avoiding unnecessary transfusion is also essential to prevent adverse events related to blood transfusion—if a transfusion does not occur, then neither will a transfusion reaction. Finally, monitor patients undergoing transfusion closely.

Do you think this is a low-value practice? Is this truly a "Thing We Do for No Reason?" Share what you do in your practice and join in the conversation online by retweeting it on Twitter (#TWDFNR) and liking it on Facebook. We invite you to propose ideas for other "Things We Do for No Reason" topics by emailing TWDFNR@hospitalmedicine.org.

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