

Prevention of febrile nonhemolytic and allergic transfusion reactions with pretransfusion medication: is this evidence-based medicine?

Allergic transfusion reactions (ATRs) and febrile nonhemolytic transfusion reactions (FNHTRs) are the two most common complications of blood transfusion. FNHTRs have been reported to occur in up to 30 percent of transfusions.¹ Although the incidence decreases to less than 1 percent with current methods that use single-donor apheresis units and leukoreduced products,²⁻⁵ FNHTRs are still a problem. The incidence of ATRs ranges from 0.4 to 3 percent of all transfusions.^{2,4,5} Transfusion reactions have plagued patients receiving blood since the early 20th century and physicians have consequently tried to prevent these reactions with pretransfusion medication.

Pretransfusion medication is used in 50 to 80 percent of all transfusions in the United States, but its use is not based on sound clinical trials.^{4,5} Much of the data supporting acetaminophen and diphenhydramine pretransfusion medication originates from the 1950s⁵ and became routine practice. However, there have been major changes in transfusion medicine over the past 50 years that include apheresis platelets (PLTs) becoming standard therapy, changes in blood storage standards, and a significant increase in product manipulations including component therapy, leukoreduction, and plasma depletion via automated cell washing techniques. Despite these transformations, the studies performed in the 1950s have formed the basis of standard pretransfusion medication regimens to prevent transfusion reactions.

In the past 10 years, three out of four studies that have been published concluded that prophylactic medication with acetaminophen and diphenhydramine does not reduce the incidence of FNHTRs or ATRs.⁶⁻⁹ The only randomized double-blind controlled trial that assessed the effectiveness of pretransfusion medications lacked power with only 15 transfusion reactions in the entire study.⁶ Thus, there are no large randomized double-blind placebo controlled trials that enable one to definitively determine whether pretransfusion medication decreases FNHTRs or ATRs.

Despite the common use of acetaminophen and diphenhydramine to prevent transfusion reactions, the medications are not without risk. Acetaminophen is gen-

erally safe, but there have been reported cases of increases in serum transaminases and hepatotoxicity is often related to drug overdose.¹⁰ Diphenhydramine is a potent anticholinergic that leads to drowsiness, dry mouth, and urinary retention. In addition, it has been estimated that pretransfusion medications may cost more than \$40,000 annually at a tertiary care hospital.⁹ Thus, pretransfusion medication of patients to prevent transfusion reactions should be critically evaluated.

In this issue of **TRANSFUSION**, Kennedy and colleagues¹¹ publish results from a randomized, double-blind, placebo-controlled trial to evaluate whether 500 mg of acetaminophen and 25 mg of diphenhydramine prevent FNHTRs or ATRs. The trial included 315 individuals with malignancies; patients were excluded if they had any known allergies to acetaminophen or diphenhydramine or a history of previous transfusion reactions. All blood products were administered using a leukoreduction filter. The study appears to be well designed with randomization, blinding, and a clear hypothesis, objectives, and outcomes. The patient demographic and clinical characteristics are also similar between arms. Of the 62 patients who had a reaction to either single-donor apheresis PLTs or red blood cells, 33 patients (1.51 reactions/100 transfusions) belonged to the placebo group and 29 patients (1.44 reactions/100 transfusions) belonged to the study group; the two groups did not differ significantly in the number of patients experiencing a transfusion reaction. Thus, the authors conclude that pretransfusion medication with acetaminophen and diphenhydramine does not reduce the overall risk of transfusion reactions.

The authors note that pretransfusion medication decreases the risk of FNHTRs. However, Kennedy and colleagues defined a FNHTR as a temperature greater than 100.5°F or an increase of 1°F of an already existing fever and did not consider isolated chills and rigors without temperature rise as a FNHTR.¹¹ The authors use a nontraditional definition of a FNHTR. In addition, it has been previously demonstrated that routine antipyretic use prevents fevers, but not other symptoms of the FNHTR such as chills, cold, and discomfort.¹ Thus, the patients in this study may still be experiencing many of the negative consequences of FNHTRs, but the reaction may not be recognized and documented since the antipyretic is masking

the fever. Overall, the study demonstrates that transfusion reactions cannot be prevented with acetaminophen and diphenhydramine.

Although ATRs and FNHTRs have been defined for more than 50 years and are among the most common complications of transfusion, the pathophysiology of FNHTRs and ATRs is still poorly understood. The mechanism of FNHTRs has been postulated to be due to white blood cell (WBC) antibodies in the recipient's plasma interacting with WBCs in the transfusion product or due to biologic response modifiers that include proinflammatory cytokines, fragments of complement, and lipid compounds.¹² These mechanisms, however, cannot fully explain all FNHTRs. Although ATRs are classically thought of as a Type I hypersensitivity reaction due to immunoglobulin E antibodies, it has also been proposed that transmission of anaphylactic reaction bodies (e.g., medications) may cause the reactions.⁵ The pathophysiology behind both FNHTRs and ATRs is most likely multivariate; thus, multiple methods or drug combinations may be necessary to prevent these transfusion reactions. An increased understanding of the pathophysiology of FNHTRs and ATRs through continued research is necessary to advance our ability to prevent these reactions.

Although the study by Kennedy and colleagues contributes to our knowledge of the lack of efficacy of the commonly selected pretransfusion medication to decrease or prevent FNHTRs or ATRs, further studies are needed.¹¹ There are very limited data on the ability of pretransfusion medication to prevent transfusion reactions among nononcology patients, pediatric patients, and individuals with a history of multiple transfusion reactions. It is unknown whether different doses of acetaminophen or diphenhydramine may be more effective, whether steroids may be beneficial, or whether further blood product manipulation (e.g., volume reduction, washing, HLA matching, or avoidance of older units) may help prevent transfusion reactions.⁴ In addition, Kennedy and colleagues use a leukoreduction filter just before transfusion, but it is unknown whether prestorage leukoreduction would affect the ability of pretransfusion medication to prevent transfusion reactions. There are also no studies that evaluate the effect of pretransfusion medication on the treatment of FNHTRs or ATRs. Thus, further clinical trials must be performed.

In the absence of definitive evidence-based studies, pretransfusion medication to prevent transfusion reactions should not be encouraged. Transfusion medicine specialists should resist efforts to make pretransfusion medication with these agents standard therapy in automated physician order entry systems. In addition, work with allergists and pharmacologists to study and evaluate other agents that might be effective as transfusion pretransfusion medication is needed; certainly new drugs

that might be beneficial have been introduced in the past 50 years since acetaminophen and diphenhydramine.

Although the article by Kennedy and colleagues strengthens the growing evidence that the current choices to prevent FNHTR and ATR are ineffective, the need to find effective therapies for these purposes is not dismissed. Transfusion specialists have a tendency to minimize the effects of these events on the patient and their families, considering these adverse reactions to be a nuisance, but any adverse effects on patients in these settings are significant bumps in their road to recovery.

Current practice paradigms dictate that clinicians should report all adverse reactions to the transfusion service where we identify, classify, and offer guidance on therapy for these events. It is commonly accepted that clinicians do not report all reactions, perhaps in recognition of their frustration with our inability to offer therapeutic advice that will benefit their patients. We should make the prevention of transfusion reactions including FNHTR and ATR a priority using blood component manipulations or pharmacology and encourage the development of new therapeutic approaches that have been proven efficacious by clinical trials.

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