Clinical Decision Support for Pediatric Blood Product Prescriptions

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Abstract

Since the beginning of the 20th century, blood products have been used to effectively treat life-threatening conditions. Over time, we have come to appreciate the many benefits along with significant risks inherent to blood product transfusions. As such, recommendations for the safe and effective use of blood products have evolved over time. Current evidence supports the use of restrictive transfusion strategies that can avoid the risks of unnecessary transfusions. In spite of good evidence, there is a considerable amount of variability in transfusion practices across providers. Clinical decision support (CDS) is an effective tool capable of increasing adherence to evidence-based practices. CDS has been used successfully to improve adherence to transfusion guidelines. Pediatric literature demonstrates strong evidence for the use of CDS to improve appropriateness of red blood cell and plasma transfusion utilization. Further studies in more diverse settings with more standardized reporting are needed to provide more clarity around the effectiveness of CDS in blood product prescriptions.

Keywords
- clinical decision support
- computerized physician order entry
- red blood cell
- platelets
- plasma
- transfusions
- pediatrics

Introduction

Throughout history, the recommendations for the use of blood products in medical practice have changed dramatically. For the first few thousand years of recorded medical history, physicians focused their attention on removing "evil" blood products from ailing patients. In the yellow fever outbreak of 1793, which claimed more than 4,000 lives, the recommended therapy of the day was mercury and jalap to induce diarrhea followed by copious bleeding. Although there was controversy regarding the practice of bleeding during that period, it was not for another 100 years before the modern era of blood transfusion began. In New York in 1908, Dr. Alexis Carrel, a French researcher (not a physician), successfully transfused a severely anemic newborn by suturing the father's radial artery to the baby's popliteal vein. Four years later, Dr. Carrel won the Nobel Prize for his work.[1] Since the beginning of the 20th century, scientific advances in blood typing, fractionation, and blood storage have allowed us to more broadly and safely transfuse blood products to patients in need.

The ability to safely transfuse blood products undoubtedly saves lives. It is no wonder that the practice of transfusing blood products has increased dramatically since the beginning of the 20th century. Red blood cells (RBCs) carry hemoglobin that transports oxygen necessary for normal cellular function. Maintenance of oxygen delivery is the premise behind most interventions provided to critically ill patients, including mechanical ventilation, hemodynamic support, and packed RBC transfusions (RBCT). Without the ability to transfuse platelets or plasma, many patients would be at risk for severe bleeding and imminent death. Given the necessary role that blood products play in health and the treatment of disease, it stands to reason that blood products

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should be freely administered to all patients with anemia, thrombocytopenia, or coagulopathy. That reasoning may be true if it were not for the fact that, while highly efficacious when administered in the appropriate settings, blood product administration also carries significant risks to patients receiving them.

Historically blood product transfusions have been fraught with severe complications including biologic incompatibility and the transmission of infectious diseases.[1] Because of advances in transfusion medicine and screening, these complications occur much less frequently now than in the past. However, in spite of scientific advances in transfusion medicine, significant risk factors remain inherent to blood product transfusions. Recent evidence has uncovered previously unappreciated significant risks associated with RBCTs.[2] Some of the negative effects from blood transfusions are secondary to the physiologic changes that occur to blood during the storage process. The effects have collectively been labeled the "storage lesion." The storage lesion alters the properties of blood resulting in RBCs with a shorter life span, less pliable membranes, decreased 2,3-DPG, and increased levels of potassium as the blood ages.[2,3] Other potential complications associated with RBCTs include alteration of immune function, increased risk of ischemic events, and the association with increased blood stream infections.[4–6] Some studies have even reported increased mortality rates in certain patient populations receiving blood transfusions.[6] Platelet and plasma transfusions also have significant and potentially life-threatening risk factors such as transfusion-related acute lung injury, transfusion-associated circulatory overload, and anaphylaxis.[7] Weighing the efficacy of blood product transfusions against potential complications poses a difficult question. When do the clear benefits of blood product transfusions outweigh the clear risks?

Variations in Transfusion Practices

Multiple studies have demonstrated that transfusion practices are highly variable among physicians with a considerable number of transfusions given outside of the recommended guidelines. A study in 2002 evaluating hospital-based pediatricians demonstrated significant variability in RBCT practices.[8,9] A recent large audit of pediatric transfusion practices in India evaluated more than 2000 transfusions including RBCs, platelets, and plasma and found that only 60% of the transfusions were appropriately given.[10] Adult studies demonstrate similar variations in RBCT practices. Audits of blood use in the United Kingdom have consistently demonstrated that approximately 20% of blood transfusions is prescribed outside of recommended guidelines.[11] A study evaluating transfusion practices across 464 adult hospitals not only highlighted widely variable RBCT practices but also determined that improvement in utilization within that cohort could reduce nearly a million transfusions a year saving more than 160 million dollars annually.[12]

There is a high degree of variability in transfusion practices, but it is not due to a lack of evidence providing safe recommendations. There have been several recent published studies that have guided evidence-based recommendations regarding transfusion practices. Scientific evidence strongly supports the use of restrictive RBC transfusion strategies.[13–15] In both pediatric and adult studies, restrictive transfusion strategies, using a threshold of 7 g/dL, have proven to be safe in hemodynamically stable yet critically ill patients.[13,15] These strategies have been safely expanded to patients and disciplines outside of the intensive care unit (ICU).[16] Restrictive transfusion practices have also been applied to adult patients undergoing surgical interventions without any evidence of increased adverse events.[14,17] In all of these studies, the application of restrictive thresholds have resulted in significantly less RBCs transfused. There are also evidence-based recommendations available for platelet and plasma transfusions that can restrict unnecessary utilization.[18,19] Evidence and guidelines exist supporting restrictive transfusion thresholds, yet there has been a very slow adoption of these practices at the bedside. As an example, a follow-up survey of RBC transfusion practices among hospital-based pediatricians in 2013 demonstrated persistent variability. Although there were an increased number of physicians who reported compliance with evidence-based practices, still more than 45% of clinicians reported practices outside of evidence-based guidelines.[20]

Barriers to Adopting Evidence-Based Practices

Slow adoption of new standards is not distinct to transfusion practices. In general, even in the presence of well-accepted data that justify a change in practice, adoption of change among practitioners occurs over a protracted time interval, resulting in a gap between published guidelines and practice. This gap, which effectively delays the application of safe and effective practices where they are most needed, is estimated to be between 5 and 15 years.[21,22] The delay in adoption of evidence-based practices may not be surprising when we quantify the amount of data that are presently generated. There are more than 2000 scientific articles with medical subject headings added to PubMed daily.[23,24] Clinicians struggle to maintain a current understanding of the literature given this massive and continuous influx of data.[24] In addition to the ongoing accumulation of new data, other barriers to adoption of evidence-based practices make change even more difficult.

Several studies have identified additional barriers to translating new evidence into practice. When a clinical or health care team is presented with new data supporting a change in practice, there are obstacles to overcome before changes can actually be adopted. These barriers include differing interpretation of data between providers, lack of self-efficacy among providers, inertia of previous practice, and the inability to effectively implement guidelines.[25–27] Understanding these obstacles helps explain why transfusion practices continue to vary among clinicians and institutions in spite of well-established recommendations derived from rigorous scientific investigation.

CDS Improves Adherence to Evidence-Based Guidelines

Automated clinical decision support (CDS) tethered to computerized physician order entry (CPOE) provides the opportunity to inform prescribing clinicians of best practice evidence-based guidelines in real time. Since the advent of CPOE, CDS has been utilized in various quality improvement and safety efforts. CDS has demonstrated profound positive effects on resource utilization and enhanced clinical performance for drug dosing.[28] CDS has been successfully utilized in the intensive care settings where data have helped support critical decisions that must be made in a timely fashion.[29]

Not all CDS tools are equally effective. Certain properties of CDS tools have been shown to augment their effectiveness. These properties include keeping the intervention simple, avoiding interruptions in work flow, asking for information only when necessary, anticipating needs, and delivering needs in real time.[22] A recent review of over a hundred CDS interventions demonstrated that CDS tools were more likely to be effective if they provided advice concurrently to patients and providers and when they required practitioners to provide reasons when overriding advice.[30] The ability to provide guidance in real time makes CDS an ideal tool capable of improving adherence to evidence-based guidelines.

CDS and Pediatric Blood Product Prescription

CDS targeting blood product transfusion has been successful at improving adherence to evidence-based guidelines. A recent review article on the effect of CDS on transfusion practices evaluated all relevant articles from 2003 to 2014.[11] The authors identified 20 unique studies during the time period. The studies included CDS for RBCs, platelets, plasma, and cryoprecipitate. Owing to the heterogeneity of the study designs, the authors were unable to perform a meta-analysis and the articles were analyzed individually. All 20 studies evaluated used historical controls. Among the 20 studies, there were 4 pediatric-specific studies, 2 studies included both adults and pediatrics, and 9 studies did not state a particular age group. The overall analysis concluded that there is good evidence that CDS is effective in improving compliance with RBC usage guidelines, but the effects on plasma, platelets, and cryoprecipitate are less clear. The authors hypothesized that the less clear effects on platelets, plasma, and cryoprecipitate were likely due to the smaller number of studies focused on these particular blood products.[11] When separated from the adult studies, the pediatric-specific studies demonstrated efficacy for CDS tools targeting RBCTs and plasma transfusions, but did not demonstrated efficacy for platelet transfusions. There were no pediatric studies evaluating the use of CDS for cryoprecipitate.

Among the four pediatric studies, there was only one that primarily targeted RBCT utilization. The research group hypothesized that the application of a "smart" CDS tool could accelerate the adoption of evidence-based RBCT practices in the pediatric ICU (PICU) and acute care wards at a large free-standing academic pediatric hospital.[31] This particular CDS tool was unique in its ability to interrogate the medical record determining when a RBCT was ordered outside of evidence-based guidelines. The tool evaluated age-specific hemodynamic parameters and the most recent hemoglobin value preceding the order. The logic supporting the CDS tool was modeled after a seminal randomized controlled trial demonstrating the safety of a restrictive transfusion strategy in stable yet critically ill pediatric patients.[13] When a RBCT order was written outside of evidence-based recommendations, a popup alert informed the clinician of the evidence and provided a hyperlink to the article should they wish to educate themselves. The tool did not constrain the clinician's ability to proceed with the RBCT order but rather provided real-time critical information. The intervention proved successful in improving compliance with evidence-based practices. This was evident in the decreased number of inappropriate transfusions represented by a reduction in transfusions per patient day and the average pretransfusion hemoglobin. Over the course of the 1-year intervention period, there were 400 fewer RBCTs and an estimated cost savings of over $160,000. In this study, there were no observed adverse outcomes to fewer RBCTs; in fact, the hospital length of stay was shorter in the intervention group.

Another large pediatric study was conducted in four regional neonatal ICUs (NICU). The authors reported that 35% of transfusions in their NICUs were given outside of the local recommended guidelines. A CDS tool was created that provided recommendations for RBC, platelet, and plasma transfusion thresholds. The tool offered decision support for transfusion thresholds given specific clinical indications. If the prescriber was not in compliance with transfusion guidelines, they were prompted to provide a justification. With this CDS intervention, the compliance rate increased from 65 to 90%. The percentage of patients receiving a blood transfusion decreased from 19 to 13% ($p < 0.001$) and the percentage of patients receiving a plasma transfusion decreased from 8 to 5% ($p < 0.001$). There was a decrease in the percentage of patients receiving platelet transfusions from 6 to 5% that was not statistically significant ($p < 0.5$). The overall increase in compliance translated into 554 fewer RBC transfusions, 174 fewer platelet transfusions, and 256 fewer plasma infusions during the 3-year study period. The estimated cost savings attributed to this intervention was $780,074.00.[32]

One study at a single pediatric institution looked at the use of an automated audit tool to evaluate platelet and plasma transfusions in the NICU. When a platelet or plasma transfusion order was written, the program evaluated the preceding platelet or prothrombin time value. If the value was outside of the pre-set thresholds, the prescriber was required to provide more information and the laboratory values were recorded for later analysis. The authors compared three separate 120- to 150-day periods including P1, which was the preintervention cohort; P2, the introduction period; and P3, the period following introduction until the end of the study period. There were no difference in transfusion practices between P1 and P2. The authors reported a decrease in the percentage of plasma transfusions given outside of the pre-set threshold recommendations from 7.8 to 0.9% ($p < 0.0001$) when

comparing P2 with P3. There was no significant difference between the numbers of platelets transfused in the preintervention versus any of the postintervention periods.[33] The fact that the change was noted between P2 and P3 and not between P1 and P2 suggests that the effects of CDS interventions are not instant and likely require a learning period where clinical practice is influenced and changed.

The final pediatric study investigated the use of CDS to improve compliance with a manual RBC exchange protocol for sickle cell disease in the PICU. The study was again a retrospective evaluation of patients who received RBC exchange before and after implementation of the CDS protocol. The authors reported a significant reduction in protocol violations with 20 violations in the control group and only 3 violations in the study group ($p = 0.02$). The study also demonstrated an improvement in the reduction of sickle cell hemoglobin from 55% in the control group compared with 70% in the study group ($p = 0.04$).[34] An interesting aspect of this particular study is that it increased compliance with a complex multistep protocol, which translated into increased effectiveness.

Overall the pediatric studies provide good evidence supporting the use of CDS to improve compliance with transfusion guidelines. Two of the four studies demonstrated improved compliance with RBCTs.[31,32] Two studies performed in the NICU demonstrated improved compliance with plasma transfusions.[32,33] There have been no pediatric studies outside of the NICU evaluating the effect of CDS on adherence to platelet or plasma transfusion guidelines. Interestingly, neither of the two pediatric studies that looked at the effect of CDS on compliance with platelet transfusion guidelines demonstrated significant improvement.[32,33] Even the adult studies evaluating the effect of CDS on adherence to platelet transfusion guidelines were unable to show a significant improvement in practice.[11] In spite of this observation, it would be incorrect to broadly say that CDS cannot significantly influence adherence to platelet transfusion guidelines. The overall number of studies remains low and the studies that have been done have been isolated to very specific patient populations.[11] Given the lack of prospective studies and heterogeneity of scientific reports to date, we can only conclude that we have much to learn to better understand how, why, and where CDS tools can be most effective in improving blood product transfusion utilization.

Future Direction and Dissemination

There have been several CDS interventions targeting the prescription of blood products that were successful at improving blood product utilization, especially RBC utilization. However, there are still areas where CDS could have a large impact but have not yet been deployed. One area in particular is blood conservation. A prospective study performed on PICU patients demonstrated that a significant excess volume of blood is drawn from critically ill patients. The excess blood drawn represented 210% of the requested volume requested by the laboratory. The amount of wasted blood was greater for patients weighing less than 10 kg than for patients weighing greater than 10 kg. The authors of this study suggested the use of closed systems to reduce the amount of necessary waste. It may also be possible to build CDS tools that can educate and make exact volume recommendations in real time, thus reducing the amount of wasted blood draws. Another area where CDS has not been deployed is the operating room where a majority of blood product transfusions are given. There is a growing body of evidence suggesting that blood products are overused in the operating room and that restrictive transfusion thresholds can be applied to complicated and invasive surgical procedures.

As implementation of electronic health records become more and more ubiquitous, the use of CDS for blood product prescription will grow as well. As individual institutions develop effective tools, it will be important to have venues where these tools and experiences can be shared and applied at different institutions. The study of Adams was so convincing in its results that several other institutions contacted the authors in an attempt to replicate the outcomes. This led the authors to found a quality improvement collaborative named *CDS Reducing Inappropriate Transfusions*.[35] This collaborative now has participants from institutions across the country, including five pediatric hospitals and more than eighty adult hospitals which are implementing a CDS rule based on the original study.

Given the fact that previous studies investigating the use of CDS on blood product prescription have all used historic controls and have had significant heterogeneity in the type of data that have been reported, there should be more standardization applied to future studies. Based on a systematic review of the CDS literature, recommendations for future studies include a clear explanation of the algorithm used by the CDS tool, provision of data on the number of times an alert is ignored, provision of data on the prescribers workflow, and standardization of the reporting of outcomes.[11] If possible, it would also be valuable to design a prospective randomized trial to remove bias inherent to historic controls. Future CDS tools should be designed with efficiency in mind and should leverage technology to build tools that will provide value to both the prescribers and patients alike. Finally, we need to recognize that recommendations change and ensure processes are in place to identify CDS tools that are outdated and update them as needed.

Conclusion

Transfusion practices and guidelines will continue to evolve over time. Blood products will remain a necessary and lifesaving medical therapy given the essential role they play in human physiology. As we learn more about the risks and benefits of blood product transfusions and develop ways to provide even safer guidelines and products, we need to be able to deliver new knowledge and therapies to the bedside when and where they are needed. CDS is an effective tool and has improved our ability to increase adherence to evidence-based RBC and plasma transfusion practices at the bedside. Future studies should focus on standardizing study design and investigating areas where little data exist, such as the effect of CDS on platelet transfusion guidelines. As we learn

more about how to effectively apply CDS tools, we can use them in concert with other effective quality interventions to ensure high-quality evidence-based transfusion practices at the bedside where it is most needed.

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