Out for blood: causal inference in clinical transfusion research

Valk, S.J.

Appendices

Summary

Blood product characteristics have intrigued researchers since, in 1667, the transfusion of docile lambs' blood was thought to cure psychiatric illness.[1] More recently, the transfusion of 'young blood' was made commercially available to invigorate those seeking to return to their youthful self.[2] Clearly, these therapies are far-fetched, not evidence-based, and should not be investigated further. However, a number of clinically relevant, unresolved questions pertaining to characteristics of blood products still puzzle epidemiologists. The research in this thesis aims to answer several research questions related to blood product characteristics, by using thorough epidemiological methods. Throughout this thesis, clinical transfusion research in different shapes and forms is the central theme. Clinical epidemiology and observational study design is an important aspect of clinical transfusion research, and new developments in this field that are applicable to future studies are covered extensively, including a tutorial to apply inverse-probability weighted marginal structural models to longitudinal transfusion data.

In Chapter 1, the different chapters are introduced and the background for the research is described. The chapter consists of two parts: a general introduction and an aim and outline of the thesis.

Chapter 2 contains a narrative review on the association between red blood cell donor sex and patient mortality. In 2017, our research group was the first to show that exposure to ever-pregnant donor red blood cell products was associated with mortality, with a hazard ratio (HR) of 1.43 (95% confidence interval (CI) 1.13-1.82) in male patients between 18 and 50 years of age.[3] This research was rooted in multiple studies consistently showing an association between female donor sex and mortality of male patients, which puzzled transfusion science.[4] However, the association between donor parity and mortality was not seen in a large observational cohort study in Sweden, Denmark, and the USA[5], and it was unclear what the biological mechanism could be that would cause these associations. This chapter brings together the available evidence on donor sex and patient mortality up to the date of publication, evaluates the different biological mechanisms that could underlie the epidemiological associations, and states donor microchimeric cell-mediated immune modulation is the most likely explanation for these associations in clinical transfusion research.

In Chapter 3, we investigated the importance of storage duration of red blood cell units in relation to donor characteristics, in a large cohort of transfusion

recipients in the Netherlands. Blood product storage has been indicated as a potential modifier of transfusion efficacy and safety, but evidence has been conflicting, with studies showing both positive and negative associations between storage duration of red blood cells and clinical outcomes. However, a small potential for harm from fresh red blood cell transfusions has not been ruled out and can be considered more plausible than benefit, based on evidence from randomized trials.[6] In this chapter, we investigated whether storage plays a role in modifying the effect of donor characteristics, namely sex and pregnancy history of the donor. Although a large initial cohort was used, due to blood product distribution practices relying on a 'first in, first out' mechanism, subgroups were small. This meant that the methods described in the later chapters of this thesis (i.e. g-methods) could not be applied, and we were not able to definitively prove storage plays a role in the effect of donor sex and pregnancy history on mortality. This chapter does, however, give a first indication that the direction of the effect is more likely to be towards harm from ever-pregnant donor units that are shortly stored.

Chapter 4 contains the first instalment of the systematic review series on convalescent plasma and hyperimmune immunoglobulin for people with COVID-19. The review was performed during the early stages of the COVID-19 pandemic in 2020, and followed Cochrane rapid review methodology. Evidence sources in this review were of insufficient quality to allow strong conclusions. More recent versions of this review were able to show convalescent plasma is not effective for patients hospitalized with COVID-19[7], with continuously updated reviews expected in the future to inform evidence-based healthcare decision making.

In Chapter 5, we present the results of a large observational cohort of first-ever transfusion recipients in the Netherlands: the MATER study ("Mortality After Transfusion of Ever-pregnant donor Red blood cells"). As we have carefully described, the marginal structural models used for this analysis capture treatment-confounder feedback previously prohibiting a causal interpretation of the association between donor pregnancy history, and mortality.[8] The results confirm that male patients between 18 and 50 years are at risk of increased mortality following transfusion from ever-pregnant donors, with a HR of 1.81 (95% CI 1.31-2.51). Importantly, this was not explained by offspring sex, which we hypothesized could play a role through the unintentional transfer of donor helper T-cells or cytotoxic T-cells targeting HY-antigens, after exposure to female donors with sons.[4] To conclude, we have extensively investigated this research question and found the risk of mortality after exposure to ever-pregnant donors continues to be present in a new cohort, which is intriguing.

Chapter 6 covers the development of a methodology to study the association between blood product characteristics and patient outcomes, when the product characteristics are associated with hemoglobin-raising capacity of the product. In addition to an extensive appraisal of the methods used in previous studies, the application of said methods to real transfusion data, and a visual representation of the epidemiological concepts applicable to this research, a detailed tutorial including R code and an example dataset are included in the chapter.

Chapter 7 contains a summary of the evidence described in this thesis, how these findings tie into the most recent literature, and a discussion of the implications for future research on this topic.

In this thesis, we have covered a range of topics in the clinical transfusion research field, located at the intersection of clinical and fundamental research. The research was performed using thorough epidemiological methods, large cohorts of patient and transfusion data, and critical appraisal of study assumptions.

References

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