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Research Article

The Appropriate Use of O RhD Positive Units in RhD Negative Patients: A Systematic Review and Meta-Analysis

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ABSTRACT

The increasing use of O RhD-negative Red Blood Cells (RBCs) in transfusion practise requires a sustainable approach. We investigate the incidence of RhD alloimmunisation in RhD-negative patients to determine the efficacy and thereof the efficiency of using O RhD-positive as part of adapting protocols.

PubMed, Scopus, EMBASE and Google Scholar were used to search for relevant articles between August 2019 to August 2024 for articles with the use of RhD-positive RBCs in RhD-negative trauma patients.

Of 6 studies (458 cases) included in the meta-analyses, the incidence of RhD alloimmunisation of RhD-patients when given at least one RhD-positive RBC was 16.4% (CI 95%, 5.6%-31.3%). In the same studies, using eligible data, we found the incidence of non-RhD alloimmunisation in RhD-negative patients given RhD-positive RBCs (207 cases) to be 7.3% (CI 95%, 2.8%-13.6%) compared with non-RhD alloimmunisation in patients given RhD-negative RBCs (2119 cases) at 6.4% (CI 95%, 3.4%-10.3%).

The risk of RhD alloimmunisation given the protocols in place and the population frequency of RhD-positive individuals in Australia is minimal and not dissimilar to the alloimmunisation of non-RhD antibodies. Recommendations for the use of O RhD-positive RBCs in emergency transfusion remains a safe and viable alternative in the conservation of O RhD-negative RBCs.

Keywords: RhD positive transfusion; RhD alloimmunisation; Emergency transfusion

INTRODUCTION

The O RhD-negative blood group has been known as the 'universal donor' and elected as the choice red cell component in uncross matched emergency transfusions. A study of ABO blood groups in Australia using data from 2019 shows that the proportion of O RhD-negative Red Blood Cells (RBCs) issued have increased from 11.7% to 17.4% but first time O RhD-negative blood donors only make up 8.7% of donations. The same study shows that O RhD-negative people make up approximately 6.5% of the population while RhD-positive people make up 85.9% of the population [1].

Blood shortages have been experienced around the world particularly during the recent pandemic which has both caused an increase in demand of precious blood and also reduction in the provision of rare blood groups like O RhD-negative. Due to the demand of O RhD-negative RBCs for emergency transfusions, the frequent shortages of this precious blood group have prompted the need for a more permanent ongoing solution. In order to maintain a supply for this limited blood group so that they can be used for patients that need them most, in late 2022, the National Blood Authority (NBA) released a change in recommendations for the emergency use of group O red cells in Australia with considerations for the usage of O RhD-positive RBCs.

Emergency group O red cells in Australia

Currently the guidelines released by the NBA recommend the usage of emergency O RhD-negative blood for females with child bearing potential (≤ 50 years) and paediatric males (≤ 18 years). Females>50 years and adult males>18 are recommended O RhD-positive RBCs. These decisions apply until a valid group is obtained. If more than 4 units of uncross matched O RhD-negative RBCs are transfused and more are needed, the supply of RBCs is switched to O RhD-positive. The priority of red cell transfusions is to maintain life but the conservation of the precious supply of O RhD-negative units for specific use is also an important concept. Clinicians are responsible for evaluating the clinical need for the provision of RBCs and ultimately

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make the final decision based on these recommendations. There are provisions for combatting the alloimmunization of RhD using intravenous anti-D immunoglobulins when using RhD-positive RBCs [2].

Blood supply in Australia

Blood collection in Australia is on a voluntary basis, 1 in 30 Australians donate blood. The Australian Red Cross Lifeblood (ARCLB) oversees the collection of whole blood and plasma which is then processed into our blood components and batch products. The ARCLB is also responsible for the management of a continuous blood supply. Governance from the NBA in its National Blood Supply Contingency Plan (NBSCP) follows a tiered risk system that ensures that there is always an adequate supply of blood and blood products to all its services. The ARCLB makes provisions for finding and retaining donors of specific rare and in-demand blood types.

Emergency group O red cell usage in other countries

Since 2019, countries like Canada, UK and North America have made provisions for the usage of O RhD-positive RBCs in the clinical management of emergency transfusions, while others continue to only recommend O RhD-negative RBCs in their protocols [3-6]. These countries have a similar population frequency of RhD blood group to Australia.

MATERIALS AND METHODS

The rationale for the recommendation to use RhD-positive RBCs is that the number of O RhD-positive RBCs used is proportionate to the O RhD-negative RBCs saved that can then be used in more clinically appropriately situations. Protocols are in place to circumvent the incidence of RhD alloimmunisation implicated in Haemolytic Disease of the Foetus and Newborn (HDFN) and Haemolytic Transfusion Reactions (HTR). It's important to remember that all transfusions carry a risk, and that there is still an inherent risk of alloimmunization to other clinically significant antibodies, even when using O RhD-negative RBCs [7].

This systematic review and meta-analyses aim to assess the incidence of RhD alloimmunisation following the use of at least one RhD-positive RBCs in RhD-negative trauma patients. It also aims to assess and compare the incidence of non-RhD alloimmunisation following the transfusion with RhD-negative or RhD-positive RBCs. The hypothesis is that the incidence of alloimmunisation in the use of RhD-negative or RhD-positive RBCs following the recommendations is minimal.

Study design

This study follows the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) protocols [8]. The quality of the literature was evaluated using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist [9].

Search strategy

The databases PubMed, Scopus and EMBASE were employed to identify suitable articles between August 2019 to August 2023. The search terms used were "transfusion" and "RhD positive" and "Massive Transfusion" or "MTP". Combinations and variations of "RhD positive" like "rhesus" and abbreviations like "pos" were also entered to ensure adequate coverage of terms used by authors. Further papers were identified by reviewing literature referenced by current articles and using Google Scholar within the search parameters.

Eligibility criteria

Articles were retrieved using the search strategy and duplicates were filtered out. Titles and abstracts were screened to ensure that included studies were based on transfusion of red cell component, assessed alloimmunisation rates and were not meta-analyses or case-reports. Reports assessed for eligibility excluded texts not available in English or translated, full-text articles not being available in the public domain or accessible via RMIT's library and articles not relevant to the protocol (such as, the use of Low Titre Whole Blood (LTWB) and where RhD-positive platelets were used).

Data extraction

Details of the included studies were compiled in Table 1, to illustrate the characteristics: author; study design; study period; country; total study size; RhD-negative patients who received RhD-positive red cells; mean number of units transfused and follow-up periods (Table 1). Raw data used in the statistical analyses was organised in Table 2, to show the incidence of alloimmunisation of RhD-negative patients given RhD-positive red cells or RhD-negative red cells for transfusion. The primary outcome was to assess the rate of RhD alloimmunisation with a secondary outcome on the incidence of non-RhD alloimmunisation.

Statistical analysis

Meta-analyses were performed using Open Meta [Analyst] version 12.11.14 developed by Brown University. Data extracted. was subject to a binary random-effects model (Maximum Likelihood) using arcsine transformed proportions to calculate the incidence of alloimmunisation. Confidence intervals were set at 95%. I2 value measured heterogeneity and p-values measure statistical significance. A p-value<0.05 was considered statistically significant in this study.

RESULTS

Study selection

Using the search strategy 8,914 articles was identified through PubMed, Scopus and EMBASE. The entries were extracted from the databases and input into Endnote (ver. 21.1) to filter and remove duplicates. 6,361 articles were then screened based on their title and abstracts. Of these, the full-text of 43 relevant articles was read to determine their eligibility. A total of 6 articles were accepted with 4 articles from the initial search and a further 2 articles identified by reference checks of included articles and manual search terms through Google Scholar shown in Figure 1 [10-15].

Study characteristics

The 6 included studies in this meta-analysis identified the incidence of alloimmunisation in either O uncross matched emergency issue red cells or RhD mismatched red cells in trauma patients. The studies were retrospective and prospective, conducted in six different countries covering a period from 2011 to 2022 [10-15]. Total study sizes were listed, however, eligible data extracted was further limited due to exclusion criteria to better represent sample sizes used in this study. The mean number of units transfused varied as one study assessed immunisation rates following massive transfusion only and the other studies included use of either/or these red cells in their whole hospital population. Follow-up periods were highlighted if reported (Table 1).

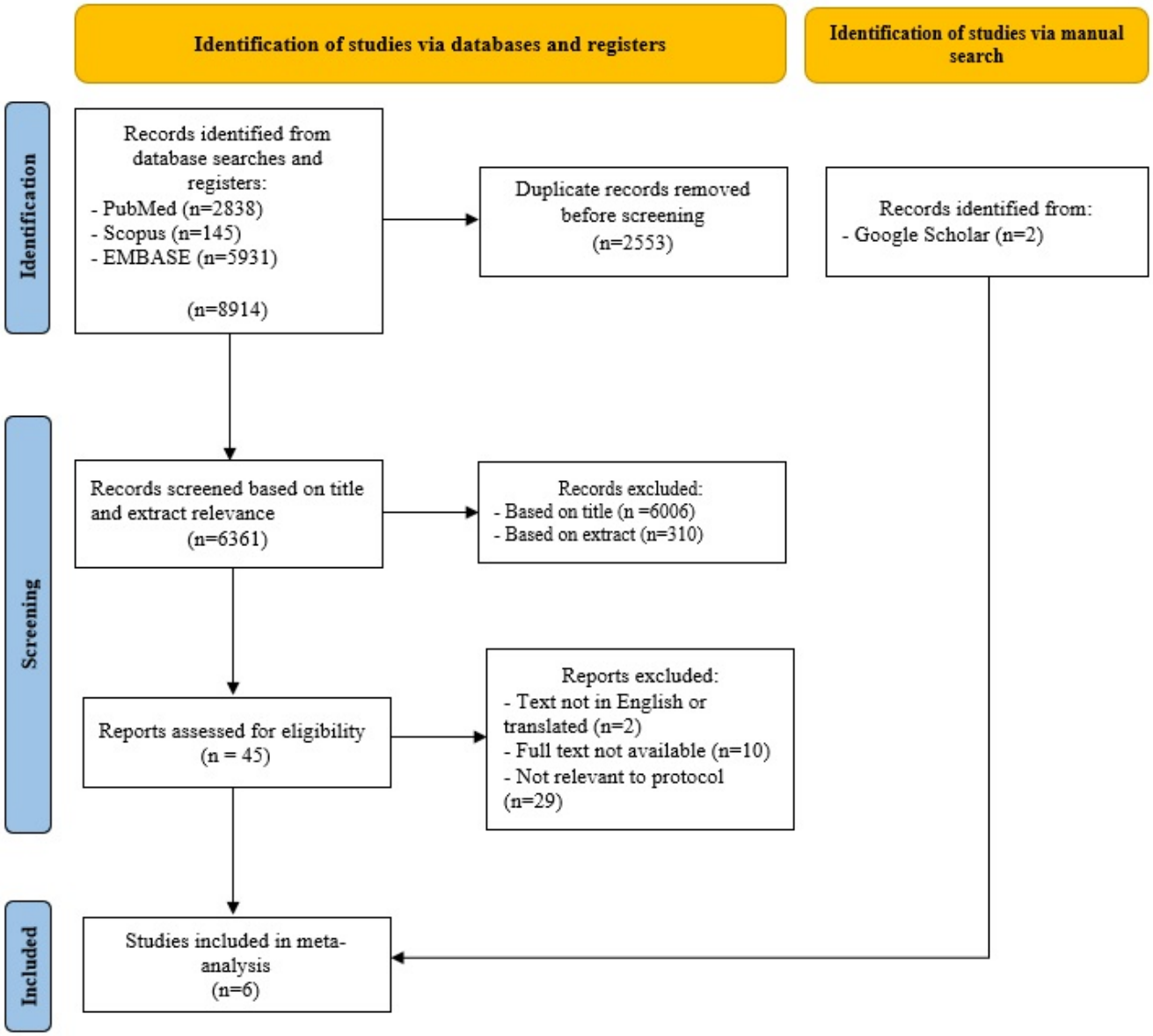

Figure 1: PRISMA flowchart for the selection of eligible studies in systematic review.

Table 1: Characteristics of included studies.

Study	Study design	Study period	Country	Total Study Size	RhD-neg patients who received RhD-pos RBCs	Mean number of units transfused	Follow-up period
Badami et al. 2022 [10]	Retrospective	2011 - 2019	New Zealand	2585	227	10 (median)	-
Chowdury et al. 2023 [11]	Retrospective	Jun 2020 – Jun 2021	Australia	1013	66	2 (median)	22 days (median)
Flommersfeld et al. 2018 [12]	Retrospective	Jan 2010 – Dec 2014	Germany	823	18	4	-
Luyten et al. 2023 [13]	Retrospective	Jan 2019 – Oct 2022	Belgium	1199	141	4.1	56 days
Pandey et al. 2020 [14]	Prospective	Dec 2014 – Dec 2018	India	20658	57	4.42	3 months
Williams et al. 2019 [15]	Retrospective	Oct 2015 – Sep 2018	United States	1198	72	5.9	6 months min.

Study quality assessment

The included studies were independently assessed for quality using the STROBE checklist summarised in Table 2. The studies fulfilled most of the criteria included in the STROBE checklist; this demonstrates significantly high quality of the included studies. Outcome data for some studies was reported as partially fulfilled as non-RhD alloimmunisation for our protocol was not part of those studies aim and therefore was not available to assess our secondary outcomes [10-12,14,15]. Follow-up periods for two studies were not specifically reported but the limitations and associated bias for this parameter was discussed in all studies [10-15].

Incidence of RhD alloimmunisation

RhD-negative patients given RhD-positive RBCs: All 6 studies were included in the meta-analysis for the incidence of RhD alloimmunisation of RhD-negative patients given RhD-positive red cells, this is demonstrated as a forest plot in Figure 2a [10-15]. The overall incidence of RhD alloimmunisation was found to be 16.4% (CI 95%, 5.6%-31.3%) with a p-value of<0.001 which makes this finding statistically significant. An I2 value of 91.68% (p<0.001) indicates that the studies included are considerably heterogeneous (Table 3).

Incidence of non-RhD alloimmunisation

RhD-negative patients given RhD-positive RBCs: 4 studies were included in the meta-analysis for the incidence of non-RhD alloimmunisation of RhD-negative patients given RhD-positive red cells, this is demonstrated as a forest plot in Figure 2b [12-15]. Badami et al. and Chowdury et al. did not release independent statistics for this parameter. The specificity of immunised antibodies includes one-of or a combination of anti-C, E, Jka and K. The overall incidence of non-RhD alloimmunisation of this cohort was found to be 7.3% (CI 95%, 2.8%-13.6%) with a p-value of<0.001 which makes this finding statistically significant. An I2 value of 53.94% (p<0.032) indicates that the studies included are moderately heterogenous.

Incidence of non-RhD alloimmunisation

Following transfusion of RhD-negative RBCs: 3 studies were included in the meta-analysis for the incidence of non-RhD alloimmunisation following the transfusion of RhD-negative red cells, this is demonstrated as a forest plot in Figure 2c [10,11,13]. Flommersfeld et al., Pandey et al. and Williams et al. did not release independent statistics for this parameter. The specificity of immunised antibodies was not particular to this cohort and therefore has not been reported. The overall incidence of non-RhD alloimmunisation for patients given RhD-negative red cells was 6.4% (CI 95%, 3.4%-10.3%) with a p-value of<0.001 which makes this finding statistically significant. An I2 value of 88.7% (p<0.001) indicates that the studies included are considerably heterogenous (Figure 2).

Table 2: Quality assessment of included studies using the STROBE checklist.

	Badami et al. 2022 [10]	Chowdury et al. 2023 [11]	Flommersfeld et al. 2018 [12]	Luyten et al. 2023 [13]	Pandey et al. 2020 [14]	Williams et al. 2019 [15]
Title and abstract	Y	Y	Y	Y	Y	Y
Objectives	Y	Y	Y	Y	Y	Y
Study design	Y	Y	Y	Y	Y	Y
Setting	Y	Y	Y	Y	Y	Y
Eligibility criteria	Y	Y	Y	Y	Y	Y
Study size	Y	Y	Y	Y	Y	Y
Outcome data	P*	P*	P*	Y	P*	P*
Discuss key results and limitations	Y	Y	Y	Y	Y	Y

Note: Y: Yes (criteria fulfilled), P: Partial (criterial partially fulfilled) and N: No (criteria unfulfilled)

Table 3: Analysis of immunological response to RhD-negative patients transfused with RhD-positive red blood cells.

Study	RhD-negative patients transfused with RhD-positive red cells		Patients transfused with RhD-negative red cells
	Alloimmunisation of RhD antibody	Alloimmunisation of non-RhD antibody(s)*	Alloimmunisation of non-RhD antibody(s)
Badami et al. 2022 [10]	0	-	95/1320
Chowdury et al. 2023 [11]	7	-	12/419
Flommersfeld et al. 2018 [12]	9	3**	-
Luyten et al. 2023 [13]	12	8**	39/380

Pandey et al. 2020 [14]	7	1	-
Williams et al. 2019 [15]	10	4**	-

Note: *Reported alloimmunisation of non-RhD antibodies include: Anti-C, E, Jka and K. **Alloimmunisation of non-RhD antibodies observed on patients with development of RhD antibody.

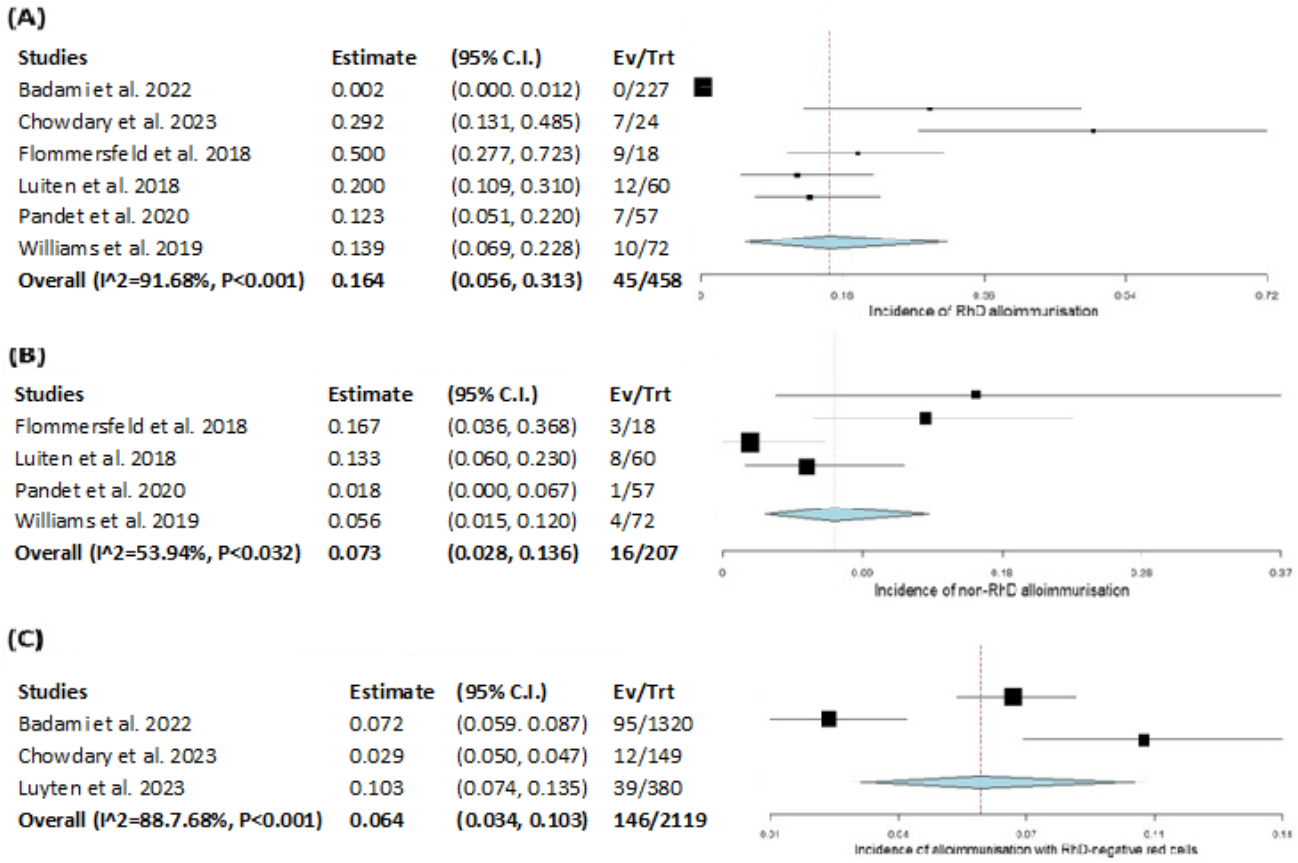

Figure 2: (A) Incidence of RhD alloimmunisation following RhD-positive red cell transfusions in RhD-negative patients; (B) Incidence of non-RhD alloimmunisation following RhD-positive red cell transfusions in RhD-negative patients; (C) Incidence of alloimmunisation following RhD-negative red cell transfusion.

DISCUSSION

RhD alloimmunisation

The clinical implications of the incidence of RhD alloimmunisation in HDFN and HTR are mostly circumvented through the use of protocols established to ensure that RhD-mismatched RBCs are not provided to women of child bearing age and paediatric males. In transfusion practise, this may not always be possible due to limited inventory of O RhD-negative RBCs or group specific RhD-matched RBCs. This is especially the case in trauma or massive transfusions where large volumes of RBCs are required.

Our study shows the incidence of RhD alloimmunisation in RhD-negative patients that receive at least one RhD-positive RBCs to be 16.4% (CI 95%, 5.6%-31.3%) which is concordant with a previously reported incidence of 14%-40% in trauma patients. Variability in RhD alloimmunisation have been reported when assessing different cohorts with a healthy population having a proportionally higher incidence of alloimmunisation (55%-74%) compared to immune-compromised (0%-8) and oncology patients (8%-16%), this is thought to be due to the immune system's inability to react to foreign bodies as readily as healthy individuals [16].

Studies by Yazer and Seheult suggest that the number of transfusions do not necessarily influence the incidence of RhD alloimmunisation, where the risk of RhD alloimmunisation is mostly attributed to the first RBC given in a multiple RBC transfusion [17,18]. This is supported by a study on the risk of alloimmunisation in massive transfusions versus regularly transfused individuals that showed negligible difference [19]. However, it has been reported that multiple transfusions of an RhD-positive RBC in a short amount of time have shown to increase the risk of RhD alloimmunisation [20].

We must consider that transfusion practises are adjuvant to surgical intervention in the prevention of anaemia in emergencies and that RBCs and other components used are chosen carefully. Laboratory guidelines for the provision of emergency uncross matched RBCs

include the collection of the patient's blood so that group and antibody matching can commence timeframes for testing and having matched allocations of blood components available in 30 minutes. Group specific issuing will decrease our risk of transfusion related incidences and also help to better manage our blood inventory. We never expect large amounts of uncross matched red cells to be issued but it is important to be ready and available.

Non-RhD alloimmunisation

While there are efforts to reduce transfusion reactions to the highly immunogenic ABO and Rh blood groups, it's important to remember all transfusions carry a risk of alloimmunisation to other non-RhD/ABO blood groups which may be clinically significant and have equal implications to HDFN and HTRs.

We found the incidence of non-RhD alloimmunisation when RhD-negative patients are given at least one RhD-positive RBCs to be 7.3% (CI 95%, 2.8%-13.6%) with antibody specificity to anti-C, E, Jka and K. The incidence of non-RhD alloimmunisation of all other patients given RhD-positive RBCs was 6.4% (CI 95%, 3.4%-10.3%), however, the antibody specificity of this target cohort was unable to be extrapolated. A study by Sood of multiply transfused patients was shown to have an incidence of alloimmunisation of 4.24% with reference to alloimmunisation rates of previous studies between 5%, 10% and even 20% [21]. A study on the specificity of antibodies on 1710 immunised individuals showed that the most common antibodies developed included anti-E (34%) and anti-K (24.9%) followed by anti-Fya, c and Jka (9%, 8.5% and 7.9% respectively) [22]. Incidence of non-RhD alloimmunisation in RhD-negative patients given RhD-positive RBCs and all other individuals given RhD-negative RBCs are comparable and similar to previously reported findings along with the antibody specificities. Our finding suggests that the incidence of alloimmunisation is the same independent of the RhD blood group and is further proof that when the RhD blood group is accounted for that the risks of transfusion remain the same.

Limitations

A study on RBC alloantibodies shows that antibody specificity had a large role in antibody formation and subsequent detection, while they found 16.8% who developed antibodies did so within 14 days after transfusion, it was shown that testing at intervals (1 month, 3 months, 6 months, and up to 5 years) still detected the development of new antibodies, this study however excluded RhD as it was said by the author to be common practice to match the RhD blood group in transfusions [22]. Despite that fact, the findings can be used to highlight that low incidence of alloimmunisation may be due to alloimmunisation being missed. Patient follow-up in our studies range from an average of 22 days to a 6-month minimum, with exclusion criteria and data loss resulting from failure to follow-up with patients. This limitation is also a caveat of retrospective study which forms a large portion of this analysis.

The eligible sample size of our study cohort is small at 1.6% of the total study sizes included. This is unfortunately a reflection of the population frequency of RhD-negative individuals and from further exclusions to define our sample population (exclusion of LTWB and RhD-positive platelet). Recommendations for the select use of RhD-positive RBCs may help us to collect more data for future analysis.

CONCLUSION

In conclusion, data collected from recent studies suggest the judicious usage of O RhD-positive blood group as emergency O uncross matched RBCs poses no additional risks compared to O RhD-negative only emergency issue RBCs. Further studies should be done to assess the outcomes of O RhD-positive RBCs given the new protocols and to continue monitoring the efficacy and improvement in blood inventory conservation.

CONFLICT OF INTEREST

Authors declare no conflicts of interest.

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