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Vaccine immune response, autoimmunity and morbidity after neonatal blood exchange transfusion

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ABSTRACT

Introduction: A blood exchange transfusion (BET) is most commonly performed to treat severe neonatal haemolytic disease. A distinct form of blood transfusion adverse reaction is transfusion-related immunomodulation. The purpose of our retrospective single-centre case-control cohort study was to investigate whether a blood exchange transfusion in the neonatal period provokes immunomodulation and affects humoral immune response to vaccination, morbidity and occurrence of autoantibodies.
Methods: Study subjects were 74 apparently healthy children, who were born at term as appropriate for gestational age and received four doses of diphtheria and tetanus toxoid vaccine. Forty-one received BET due to neonatal hemolytic disease and no other blood product afterwards, while 33 did not receive any blood products. Analysis of diphtheria, tetanus and autoimmune antibodies was performed and their medical records were analyzed for infectious, allergic, cancerous and autoimmune diseases.
Results: A clearly exaggerated immune response to diphtheria (1.016 IU/mL, 95% confidence interval (CI) 0.662–1.369 IU/mL vs. 0.515 IU/mL, 95% CI 0.363 to 0.626 IU/mL, P = 0.011) and slightly exaggerated immune response to tetanus vaccine (1.798 IU/mL, 95% CI 1.180–2.416 IU/mL vs. 1.036 IU/mL, 95% CI 0.398–1.673 IU/mL, P = non-specific) were observed in BET subjects. A propensity towards autoimmunity (25.8% vs. 12.5%, P = non-specific) was observed in BET subjects. However, BET in the neonatal period did not influence the occurrence of bacterial, childhood viral diseases with exception of varicella (43.9% vs. 21.2%, P = 0.040), autoimmune and cancer diseases.
Conclusion: BET impacted humoral immune response to diphtheria and tetanus vaccine and occurrence of autoimmune antibodies, but did not affect morbidity and the occurrence of autoimmune diseases. These effects could be related to massive antigenic load of BET and an accelerated priming of immune cells and consequent immunomodulation.

1. Introduction

A blood exchange transfusion (BET) involves gradual removal of patient's blood and simultaneous isovolumetric replacement with fresh donor blood. In the neonatal period this procedure is most commonly performed to treat severe neonatal haemolytic disease (NHD).

A distinct form of blood transfusion adverse reaction is transfusion-related immunomodulation (TRIM), defined as a constellation of laboratory features in recipients of various blood components in the transfusion product, including plasma, white and red blood cells (RBC(s)). As the exact mechanism of TRIM has still not been fully understood, several hypotheses propose different cellular and molecular pathways, leading to impaired natural killer cell function, decreased neutrophil function, decreased monocyte/-macrophage function, defective antigen presentation and suppressed T lymphocyte proliferation and function [1–8]. These mechanisms could be triggered by numerous soluble and insoluble mediators, released from white blood cells (WBC(s)), RBC(s) and platelets. Some of the most commonly proposed mediators of TRIM are soluble Fas-ligand (Fas-L), transforming growth factor ß (TGF-ß), human leukocyte antigen (HLA) molecules, cytokines,

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cell-free haemoglobin, haeme, iron, ubiquitin, bioactive lipids and extracellular vesicles [2–7,9–15].

To our knowledge, there are only scarce studies investigating TRIM after red blood cell transfusion in the neonatal period and no studies exploring TRIM after BET in this life period. Therefore, the purpose of our study was to determine whether BET in the neonatal period affects humoral immune response to vaccination, occurrence of autoantibodies and morbidity.

2. Methods

2.1. Study design and participants

This retrospective single-centre case-control cohort study was conducted in a tertiary referral neonatal department. Study subjects were 74 apparently healthy children, who were born at term as appropriate for gestational age and received four doses of diphtheria and tetanus toxoid vaccine. Forty-one (18 male, 23 female) received BET due to NHD and no other blood product afterwards, while 33 (18 male, 15 female) did not receive any blood products.

According to national immunization schedule, all study subject received four doses of combined diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, *Haemophilus influenzae* type b vaccine (Infanrix-IPV + HIB, GlaxoSmithKline Biologicals, Rixensart, Belgium), containing 30 I.U. of diphtheria toxoid and 40 I.U. of tetanus toxoid. Healthy controls were vaccinated at 3, 4–5, 6 and 12–24 months of age, and BET subjects at 6, 7–8, 9 and 15–24 months of age. Medical records of all subjects were analysed for their past and current infectious, allergic, cancerous and autoimmune diseases and completed vaccinations. Analysis of autoimmune and specific diphtheria and tetanus antibodies was performed. Blood sampling for the purpose of the study was performed simultaneously with the routine blood testing at the time of the regular well child check-up.

The study was approved by The National Medical Ethics Committee. A written informed consent was obtained after the nature and possible consequences of the study had been fully explained to the parents or guardians of the children who served as subjects of the investigation before their inclusion in the study.

2.2. Blood exchange transfusion

Standard double volume BET was performed in all 41 study subjects, i.e. a gradual 20 ml exchange of twice the volume of the newborn's blood with a reconstitution solution of fresh (aged less than five days from the collection) packed RBC(s) and plasma with final haematocrit around 55%. All transfused blood products were leukoreduced before storage (six hours after collection) and irradiated just before transfusion. Leukoreduction was achieved by filtration of RBC(s) and a filtered unit of packed RBC(s) finally contained less than 5×100.000 of donor leukocytes. The irradiation with Cs-137 at a dose of 30 Gy for five minutes was done just before BET in order to inactivate T lymphocytes.

2.3. Analysis and measures

Venous blood samples were obtained from the study subjects. Antinuclear antibodies (ANA) were determined in serum samples using a standard indirect immunofluorescence technique on HEp-2 cells (Immuno Concepts, Sacramento, CA, USA) [16]. ANA serum titers at >1:80 were considered positive. Antibodies against extractable nuclear antigens (anti-ENA) were detected in serum samples by counterimmunoelectrophoresis in agarose, as previously described [16]. For the detection of anti-double stranded DNA antibody (anti-dsDNA) in samples of venous blood containing no anticoagulants the in-house FARR-RIA method, established in the Immunology laboratory since 1976, following the first published protocol with some adaptations was used [17,18]. Anticardiolipin antibodies (aCL) and anti-ß$_2$ glycoprotein I antibodies (anti-β_2 GPI) were detected by a solid-phase in-house ELISA as described [19,20]. Tetanus toxoid and diphtheria toxoid specific immunoglobulin G (IgG) was determined in serum samples by IgG-specific enzyme-linked immunosorbent assay (ELISA). Serum concentrations >0.1 IU/mL were considered protective.

2.4. Statistical analysis

Data were analysed using IBM SPSS Statistics Version 22.0 software (IBM Corp, Armonk, NY, USA). We performed t tests, F tests, Chi-square tests, Fisher's exact test, Leven's test and Mann – Whitney *U* test. The non-parametric tests (Mann – Whitney *U* test and Fisher test) were used when the normal distribution assumption was not met and where the expected count in crosstab cell was less than 5. Statistical significance level was set at 0.05.

3. Results

The time-period of the study was between December 2010 and March 2017. During this period 74 study subjects were enrolled. All 41 subjects from the experimental group received BET due to NHD. BET was performed at a mean age of 1.7 ± 0.9 days. In 2 (4.9%) cases, BET was performed twice due to severe NHD. All BET procedures were completed without complications. No intravenous immunoglobulin treatment was used in any study subject. The occurrence of autoantibodies and immune response to vaccine antigens was assessed in 55 study subjects, as 19 refused the blood withdrawn. Medical records of all study subjects were analysed.

3.1. Immune response to vaccine antigens

There was an obvious twofold increase in the lowest, mean and highest measured concentrations of diphtheria antibodies in BET subjects. Seven BET subjects (22.5%) and no healthy controls presented with antibody concentrations above 2.0 IU/ml. All subjects from both groups presented with sufficient protective antibody concentrations above 0.1 IU/ml after four vaccine doses.

The humoral immune response to vaccination with tetanus toxoid did not show important overall differences in specific antibody serum concentrations between BET subjects and healthy controls. All subjects from both groups presented with sufficient protective antibody concentrations above 0.1 IU/ml after four vaccine doses. Comparing the lowest, mean and the highest measured concentrations revealed two- to threefold increase of tetanus antibodies in BET subjects. Eight BET subjects (33.3%) and 2 healthy controls (3.7%) presented with antibody concentrations above 2.0 IU/ml. Three BET subjects (9.7%) and no healthy controls presented with diphtheria and tetanus antibody concentrations above 2.0 IU/ml. Five BET subjects (16.1%) and no healthy controls ($p = 0.035$) presented with any autoantibody and diphtheria or tetanus antibody concentrations above 2.0 IU/ml. Serum diphtheria and tetanus IgG concentrations in BET subjects and healthy controls are presented in Table 1.

3.2. Occurrence of autoantibodies

The results did not show correlation between BET and the occurrence of autoimmune diseases. However, propensity towards autoimmunity was observed in the group of BET subjects, who presented with heterogeneous autoantibodies such as ANA, aCL and anti-ß$_2$ GPI. Nine BET subjects (29.0%) and 3 healthy controls

Table 1
Serum diphtheria and tetanus toxoid IgG concentration in BET subjects and healthy controls.

Group	BET subjects (N = 31)	Healthy controls (N = 24)	P value
Gender, male/female	14/17	15/9	NS
Age in years, mean (range)	5.3 (1.6–9.7)	5.0 (1.6–7.8)	NS
Serum diphtheria toxoid IgG concentration (IU/mL), mean (95% confidence interval)	1.016 (0.662–1.369)	0.515 (0.363–0.662)	**0.011**
Serum tetanus toxoid IgG concentration (IU/mL), mean (95% confidence interval)	1.798 (1.180–2.416)	1.036 (0.398–1.673)	NS

Legend: NS – Non-significant.

(16.7%) presented with any autoantibody. Two different autoantibodies (ANA and aCL) were found in two BET subjects (6.5%) and in one (4.2%) healthy control. The occurrence of autoantibodies is presented in Table 2.

3.3. Occurrence of infectious, allergic, autoimmune and cancerous diseases

BET in the neonatal period did not influence occurrence of bacterial infections, including omphalitis, neonatal and postneonatal sepsis, pertussis and scarlet fever. Likewise, BET did not influence the incidence of childhood viral diseases such as exanthema subitum, erythema infectiosum, rubella, mumps, herpetic gingivostomatitis and infectious mononucleosis. On the other hand, BET subjects had two times higher incidence of varicella-zoster virus (VZV) infection. The evaluation of allergic diseases, including food allergy, asthma, allergic dermatitis, drug and vaccine allergy, did not show any differences between the two groups. No cases of any kind of cancer were found among BET subjects and their controls. The occurrence of infectious, allergic, autoimmune and cancerous diseases in BET subjects and healthy controls is presented in Table 3.

4. Discussion

The study evaluated the influence of BET in the neonatal period on immune response to vaccination, occurrence of autoantibodies and morbidity.

A remarkable finding was a clearly better immune response to diphtheria toxoid vaccine and two- to threefold higher tetanus toxoid antibody concentrations in BET subjects. All study subjects from both groups received four doses of diphtheria and tetanus vaccines and there was no important difference in age between groups. However, BET subjects were on average 117 days older, but they also started their vaccination schedule approximately three months later, so no important age effect was involved. Better immune response to toxoid vaccine could be related to TRIM as the enormous antigenic load after BET might lead to accelerated immune priming and more efficient immune response after multiple doses of both vaccines, compared to healthy controls. To our knowledge, no previous study investigated vaccine response in the light of possible immunomodulation after transfusion, especially BET. This research field therefore awaits further investigation.

The study showed that the occurrence of autoimmune diseases was not affected by BET, but a difference between the two groups was noted in the occurrence of autoantibodies. BET subjects presented with higher occurrence of autoantibodies as well as with an exaggerated immune response to diphtheria and tetanus vaccine. The co-occurrence of autoantibodies and vaccine toxoid antibodies in BET subjects could be explained by early priming of immune cells by a massive antigenic load of BET and the consequent autoimmune phenomena and more efficient immune response to vaccines. As the study is lacking a follow-up evaluation of autoantibodies, the answer whether these antibodies were persistent or not is missing. All the subjects were without any acute disease at the time of testing, so the causes for temporary presence of autoantibodies such as viral infections or drugs were less likely. The absence of similar studies makes interpretation of our results difficult, but so far BET and possibly TRIM were not associated with the development of autoimmune phenomena. Transfusion of RBC(s) could lead to the formation of autoantibodies due to alloimmunization with donor RBC(s) and further to autoimmune haemolytic

Table 2
Occurrence of autoantibodies in BET subjects and healthy controls.

Group	BET subjects (N = 31)	Healthy controls (N = 24)	P value
Gender, male/female	14/17	15/9	NS
Age in years, mean (range)	5.3 (1.6–9.7)	5.0 (1.6–7.8)	NS
Autoantibody, presence:			
Any autoantibody	8 (25.8%)	3 (12.5%)	NS
Antinuclear antibody	5 (16.1%)	2 (8.3%)	NS
Anti-extractable nuclear antigen antibody	0 (0.0%)	0 (0.0%)	NS
Anti-double stranded DNA antibody	0 (0.0%)	0 (0.0%)	NS
Anticardiolipin antibody	3 (9.6%)	3 (125%)	NS
Anti-β_2 glycoprotein I antibody	2 (6.5%)	0 (0.0%)	NS
Two different autoantibodies	2 (6.5%)	1 (4.2%)	NS

Legend: NS – Non-significant.

Table 3
Occurrence of infectious, allergic, autoimmune and cancerous diseases in BET subjects and healthy controls.

Group	BET subjects (N = 41)	Healthy controls (N = 33)	P value
Gender, male/female	18/23	18/15	NS
Age in years, mean (range)	5.3 (1.6–9.7)	5.0 (1.6–8.1)	NS
Infectious diseases			
Omphalitis	0 (0.0%)	0 (0.0%)	NS
Neonatal sepsis	0 (0.0%)	0 (0.0%)	NS
Postneonatal sepsis	0 (0.0%)	0 (0.0%)	NS
Pertussis	1 (2.4%)	0 (0.0%)	NS
Scarlet fever	2 (4.9%)	1 (3.0%)	NS
Exanthema subitum	6 (14.6%)	14 (42.4%)	NS
Erythema infectiosum	5 (12.2%)	3 (9.1%)	NS
Rubella	0 (0.0%)	0 (0.0%)	NS
Mumps	1 (2.4%)	0 (0.0%)	NS
Herpetic gingivostomatitis	5 (12.2%)	0 (0.0%)	NS
Varicella	18 (43.9%)	7 (21.2%)	**0.040**
Infectious mononucleosis	0 (0.0%)	0 (0.0%)	NS
HIV infection	0 (0.0%)	0 (0.0%)	NS
Allergic diseases			
Food allergy	5 (12.2%)	6 (18.2%)	NS
Asthma	1 (2.4%)	1 (3.0%)	NS
Allergic dermatitis	0 (0.0%)	0 (0.0%)	NS
Drug allergy	3 (7.3%)	1 (3.0%)	NS
Vaccine allergy	1 (2.4%)	0 (0.0%)	NS
Cancer	0 (0.0%)	0 (0.0%)	NS
Autoimmune diseases			
Diabetes mellitus type I	0 (0.0%)	0 (0.0%)	NS
Thyroid autoimmune disease	0 (0.0%)	0 (0.0%)	NS
Connective tissue autoimmune disease	0 (0.0%)	0 (0.0%)	NS
Inflammatory bowel disease	0 (0.0%)	0 (0.0%)	NS
Liver autoimmune disease	0 (0.0%)	0 (0.0%)	NS

Legend: NS – Non-significant.

anaemia [21], so further research of autoimmunity after transfusion should be conducted.

Morbidity due to bacterial infections was not influenced by BET in the neonatal period. Several studies, though, report a higher incidence of bacterial infections as a consequence of TRIM, especially after surgery and in critically ill patients, and the risk of infection increases incrementally with each unit of blood transfused [22,23]. No subject in our study was critically ill and everyone received only one BET fulfilling strict safety criteria and no further blood products. These might be a sufficient reason for minimizing the risk of TRIM and consequent bacterial infections.

In our study, BET subjects had two times higher incidence of VZV infection. This could be partly explained by on average three months older BET subjects, resulting in possibly longer exposure time, though there was no important overall age difference between the study and control groups. Exposure to VZV also increases if siblings are present and if the subject or siblings attend nursery, but no difference in these factors was noticed in our study groups. Severe VZV infections occur more commonly in immunocompromised persons with deficient innate and/or adaptive immune response, either congenital or acquired [24–28]. Since all varicella cases in both groups were self-limiting and without serious complications, we assumed that the intergroup difference in varicella incidence did not implicate any important immunodeficiency.

The occurrence of other investigated viral diseases was not influenced by BET. This also included infectious mononucleosis, a disease caused by Epstein-Barr virus (EBV), which has been noted to cause transfusion-associated illnesses in susceptible recipients of blood from EBV seropositive donors. Since all RBC(s) components used for BET in our study were of unknown EBV status, the virus could potentially be transferred, but as leukoreduction was found to be an effective means of EBV removal from RBC(s) components, this complication was highly unlikely [29]. TRIM and a consequent increased risk of viral infection was proven for cytomegalovirus (CMV) and human immunodeficiency virus (HIV) infection and no other viral diseases [9,30]. There were no cases of HIV infection in our study subjects. CMV infection, which has usually very unspecific clinical course, was not evaluated in our study.

The evaluation of allergic diseases showed no difference between the two groups. Our hypothesis of immunomodulation in BET subjects and possibly altered incidence of allergic diseases was not confirmed. As the literature review shows that this topic is still unexplored, further studies are required to obtain more data and clearer conclusions. The same was true for cancer occurrence since no cases were found in both study groups. As the overall cancer incidence is low in children, this came as no surprise in such a small study group. Though, TRIM is related to cancer treatment outcome and reoccurrence, probably due to the interplay of several different factors, such as residual leukocytes and platelets, cytokines, TGF-ß an extracellular vesicles [31].

The safety profile of transfused blood components for newborns, especially for BET, is particularly high. One of such safety precautions is almost exclusive use of fresh RBC(s). This diminishes biochemical, structural, and physiological changes of RBC(s) membranes and release of microparticles (cell-free haemoglobin, haem, ubiquitin, iron, extracellular vesicles), collectively known as a storage lesion, which increases with storage time [32]. Our study subjects received only fresh RBC(s) units, aged less than five days from the collection, therefore we assumed that the amount of potentially transfused amount of microparticles was low and the consequent immunomodulation less probable.

An important immunological aspect of BET in our study was prestorage leukoreduction and gamma irradiation. Leukoreduction by filtration reduces WBC(s) to minimum, and if this process is done before RBC(s) storage, the amount of accumulated TRIM mediators such as, Fas-L, TGF-ß and HLA are drastically reduced, too. Both mechanisms diminish possible immunomodulatory effects in blood component recipients.

Persistence of donor leukocytes in blood recipients, termed transfusion-associated microchimerism (TA-MC), might also have immunomodulatory impact in blood recipients manifesting as transfusion-associated graft versus host disease and autoimmunity [33,34]. The studies confirming TA-MC were conducted predominantly in adult trauma patients and data on TA-MC in paediatric and neonatal populations are lacking. Newborns could potentially represent a high risk group for the development of TA-MC due to their immature immune system and transfusion of fresh blood components of shorter storage time, which could contain viable donor leukocytes. Leukoreduction itself was demonstrated ineffective in prevention of persistent TA-MC [35], but a combination of leukoreduction and gamma irradiation of cellular blood components was proven effective in the prevention of persistent TA-MC both in paediatric and adult patients [36]. Pre-transfusion gamma irradiation of blood components is primarily intended to inactivate cellular blood components, particularly T lymphocytes that rest in the leukoreduced blood components and prevent their proliferation [37,38]. To achieve this effect, a dose of at least 25 Gy is needed. As all blood components for BET received by subjects of our study were leukoreduced and gamma irradiated, we presume that the risk for development of TA-MC in our cohort was very low.

The weakness of the study represents the fact that, due to restrictions of blood samples, our study focused mainly on humoral immunity and autoimmunity and did not examine cellular immune responses.

5. Conclusions

The present study provides an insight into possible immunomodulation after BET in the neonatal period. Based on our results, we conclude that BET impacts humoral immune response to vaccination with diphtheria and tetanus toxoid and the occurrence of autoimmune antibodies but does not affects morbidity and the occurrence of autoimmune diseases. The observed exaggerated immune response to toxoid vaccines and the occurrence of autoantibodies in BET subjects could be related to a massive antigenic load of BET which might lead to early and accelerated priming of immune cells and consequent immunomodulation. The vaccination with toxoid vaccines in BET subjects is therefore efficient and at least comparable to vaccine efficacy in healthy subjects. Our recommendation is that BET subjects should follow official vaccination schedule for healthy children for these two vaccines. The efficacy of other types of vaccines in BET subjects is yet to be established. To further explore possible immunomodulatory effects of TRIM after BET in the neonatal period, a prospective clinical trial is required, focusing both on classical and yet unexplored manifestations of TRIM, including both humoral and cellular immunity and autoimmunity.

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Contributors

All of the authors contributed to the conception and design of the study. GN collected, analysed and interpreted the data and

wrote the manuscript. AI, ANK and SČ carried out laboratory analyses. DPP and TA helped to interpret the results and critically reviewed the manuscript. All of the authors revised the manuscript and approved the final version submitted for publication.

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Declaration of Competing Interest

None declared.

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