



Deliverable 5.3: Recommendations on protection of plasma donors

Work package: WP 5 – Plasma donor protection best practices

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2. INTRODUCTION

As plasma donation is scaled up across Europe, it is of paramount importance to ensure that plasma donation is safe prompting the questions:

- Which preventive measures should be implemented?
- How much plasma can be collected per donation?
- What is the optimal interval between two donations?
- Should there be an annual limit of plasma collected per donor?
- Should there be a lower limit for concentrations of total plasma protein and/or IgG?
- Which selection criteria are necessary to prevent adverse events?
- Should special attention and strategies be taken to mitigate the risk of adverse events among specific groups of donors?

Plasma donor protection practices should be evidence-based to mitigate adverse reactions to plasma donation. Safe donation will ensure that the scale-up of plasma donation is ethically sound and can also help in the recruitment of donors and subsequently secure the supply.

The objective of WP5 of the SUPPLY project is to facilitate evidence-based plasma donor protection practices. The specific aims are to:

- Collect information on current plasma donor protection practices (T5.1, D5.1)
- Evaluate the available scientific evidence on plasma donor protection practices (T5.2)
- Describe requirements for a support tool on standardized donor vigilance data to be collected (T5.3, D5.2)
- Formulate (evidence-based) recommendations (T5.4, D5.3)

We surveyed the inventory of existing plasma donor protection practices. We received 18 complete responses, constructed a 'modal' donation procedure based on the responses, and performed an analysis report (D5.1). We also reviewed the literature to identify evidence on plasma donation safety, plasma donation-related adverse events, and plasma donor protection practices. The scoping review provided an overview of the (types of) available evidence and evidence gaps, which were visualized in an evidence gap map. The scoping review was followed by a systematic review of the impact of frequent plasmapheresis on adverse events, cardiovascular health, and protein levels in plasma donors. The survey on the inventory of existing plasma donor protection practices and the identified evidence gaps provided input for the support tool on standardized donor vigilance data to be collected (D5.2).

In this report, we outline the results of tasks 5.1 and 5.2, and for task 5.3 (D5.2) subsequently provide recommendations on future policies and research to enhance plasma donor health protection. This report reflects the view of a majority of WP5 members, while two WP members dissent regarding the recommended plasma donation frequency.

3. BACKGROUND

3.1. Collect information on current plasma donor protection practices (T5.1, D5.1)

Survey

We aimed to take inventory of the range of practices that are used across Europe (and beyond) to protect the health of plasma donors regarding plasmapheresis for fractionation. Therefore:

- We created a survey based on a previous International Plasma and Fractionation Association (IPFA) survey. The survey included questions about plasma collection purposes, donor selection criteria, donation procedures, donor vigilance and registration, and studies related to plasma donor protection.
- The outcomes were documented in an analysis report (D.5.1 May 2023 by MS, KvdH) that inventoried existing plasma donor protection practices.

Responses

We received eighteen complete responses from 17 countries: Norway, Latvia, Canada, England, Denmark (two blood centers), Finland, Germany, the USA, Sweden, France, Lithuania, Scotland, Croatia, Estonia, Malta, Luxembourg, and the Netherlands. We excluded two organizations that only collected recovered plasma.

Donation frequency

The maximum allowed number of annual plasma donations ranges from 12 (Luxembourg) to 104 times (USA). The minimum donation interval ranges from two to 28 days.

Selection criteria

All organizations use most of the following criteria to determine donor eligibility: suitability (e.g., veins, donors has to be able to withstand the procedure), weight/height/blood volume, hemoglobin level (Hb) or hematocrit, use of medication or drugs, cardiovascular events or disease, malignancies, pregnancy, infectious and autoimmune diseases, and blood pressure.

Donation procedure

A minimum of 10 different machines are in use. Every organization sets a cap on donation volume, ranging from 400 to 896 ml. Among these 18 organizations, 12 employ sex, weight and/or height data to determine the collection volume. Six organizations use replacement fluids (saline infusion). All organizations use citrate-based anticoagulants, yet with different percentages of citrate (ranges from 3% to 8%). Eleven organizations use standard settings for the draw flow rate (ranges from 40 to 120 ml/min) and for the return flow rate (ranges from 30 to 150 ml/min) based on the advice by the machine's manufacturer.

Adverse events

The most frequently used methods for preventing adverse events are advice on water loading or hydration before, during, and after the donation (12 organizations), well-trained staff (7 organizations), and special attention for new donors (5 organizations). All organizations have a donor vigilance system in place. The majority of organizations can register multiple adverse events per donor or donation and record the grade or severity of adverse events. Five organizations registered potential long-term adverse events, such as skin and vein fibrosis (4 organizations) and lowered bone density (1 organization).

Testing

All 18 organizations assess total protein levels, although at differing intervals: Twelve organizations have a lower limit (ranges from 50 to 63 g/l) and seven have an upper limit (ranges from 82 to 100 g/l). Almost all organizations make case-by-case decisions on temporary or permanent deferral. Seven organizations test total IgG levels, at differing intervals: Five organizations have a lower limit (ranges from 4 to 7 g/l) and three organizations have an upper limit of 16 g/l. Twelve organizations test for irregular blood group antibodies. Eight organizations perform additional tests, e.g., blood type, AST and ALT, ferritin (once per year), HLA antibodies (once for women), and platelet, red cell, and leucocyte counts.

Crisis

Regarding crisis preparedness, seven organizations have contingency plans in place to ensure adequate plasma supply. Six did not, and 3 responders were unsure whether their organization had such plans.

New studies

Seven organizations are planning, conducting or have recently finished studies. Most of them are related to the effects of procedural changes, donation intervals/frequency, or donor characteristics on parameters such as adverse events, protein levels, or the occurrence of infection.

'Modal' donation procedure

We constructed a 'modal' donation procedure based on the interpretation of data gathered from the survey responses:

The modal plasma donation is collected via apheresis from donors aged 18-65 with a minimum weight of 50kg. Donors can donate every 14 days, but once a month seems ideal. Hemoglobin is tested before every donation using a fingerprick and a photometer, and donors with values < 125 g/l (women) or < 130 g/l (men) are temporarily deferred. To prevent adverse events, the organization informs donors about the importance of hydration before, during, and after the donation, and offers refreshments on-site. Flow rate settings of the apheresis machines are usually determined mostly by the manufacturer, and may also be adjusted to prevent adverse events. For anticoagulation, either citrate dextrose-A (3% citrate) or tri-sodium citrate (4% citrate) is used, with a ratio of 1:16. Total protein levels are tested at least once a year and IgG levels 1-4 times per year; both may lead to temporary deferral. The presence of irregular antibodies is tested at every first donation and after every possible immunization event (e.g., pregnancy, transfusion), and positive results lead to permanent deferral for plasma donation. Finally, adverse events are registered with an assessment of grade and imputability.

3.2. Evaluate the available scientific evidence on plasma donor protection practices (T5.2)

We reviewed the literature to identify evidence on plasma donation safety and plasma donation-related adverse effects and identified evidence gaps.

We performed a scoping review to create an overview of available evidence (gaps) underlying current

plasma donation practices, including safety, health effects, and adverse events occurring during or after plasmapheresis donation. The scoping review mapped research studies that investigated the following aspects of plasma donation:

- Adverse events occurring during/after plasmapheresis
- The effects of preventive measures on donor safety and health
- The association between donation count/frequency and donor safety or health
- Long-term follow-up of plasmapheresis donors

In addition, the included literature was visualized in an evidence gap map. The scoping review was followed by a systematic review of the impact of frequent plasmapheresis on adverse events, cardiovascular health, and protein levels in plasma donors.

3.2.1. Scoping review and evidence gap map

The scoping review is published in Vox Sanguinis [1] and published as a preprint on medRxiv [2] (by HvR, NS, TD) titled *Safety and protection of plasma donors: A scoping review and evidence gap map*.

Methodology

To obtain an overview of the current scientific literature regarding the safety of plasmapheresis donation, a systematic search was performed. We searched for eligible studies on 13 October 2022. A [study protocol](#) was published on the Open Science Framework ([OSF](#)) before finalizing the screening process.

Overview of available evidence (gaps)

We identified 94 research articles and 5 registrations investigating adverse events and/or health effects in plasmapheresis donors. These were published between 1956 and October 2022. The full reference list is published on medRxiv [2]. The included literature is visualized in an evidence gap map (see Figure 1 for a screenshot and <https://cebap.org/storage/cebap/schroyens-2023-egm.html> for an interactive version).

Figure 1. Screenshot of the evidence gap map



Among the included studies, 38 studies assessed adverse events and 77 studies included health effects. Around 90% were observational studies. Of those, 57 were controlled observational studies and 33 were uncontrolled observational studies, monitoring a group of donors (before and) after donation(s). Most of the studies were performed in Europe (55%) and the USA (20%).

Factors studied about donor health and the occurrence of adverse events included donor characteristics such as age, body weight, or sex (n=27), the cumulative number of donations (n=21), donation

frequency (n=11), plasma collection device or program (n=11), donor status (first-time vs. repeat) (n=10), donation volume per session (n=8), and preventive measures (n=2). Some of the frequently studied adverse events were vasovagal reactions and phlebotomy injuries.

Intermediate-term health effects of plasma donation included effects on physiological parameters (e.g., blood pressure, heart rate), haematological parameters, iron metabolism, coagulation factors, total protein, albumin, immunoglobulin (mostly IgG), and other parameters.

Thirty-six studies assessed the effects of plasma donation after 1 week or longer. Of those, 12 assessed adverse events and 27 assessed health effects (e.g., iron metabolism, coagulation, total protein, albumin and IgG). Five studies assessed the effect of a single plasma donation during a follow-up period of 1 week to 1 month. Thirty-two studies assessed the effect of multiple donations during a follow-up period of 1 week or more.

3.2.2. Systematic review

Based on the results of the scoping review, we decided to analyze, synthesize and critically appraise the best available evidence that investigates the impact of plasma donation frequency on adverse events, cardiovascular health, and protein depletion.

In the scoping review we did not identify any existing systematic reviews and this ongoing systematic review on donation frequency is presumably the first one to focus on the impact of plasmapheresis on donor health.

The research question was structured according to the PICO framework (Patient-Intervention-Comparison-Outcome): What is the impact of plasmapheresis frequency (I) on the safety or health (O) of healthy donors (P)?

Methodology

The protocol was planned and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist extension for protocols (PRISMA-P) [3] and registered in the PROSPERO database (<https://www.crd.york.ac.uk/prospero/>, ID: 405419) (by HVR, NS, TD) under the title *The impact of frequent plasmapheresis on adverse events, cardiovascular health, and protein levels in plasma donors: Protocol for a systematic review of controlled experimental and observational studies*. We searched for eligible studies in May 2023.

Evidence conclusions

We included:

- four observational studies (cohorts): 3 published in the 1970s-1980s and 1 study from 2013 [4-7]
- two experimental studies (1 non-randomized controlled trial (RCT) and 1 RCT) [8,9]
- one ongoing experimental study (RCT) [10]

According to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach [11], the initial quality of the 4 observational studies was considered low [4-7]. Due to methodological flaws and small sample sizes, the quality was downgraded to very low. This makes any effect estimates highly uncertain [12].

The two experimental studies were a Canadian non-RCT from 1993 and a Belgian RCT from 2023.

- In the Canadian study among repeated, voluntary plasma donors a donation frequency of once per week was compared with a donation frequency of once every 2 weeks (or longer) for 6 months. They donated 500-600 ml of plasma per donation. Total protein, IgG, IgA, and IgM were measured.

Results showed that the average levels of total protein and IgG were statistically significantly lower in the weekly donation group compared with the bi-weekly donation group, however the concentrations remained within the normal range. In the weekly donation group mean total protein level fell significantly during the first 3 months, but levels almost returned to baseline levels at the end of the study. They found no statistically significant difference from the initial levels during monthly measurements of IgG, IgA and IgM among any of the groups [8].

- In the Belgian RCT, 72 voluntary plasmapheresis donors were randomly assigned to one of four donation frequency groups for a period of 12 weeks: very high frequency (VHF, 2 donations per week), high frequency (HF, 3 donations per month), low-frequency (LF, 1 donation per month), and placebo (participants had a sensation of undergoing a plasma donation, once per month). Adverse events (categorized according to international standards [13]), (non-)biochemical cardiovascular health markers and different protein levels were assessed. They found adverse events in the VHF and HF groups: 5 haematomas (3 in HF and 2 in VHF), 5 vasovagal reactions (1 in HF and 4 in VHF), and 6 anaemic events in the VHF group. Hb levels were reduced in the VHF group compared to the LF and placebo groups, but levels were within the normal range. Ferritin levels were reduced in the HF and VHF groups compared to the LF and placebo groups, and this difference was considered as clinically relevant since mean ferritin levels fell below the normal limit. IgG levels were reduced in the VHF and HF groups compared to the placebo group. For the VHF, IgG levels dropped below the lower limit of 6 g/l. No differences were observed for IgA and IgM levels. Albumin levels were reduced in the VHF group, but levels were within the normal range. Several cardiovascular health markers were assessed (glycaemia, HbA1c, insulinaemia, total cholesterol, blood pressure, body composition, and exercise-related parameters). Although glycaemia and HbA1c were reduced in the HF and VHF groups, all observed differences were considered to be clinically irrelevant.

In summary, in this study, few minor adverse events and no major adverse events were reported in the HF and VHF groups. Very high-frequency plasmapheresis (twice per week) resulted in a large reduction in ferritin and IgG levels. (Very) high-frequency plasmapheresis resulted in little to no difference in albumin levels and cardiovascular health markers [9].

The initial quality of the evidence of experimental studies was high because this type of trial is considered as the gold standard to assess causality. However, the certainty of the evidence from the two included experimental studies was downgraded due to methodological limitations and limited sample sizes, which finally resulted in low-certainty evidence. This means that further research is needed because future research studies are very likely to have an important impact on our confidence in the estimate of effect and will likely change the estimate.

3.3. Developing a support tool for the standardized collection of donor vigilance data (T5.3, D5.2)

Donor vigilance systems for recording plasma-related adverse events are established in many EU member states. To evaluate and compare data from different organizations, it is necessary to collect the required data in a defined, uniform way. The product of this task (D5.2 by TB, TT, KB) includes a description of requirements for a tool to record donor vigilance data, based on the collected information on current plasma donor protection practices and the gap analysis.

This haemovigilance system will provide a standardized classification of adverse events and will make

suggestions to correlate these data with donor, donation, and equipment data. This haemovigilance system can build the basis for an EU-wide IT-integrated solution and database. The support tool we will design is the first approach to lay the foundations for the further development and design of an EU-wide collection of data, risks and side effects.

4. LESSONS LEARNED AND RECOMMENDATIONS

The objective of our project is to facilitate evidence-based plasma donor protection practices. The scoping and systematic reviews highlight the need for more controlled experimental studies that investigate both adverse events and health effects related to plasma donation and associated factors, in the short as well as the long term.

Even though research within the field of plasmapheresis donor safety has expanded in recent years, most studies are observational. Observational studies face challenges in detecting the long-term effects of plasma donation due to the healthy donor effect, wherein only eligible and healthy donors have the surplus to report for donation. Nonetheless, an observational design is the only approach to assess long-term effects of plasma donation. Consequently, to establish conclusive evidence RCTs may be necessary.

While some experimental trials exist, conclusions are hindered by methodological limitations and limited sample sizes as illustrated in the systematic review.

We identified several important gaps categorized as either evidence gaps or procedural gaps, as listed and further elaborated upon below:

Evidence gaps:

1. preventive measures including the impact of the technologies used on the safety of donors
2. selection criteria including total plasma protein levels, IgG, and Hb
3. different donation frequencies and the effect on donor safety
4. long-term health effects of plasma donation

Procedural gap:

5. the registration of adverse events

1) In the survey, we observed that plasma donor protection practices vary between plasma collection centers. Different apheresis machines with different settings are used, the effect of which is (largely) unknown. Not all centers have implemented special attention and strategies to mitigate the risk of adverse events among special donor groups (e.g., first-time donors). The majority use advice on hydration before, during, and after the donation. To formulate recommendations regarding hydration, more evidence of the optimal fluid intake and the possible impact on transient haemodilution is needed. High-frequency donors risk iron loss [9]. This risk could be mitigated by sampling from the product and rinsing the residual blood from the apheresis equipment with saline post-procedure and monitoring and limiting procedural failures resulting in incomplete return of red cells. In an observational study, saline administration at the end of the plasma procedure was associated with decreased frequency of vasovagal reactions [14], a finding to be verified in a multivariate analysis and ideally, a randomized controlled trial.

2) All organizations included in the survey use similar selection criteria (e.g., vein suitability, minimum body weight, and Hb), although sometimes with different acceptance criteria. Many blood banks have implemented minimum levels of e.g., Hb, total protein, and IgG to ensure donor health, reduce the risk of iron deficiency, and prevent depletion of total protein and IgG. Low immunoglobulin levels (outside

the remit of plasma donation) have been associated with increased risk of infection. In most of the organizations, donation volume is calculated according to the donor body weight. Previous studies found that female sex and low body weight increase the risk of adverse events. However, to formulate recommendations regarding optimal selection criteria for body weight and levels for IgG and Hb further research is needed.

3) The survey demonstrates a notable variation in the maximum permitted plasma donation frequencies across different countries. There is a lack of controlled experimental studies investigating the impact of various donation frequencies on donor safety, which leaves the safe upper limit for plasma donation frequency undetermined. In the sole recent RCT conducted [9], it was observed that donors donating 3 times per month (equivalent to 36 donations per year) experienced a decline in IgG levels, albeit not falling below the accepted lower limit as per the Blood Guide (21st edition 2023) [17]. The implications of any decrease in IgG levels regarding donor safety remain undocumented. Moreover, the rationale behind establishing 6 g/L as the lower acceptable IgG level lacks robust evidence. In the mentioned RCT, a frequency of one donation per month resulted in a limited reduction in IgG levels (6% after 12 weeks). While this does not imply that higher donation frequencies are unsafe, it underscores the absence of evidence needed to recommend increased donation frequencies.

4) As shown in the systematic review, there is a general lack of data on the long-term health effects of (intensive) plasmapheresis. Current studies of prolonged plasma donation and the effect on different health effects are ambiguous. To obtain conclusive evidence, more controlled prospective studies are warranted. Ideally, these studies would monitor dropout rates and reasons, as well as the long-term health. Furthermore, to assess the long-term effects of plasma donation, register-based studies using data from health registers [15] are needed. Relevant outcomes include ICD-10 codes from contacts with the healthcare system, relevant prescriptions of medicine, etc.

5) All organizations register plasma-related adverse events, although these were not necessarily uniformly registered. Considering the incomplete reporting on adverse events in several identified studies, we recommend that future studies specify the exact timing of outcome measurement, and describe the adopted surveillance tools or the specific adverse events that are being monitored. Furthermore, we recommend alignment of selection criteria and hemovigilance procedures between plasma collectors. A Danish study [16] showed large regional differences in the registration of adverse events in a new national donor vigilance system and highlighted the need for aligned definitions on an international level. A recommendation to the European Commission and national haemovigilance authorities is to gather standardized haemovigilance data on a mandatory basis as defined in deliverable 5.2. This will make data from different countries comparable and thereby provide data for studies that can formulate recommendations on evidence-based health protection of plasma donors.

Conclusions

We recommend adherence to the Blood Guide (21th edition 2023) [17] until further evidence is acquired. However, the guide's suggestion of a maximum of 33 donations per year lacks supporting evidence in terms of ensuring donor safety. Our recommendations are as follows:

- A maximum of two plasma donations per month, pending sufficient evidence confirming the safety of higher donation frequencies. This recommendation is based on expert opinion and reflects the view of a majority of WP5 members.*

- Monitoring IgG levels. Evidence of optimal IgG algorithms and test intervals are lacking.
- Urgent initiation of prospective studies to examine the health consequences of plasma donation at varying frequencies.
- Implementation of a register for standardized haemovigilance data on a mandatory basis as defined in deliverable 5.2.

These recommendations stem from the precautionary principle, prioritizing donor safety until more information is available. For more precise recommendations regarding selection criteria, preventive measures, volume of plasma collected per donation, and donation frequency, further controlled experimental studies are necessary. These studies should explore both the health effects, adverse events, and associated factors related to plasma donation, in both short- and long-term contexts. As revealed in the survey, several studies concerning procedural changes, donation intervals/frequencies, or donor characteristics are either about to commence, ongoing, or have recently concluded. However, as highlighted in the systematic review, enhancing the quality of studies (including methodology and sample sizes) is crucial. Future practices may consider individual differences among donors. Personalized donation practices, for instance, could allow for varied recommended interdonation intervals between donors.

* Alternative recommendation, supported by two WP5 members: A maximum of two plasma donations per month, pending sufficient evidence confirming the safety of higher donation frequencies, unless a donor health and IgG management system is established by the respective blood establishment.

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