Blood Reviews 26 (2012) 33–42

Contents lists available at SciVerse ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/blre

REVIEW

Adverse events and safety issues in blood donation—A comprehensive review

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ARTICLE INFO

Keywords:
Blood donor safety
Blood donor care
Risks
Complications
Adverse effects
Haemovigilance

ABSTRACT

Although blood donation is generally safe, a variety of risks and complications exist, the most common being iron deficiency, vasovagal reactions and citrate-related events. In the last decades, extensive efforts have significantly improved recipient and product safety, but there is still great potential to optimise donor care. Many therapies in modern medicine depend on the prompt availability of blood products, therefore it is crucial to maintain a motivated and healthy donor pool in view of a limited number of healthy volunteers willing and able to give blood or blood components. We present a comprehensive review on adverse events addressing all types of blood donation including whole blood, plasma, platelet, peripheral blood stem cell, leucocyte and bone marrow donation. In addition, we outline strategies for the prevention and treatment of these events and give a blueprint for future research in this field.

1. Introduction

Traditionally, safety issues in transfusion medicine have been concentrating on product and recipient safety. For this reason, inclusion criteria have become exceedingly strict during the last years, thus significantly limiting the pool of potential donors. Blood donors are healthy volunteers who give either whole blood or blood components by apheresis including platelets, plasma, red blood cells, peripheral blood stem cells and leucocytes or a combination of blood components. They represent a large, healthy population exposing themselves voluntarily for altruistic, sometimes financial motives to potential complications and risks. According to global data, up to 6.5% of the population are blood donors.[1,2] Adverse events are generally more common in women, in younger and in first-time donors.[3–6] In some countries, donors as young as 16 years are allowed to donate, but they exhibit a relatively high incidence of adverse events. The overall incidence of complications directly related to blood donation is 1%.[7] Although this seems to be a small number, it is of great importance given the large quantities of blood units collected each day worldwide. In 2004, the European Haemovigilance Network (EHT) and the International Society of Blood Transfusion (ISBT) set up a Common Working Group on Complications Related to Blood Donation (DOCO) in order to create standardised and internationally accepted definitions for donation-related adverse events. So far, 18 categories have been defined.[8] Although this is certainly a step in the right direction, the suggested definitions will need to be constantly expanded and, more importantly, used prospectively across different regions of the world.

So far, studies on donor safety have focused on immediate adverse events and iron balance. Nevertheless, currently no comprehensive review on adverse events concerning blood donors is available. In contrast to medical procedures in a patient, special circumstances apply to blood donation. For various reasons, donors to date often do not receive detailed information on the procedure itself and possible complications. Often physicians involved in the donation process are not aware of less frequent potential risks. On the one hand, it is an ethical duty not only to care for our patients but also to inform donors of possible adverse events to enable them to a) give a real informed consent to any donation procedure and b) take action for preventing or attenuating adverse effects. On the other hand, optimal care of the ever more limited number of blood donors is important to warrant the amount of blood and blood products needed in modern medicine. We therefore aim to give a comprehensive overview in order to facilitate this difficult task for physicians working in haematology and transfusion departments as well as mobile blood donation services. Family physicians might also profit to have a basic knowledge of these issues to identify their patients who are regular blood donors.

2. Whole blood donation

Although whole blood collection has been performed for decades and is therefore perceived to be safe, manual collection is associated with numerous potential complications. The focus on this issue is

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doi:10.1016/j.blre.2011.09.003

twofold. The first is on complications which occur immediately or within several hours after the donation procedure such as venipuncture-related complications or circulatory effects. The second is on long-term effects like iron deficiency. An overview on risks and complications related to whole blood donation is provided in Table 1.

2.1. Circulatory effects

Vasovagal reactions (VVR) to blood donation have been reported since the early beginning of organised blood collection.[9,10] The symptoms are weakness, dizziness, pallor, hypotension, apprehension, bradycardia and diaphoresis. These reactions occur during or shortly after blood donation. The overall prevalence is 1.4% to 7% (moderate) and 0.1% to 0.5% (severe reactions).[11–15] The hospitalisation rate due to complications of blood donations has a reported incidence of 1/198,000, however two-thirds of these events are related to VVR. The main cause was fall-related injury, particularly in female donors.[14,16] Important predictors for VVR include: young age, low weight and donation status (first time vs. repeat donor).[15,17,18] In a recent study, female sex, nonblack race, low body mass index, small estimated blood volume, rapid pulse and low systolic and/or diastolic blood pressure before donation were predictive for VVR. A calculated blood volume of less than 3500 mL using the formula of Nadler et al.[19] was an independent risk factor with the greatest predictive value for an adverse reaction. In 5% of blood donors with a weight of more than 50 kg blood volumes less than 3500 mL were found.[11]

2.2. Venipuncture-related complications

Blood donation can cause venipuncture-related-complications, in some cases even permanent disability. A frequent event is a sore arm occurring more often in women than in men (12.5% vs. 6.9%).[20] Haematoma occurs after extravasation of blood and represents the most common problem in blood donation. The complication rate is 9–16%.[21,22] When donors were interviewed 3 weeks after the donation, the reported incidence on bruises was up to 22.7% suggesting that haematomas are an underrecognised event.[20] Puncture of the brachial artery is rare with an incidence ranging from 0.003% to 0.009%.[23] The American Red Cross Blood Services reports an incidence of 0.011%.[24] Haematoma is the most common complication of arterial puncture and occurs in 33%.[25] Rare complications after arterial puncture include pseudoaneurysm,[26,27] arteriovenous fistula[22,28,29] and compartment syndrome.[22] Local nerve irritations or injuries are frequent as variations in nerve branch anatomy are common.[30] Phlebotomy technique also has an impact on nerve injuries.[26] According to donor interviews, sensory changes in the forearm and hand were reported in 0.9% of whole-blood donations.[20] Newman described an incidence of 0.016% in this context in a large case series involving 419,000 blood donations.[31] The symptoms in the 66 affected donors were numbness and/or tingling (82%), excessive or radiating pain (65%) and loss of arm strength (12%). Complete recovery within weeks is described for the majority of donors. In four donors injuries persisted for three months or more. In a large population based prospective study (n = 2,616,538),[32] the rate of disablement caused by needle injury was comparable with previous data (0.0022%).[30,31,33] The rate of complications leading to long-term morbidity was 0.005%.

Table 1
Whole blood donation.

Adverse event	Frequency
Iron deficiency[34,36,39,42]	Regular blood donors: overall iron depletion of >20% Total of 15% with absent iron stores (AIS) and 41.7% iron-deficient erythropoiesis (IDE) Frequent donors: men: 16.4% (AIS), 48.7% (IDE); women: 27.1.% (AIS), 66.1% (IDE)
Restless legs syndrome (RLS) due to iron deficiency[44–46]	14–25%
Vasovagal reactions[11–15]	1.4–7% (moderate) and 0.1–0.5% (severe)
Nerve injury[20,30–33]	0.016–0.9%, disablement 0.0022%
Bruises[20–22]	9–23%
Arterial puncture[23]	0.003%–0.011%

2.3. Iron deficiency and restless legs syndrome

Iron deficiency is common among regular whole blood donors. Each donation causes a loss of 213 to 236 mg of iron,[34–36] leading to a continuous depletion of body iron stores.[37] For the quantitative assessment of body iron stores, plasma ferritin and soluble transferrin receptor (sTfR) concentrations are the best laboratory measures currently available.[38] In the RISE-study, one of the largest studies published on the topic (n = 2425 red blood cell donors), Cable et al. showed that among frequent donors, 66.1% of women and 48.7% of men had iron-deficient erythropoiesis (log (sTfR/ferritin) value of 2.07 or greater).[39] Absent iron stores (ferritin < 12 ng/mL) in the same cohort were seen in 16.4% and 27.1% in men and women, respectively. In concordance with previous studies,[34,36,40] donation frequency had the greatest impact on iron deficiency. Further risk factors were lower weight and female gender. In premenopausal women, the daily amount of required iron is higher than in men (1.5 mg vs. 1.0 mg) due to menstrual blood loss or the result of a pregnancy. Furthermore women have lower iron reserves.[41] Iron supplementation of blood donors showed a marginal effect on the risk of iron deficiency and dietary variables none.[39] Besides iron deficiency anaemia, iron loss can lead to fatigue, decreased physical and job performance and cognitive changes.[42,43] Iron deficiency has additionally been found to be a cause of restless legs syndrome (RLS). Lack of dopamine is thought to be a cause for RLS and iron is an essential cofactor for the production of dopamine. The reported prevalence of RLS in blood donors is 14%–25%[44–46] .

2.4. Allergic reactions

Local allergic reactions to the disinfecting agent or adhesive tape have been described but are usually self-limiting and harmless.[22]

2.5. False positive screening tests

Interference in immunoassays resulting in false positive or even false negative findings is a widely known phenomenon.[47,53,55,65] In blood banking, optimal sensitivity is emphasised at the expense of specificity. Hence, interference in virus detection assays has become a problem[48,49] since false positive results lead to a disposal of blood products[50] and more so to donor deferral.[51,52] Causes for interferences are multifaceted (for review see[53]) and often cannot be ascertained. Common sources are rheumatoid factor positivity,[54–56] autoimmune diseases,[55,57] recent vaccination,[48,58] infections,[59,60] anti-animal antibodies[55,61-63] or medication.[64] Even age-dependant plasma proteins and demographic factors are suspected to create false positive results.[51] Generally, prevalence of interference in immunoassays is dependent on the type of interference and varies between 0.05 and ≥6%.[53,65] In Sweden's blood donation centres, Tynell et al.[52] found false-reactive rates of 0.01–0.16% for anti-HCV, 0.02–0.2% for anti-HIV 1/2 and for HBsAg 0.01–0.09%. Donors who receive notification letters about these findings react with a whole range of negative feelings, including worry, confusion, disbelief and fear.[52,66] They also find it difficult to accept the fact of being permanently deferred despite existing health.[67] From a sociological point of view, donating blood has a beneficial effect on donors[68] which explains why donor deferral can be a sensitive issue. There are concepts to reduce permanent exclusion of donors. One is to defer a donor only after a third time of false positive results.[52] A further approach is a retesting algorithm, where donors are released for donation after a