Last Line to Secure Transfusion Safety: Pathogen Inactivation/Reduction Methods in Blood Products-Current Approaches and Perspectives

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Introduction

The residual risk of transfusion transmitted infection (TTI) had been decreased greatly since the donor screening methods, especially the nucleic acid testing (NAT), were introduced. NAT can shorten the period between infection and detection (window period) to several days after infection [1]. However, transfusion safety still faces challenges due to limitations of test sensitivity and more importantly the unexpected appearance of new pathogens. The newly discovered or re-emerging viruses such as West Nile virus, human parvovirus B19 and latest reported severe fever with thrombocytopenia syndrome bunya virus [2] in the donor blood endangered blood safety. Pathogen inactivation/reduction (PI/PR) strategies provide last line of defence against various pathogens to secure transfusion safety.

PI/PR refers to any technology that inactivates or reduces all types of blood borne pathogens. Different methods were designed for different blood products such as plasma, platelets and red blood cells (RBCs). An ideal PI/PR is expected to inactivate all blood borne pathogens without damaging the quality of blood or blood products. Some common PI/PR methods include treatment with solvent/detergent (S/D), Methylene blue, Psoralens, Riboflavin. Some new technologies for PI/PR are under development.

PI/PR by Solvent/Detergent (S/D)

S/D technology is a combination of solvent and detergent. The most- commonly used protocol is: Treat blood sample with 1% tri-(N-butyl)-phosphate (TNBP) and 1% Triton X- 100 for 4 hours at 30°C, then remove S/D reagents by vegetable oil extraction and subsequent reverse-phase chromatography on C18 resin. This method inactivates pathogen by disrupting the lipid enveloped membrane, so it can’t be used for blood components with cellular structure. The S/D treatment was first licensed by the US FDA in 1985 for use in the manufacture of an anti-hemophilic factor (AHF) concentrate [3], and then applied in coagulation factors and pooled plasma. S/D can rapidly inactivate different lipid enveloped virus, such as vesicular stomatitis virus (VSV) (virus titer reduction ≥ 7.5log), sindbis virus (≥ 6.9log), HIV (≥ 6.2log), hepatitis B virus (HBV) (≥ 6log) and hepatitis C virus (HCV) (≥ 5log) [4]. However, S/D can’t inactivate non-enveloped virus, such as hepatitis A virus (HAV) and parvovirus B19. Various studies [5-7] showed that treatment of S/D could reduce the activity of coagulation factors (CFs), inhibitors, immunoglobulins and other plasma proteins by about 5-20%. S/D treatment is safe and the final S/D reagents removal step ensures the final product is non toxic.

PI/PR by Methylene Blue

Methylene blue (MB) is a phenothiazine compound that can be activated by visible light to generate reactive oxygen species (ROS), mostly singlet oxygen, through a Type II photodynamic reaction. These highly active molecules contribute to methylene blue’s pathogen-inactivating activity [8]. The first MB treatment system was developed by the Institute Springe in Germany. The conventional MB treatment included white blood cell (WBC)-reduction filtration, MB Pill dissolution, illumination and MB removal. Because of cell filtration step, this method was only applied to single donor plasma. The PI/PR efficacy of MB treatment for lipid enveloped virus is significant for both double and single- stranded RNA and DNA viruses, but for the non lipid-enveloped virus, the effect is inconsistent. Non-lipid enveloped virus like human parvovirus B19 could get a 4log or more reduction, while others like HAV are not affected by MB treatment [9]. Although MB can cross cell membrane by simple diffusion, its low concentration within cells makes it impossible to inactivate intracellular viruses, bacteria and protozoa. While it is effective for some pathogens, MB treatment affects the activity of some plasma proteins, such as CF VIII and fibrinogen [10,11]. MB PI/PR was licensed for use in Europe, Brazil, and Austria. The safety profile of MB PI/PR was validated by many studies, although allergic reactions to MB have been reported [12].

PI/PR by Psoralens

Psoralen is a naturally occurring photoactive substance found in a number of plants. PI/PR by psoralen has been successfully developed as a commercial product- INTERCEPT system [13]. It utilizes amotosalen, a synthetic psoralen (formerly S-59-HCl) as active compound. The amotosalen contains a tricyclic molecule structure, thus it can pass cellular membranes and interact with nucleic acids freely. Upon the illumination of UVA light (300-400 nm), it forms covalent cross links to pyrimidines in RNA and DNA and blocks the replication and transcription of mRNA. After treatment, the residual amotosalen and photoproducts are absorbed by silicon which is fixed in the treatment set. The psoralens PR were proved effective against almost all blood borne pathogens, including viruses, bacteria and protozoa. This method was approved by several Europe countries and applied for plasma and platelets. Studies show that this treatment slightly influences the function of blood components without damaging the overall quality [14]. The toxicological studies and clinical trials demonstrated that this treatment is safe [15].

PI/PR by Riboflavin

Riboflavin (vitamin B2) is present in food and natural products. Riboflavin combined with UVA (280-360 nm) was used to inactivate various pathogens. The UVA light can damage the nucleic acids of...


