PATHOGEN INACTIVATION
IN DONATED BLOOD

HEALTH TECHNOLOGY ASSESSMENT SECTION

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EXECUTIVE SUMMARY

Introduction

Several pathogen inactivation methods are available such as Chemical treatment, Photochemical, Leukocytes depletion, Ultraviolet B irradiation and others. Worldwide numerous infectious agents, have been identified as potential threats to blood supply. Newly discovered agents namely transfusion transmitted virus (TTV), SEN-V (SEN virus), Human herpes virus-8 (HHV-8), Hepatitis G Virus (HGV), West Nile Virus and Prions present a unique challenge in assessing the possible risk to safety of blood and plasma products. Current blood donor screening and disease testing have shown to reduce the incidence of blood transfusion-transmitted diseases. Pathogen inactivation or reduction technology represents a proactive approach to blood safety. The ultimate goal of pathogen inactivation is to maximally reduce the transmission of potential pathogens without significantly compromising the therapeutic efficacy of the cellular and protein constituents of blood. This must be accomplished without introducing toxicities into the blood supply, neoantigen formation and subsequent antibody production. Investigations into some technologies are at an advanced preclinical or already in clinical stages. Evidently, the use of such procedures raises a number of issues, including efficiency, the damage inflicted to labile blood products, toxicity in patients, and cost-effectiveness.

This review was requested by a Senior Consultant Pathologist, Y. Bhg. Datin Dr. Nor Azian Azlan A. Samad from Pathology Department of Melaka Hospital

Aims/objectives

To assess the safety, efficacy, effectiveness, and cost effectiveness of pathogen inactivation or pathogen reduction technology used to treat blood products such as plasma, platelet and red blood cells (RBC) for safe blood and blood products.

Results and conclusion

A. PLASMA

Safety

i) Photochemical Treatment (Amotosalen)
Fair level of evidence on the safety aspect of photochemical treatment (Amotosalen) used for pathogen inactivation in plasma.

ii) Chemical treatment (Solvent/ detergent [SD-treated])
Evidence showed SD (treated) - plasma caused some deaths in liver transplant, severe liver disease and known coagulapathies patients

iii) Methylene Blue
Poor evidence on the safety aspect of Methylene Blue technology used in plasma products. There was no long term studies conducted on carcinogenicity and reproductive toxicity in Methylene blue treated plasma.

Effectiveness

i) **Psoralen light treatment (Amotosalen- HCL)**
Fair evidence on the effectiveness of INTERCEPT blood system when used on Platelet-plasma.

ii) **Riboflavin light treated (RLT)**

Poor evidence on the effectiveness of Riboflavin light treated (RLT) technology when used in plasma. Clinical studies using Mirasol (riboflavin) pathogen inactivation technology is still underway.

iii) **Solvent Detergent (SD- plasma)**
Fair evidence on the effectiveness of solvent detergent technology, when used for plasma and fresh frozen plasma.

Cost Effectiveness

i) SD- FFP transfusion was cost effective in patient's ≤ 48 years of age and in older patients with good clinical prognosis.
ii) In another baseline study on cost effectiveness of transfusing virus-inactivated plasma instead of standard plasma showed a cost-effectiveness ratio of $2,156,398 +/- $257,587 per quality-adjusted life year gained. The transfusion of virus-inactivated plasma produces little health benefit at a very high cost.
iii) There is no retrievable evidence on cost effectiveness for other pathogen inactivation technologies used for plasma.

Recommendation

Based on the above review:

- Photochemical treatment (Amotosalen) and Solvent detergent (SD- plasma) may be recommended as pathogen inactivation technology for plasma.
- However, SD – treated plasma is not recommended for patients after liver transplant, severe liver disease and with known coagulopathies.
- Insufficient evidence to recommend Methylene Blue and Riboflavin light treated technologies as pathogen inactivation technologies for plasma. Hence, more clinical research is warranted before considering the technologies for plasma or fresh frozen plasma.

B. PLATELETS

Safety

i) Amotosalen and Mirosal (Riboflavin)
Good evidence was obtained on the safety aspect of Amotosalen (photochemical treatment) and Mirosal (Riboflavin) used as pathogen inactivation technology for platelets. There was good patients tolerance for platelets treated with amotosalen. Both Amotosalen and Mirosol technologies did not affect the quality of platelets concentrates.

Effectiveness

i) Amotosalen and Mirosal (Riboflavin)
Fair evidence was obtained with regards to the effectiveness of Amotosalen (photochemical treatment) and Mirosal (Riboflavin) pathogen inacativation technology for platelets

ii) Thionine/UV Light
Low level of evidence on the effectiveness of Thionine/UV Light used as pathogen inactivation technology for platelets.

Cost effectiveness

i) Amatosalen
Sufficient evidence to show that Amatosalen (photochemical technology) is cost effective compared with non treated plaletets used for transfusions.

Recommendation

Based on the above review:-

- Amotosalen and Mirasol (Riboflavin) pathogen inactivation technologies can be used for platelet concentrates.
- More research is warranted on Thionine /UV Light when used as pathogen inactivation on platelet concentrates.

C. RED BLOOD CELLS (RBCs)

Safety

i) S 303

Fair level of evidence to show the safety of S303 when using as pathogen inactivation technology for RBC.

Effectiveness

i) S 303

Fair evidence obtained on the effectiveness of S303 as a pathogen inactivation technology when used on RBC.

ii) PEN110

Poor evidence for the effectiveness of PEN110 as a pathogen inactivation technology when used on RBC.

Cost effectiveness

No retrievable evidence on the cost effectiveness of S303 and PEN110 pathogen inactivation technologies when used for RBC.

Methods

This review was based on two Health Technology Assessment (HTA) reports, a World Health Organisation guideline, seven Randomised control trials (RCT), two laboratory experiment study design, two cost effectiveness studies, three narrative reviews and an abstract on pathogen inactivation or pathogen reduction technologies.

PATHOGEN INACTIVATION IN DONATED BLOOD

1. INTRODUCTION

The approach to reduce pathogens in the blood supply depends on a combination of activities such as donor education; donor selection (volunteer and nonremunerated); donor screening, direct questioning on risk behaviour; testing for selected known causative agents; consulting lists of previously deferred donors; meticulous examination, and others. Blood is still not a safe product for many reasons. Most of the screening techniques cannot detect the pathogens in the blood sample during the "window period" of a disease. Pooling of blood fractions from many asymptomatic infected blood donors, in order to raise product yield, can raise the infection rates [1]. There is also possibility of introducing a new emerging pathogen into the blood supply, for which no contemporary test exists. A very good example to illustrate this is the transmission of the Human Immunodeficiency Virus (HIV) in the late 1970's and early 80's, to thousands of haemophiliac patients (Corash, 1998). To further reduce the risks of pathogen transmission via blood transfusion pathogen inactivation steps have been routinely applied to labile blood product such as fresh frozen plasma (FFP) and blood cellular components. Several pathogen inactivation methods are available such as solvent/ detergent treatment of FFP, Methylene treatment of FFP, Leukocytes depletion, Ultraviolet B irradiation and Gamma Irradiation. [1] Numerous infectious agents (found worldwide) have been identified as potential threats to blood supply. These newly discovered agents namely transfusion transmitted virus (TTV), SEN-V (SEN virus), Human Herpes virus-8 (HHV-8), Hepatitis G Virus (HGV), West Nile Virus and Prions present a unique challenge in assessing the possible risk on safety of blood and plasma products. This makes pathogen inactivation even more important.[2] Current blood donor screening and disease testing has shown to reduce the incidence of transfusion-transmitted diseases. Pathogen inactivation of blood products represents a proactive approach to blood safety.[3] The ultimate goal of pathogen inactivation is to maximally reduce the transmission of potential pathogens without significantly compromising the therapeutic efficacy of the cellular and protein constituents of blood.

This must be accomplished without introducing toxicities into the blood supply and without causing neoantigen with subsequent antibody production. Investigations into some technologies are at an advanced preclinical or already in clinical stages. Evidently, the use of such procedures raises a number of issues, including efficiency, the damage inflicted to labile blood products, the toxicity in patients, and the effectiveness.

This review was requested by a senior consultant pathologist, Y.Bhg. Datin Dr. Nor Azian Azlan A. Samad from Pathology Department of Melaka Hospital. This review was requested in order to obtain information regarding safety and effectiveness of pathogen reduction or inactivation technologies used on donated blood.

2. OBJECTIVES

To assess the safety, effectiveness, efficacy, and cost effectiveness of pathogen inactivation or pathogen reduction technology used to treat blood products such as plasma, platelet and red blood cells (RBC) for safe blood and blood products.

3. TECHNICAL FEATURES

Pathogen reduction technologies on blood products (such as plasma, platelets and red blood cells (RBCs) can be categorized into three categories namely Chemical treatments, Photochemical treatment and photodynamic treatments.

There are several pathogen inactivation technologies used in Plasma, Platelets and RBCs. Pathogen inactivation techniques used for plasma includes the Solvent detergent, Amotosalen + UV, Methlene blue + Light, and Riboflavin. As for platelets the pathogen inactivation technologies used are the Amotosalen+ UV, Riboflavin + UV and UV (± thionine). Inactine, S303, Riboflavin + UV, and thiopynilium +light are used as pathogen inactivation technologies for red blood cells. The status of pathogen inactivation technologies for blood products (such as plasma, platelet and red blood cells) are described in Table 1.

Table 1: Status of pathogen inactivation technologies

Blood Component	Company	Method	US status	EU status
Plasma	• Octapharma • Cerus • Macopharma • Navigant	Solvent detergent Amotosalen +UV Metylene blue + Light Riboflavin +UV	Licensed Phase III - -	Licensed Licensed Licensed Licensed
Platelet	• Cerus • Navigant • Macopharma	Amotosalen +UV Riboflavin +UV UV (±thionine)	Phase III Phase II Preclinical	Licensed Licensed Preclinical
Red Cells	• Vitex • Cerus • Navigant • America red cross	Inactine S-303 Riboflavin +UV Thiopyrilium + light	Abondoned Phase II Preclinical Preclinical	Abondoned Licensed Licensed Licensed

Note: Phase 1 volunteer safety studies, Phase II: Patient safety studies. Phase III: Patient efficacy studies. Licensed: by FDA in USA and/or CE marked in Europe .[4]

3.1 PLASMA

Photochemical treatment

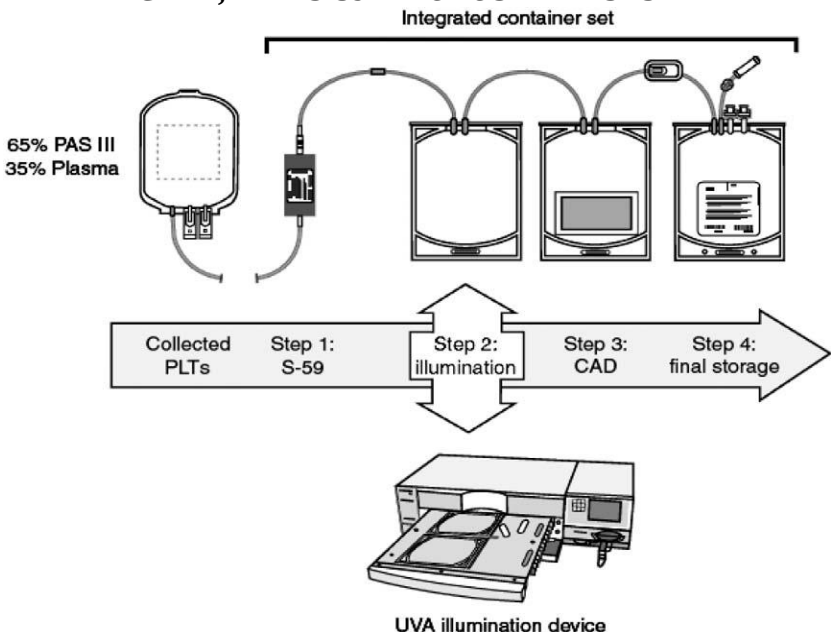
3.1.1 Methylene Blue (MB)

First-generation MB systems involved the addition of an MB stock solution to each thawed plasma unit for a final concentration of 1μM. Then the MB-treated plasma is subjected to a white light luminescence of 45000 lux or more for 1 hour. A more advanced commercially manufactured MB system by MacoPharma (Mouvaux, France) uses an inline system consisting of a membrane filter, MB dye, illumination bag, elimination filter, and storage bag. The 0.65-μm membrane filter removes platelets, leukocytes, and debris. The plasma then passes through tubing containing an MB pill that dissolves as the plasma flows through the tubing into the illumination bag. The MB-containing plasma is subjected to double-sided illumination by sodium high-intensity low-pressure lamps emitting yellow light at a wavelength of 590 nm for 15 to 20 minutes. Plasma is then passed through an MB elimination filter that removes greater than 95% of the residual dye and photoderivative byproducts (especially phenothiazide dyes azure A and B) that exhibit in vitro mutagenic properties. The Macro pharma system is CE marked and implanted under good manufacturing practices(GMP) in several europian countries. However, a question still remains concerning the genotoxicity of MPB and may introduce long term side effects. [5]

3.1.2 *Psoralen light treatment (PLT- Plasma) or Amotosalen Ssystem*

A photochemical treatment system using a novel psoralen material (S-59, developed by Cerus and Baxter Corporations) and UV-A (long wavelength) ultraviolet light, has been developed to inactivate viruses in single donor units of Fresh frozen Plasma (FFP). Upon exposure to UVA, the S-59 forms non-reversible covalent monoadducts with DNA and RNA. This system can be used to treat single 250-300 mL plasma units or jumbo units containing 500-600 mLs of plasma. During the photochemical treatment with psoralen-UVA, individual units of plasma are either separated from whole blood or collected by apheresis technology and transferred into a plastic container. S-59 is added to a concentration of 150 μM through an integral closed system into a UV-A transparent vessel containing the plasma. After five minutes incubation, the S-59 treated plasma is illuminated with shaking for three minutes in a high intensity UV-A-light box. After illumination process the plasma is transferred to another container with an S-59 reduction reduction device (SRD), which is used to remove most of the photoproducts caused by light activation of the S-59. After S-59 reduction device processing for 1 hour, the plasma is transferred via a closed system into a final container for freezing at 18˚C and can be stored for up to 1 year.

INTERCEPT, THE S-59 AMOTOSALEN SYSTEM



3.1.3 Riboflavin light treated plasma (RLT-plasma)

Another Method applies essential natural vitamins (Vitamin B2 or riboflavin) that absorb both visible lights (the Mirasol system). Riboflavin and UV light (280- 360) damage nucleic acids by direct electron transfer, production of singlet oxygen and generation of hydrogen peroxide with formation of hydroxyl radicals hence damage the DNA/RNA of pathogens and it can proceed in the absence of oxygen. Currently, riboflavin is classified as a Generally Regarded As Safe (GRAS) compound by US FDA. [5]

3.1.4. Solvent Detergent (SD)

SD viral inactivation technologies were first licensed for treatment of clotting factor concentrates in 1985. Before 1984, a combination of ethyl ether (20%) and Tween 80 (1%) were found effective in inactivating HBV and NANBHV in factor VIII and IX concentrates with minimal loss in activity. In 1986, TNBP and 0.2% sodium cholate were shown to be effective at inactivating HBV, NANBHV, and HIV.

Solvent detergent (SD) treatment disrupts the membranes of enveloped virus, bacteria, and eukaryotes. Infectivity is lost via this action. Many combinations of tri-(n-butyl)- phosphate (TNBP) or ethyl ether (organic solvents) with Tween 80, sodium cholate, and Triton X-100 (non-ionic detergents) have been used in the past. The SD combination most often used now is TNBP with Triton X-100.This compound acts as an organic solvent and removes lipids during SD processing by extracting and sequestering them into a separate micellar (colloidal) phase. This non-ionic detergent disrupts lipid bilayers for easier extraction and stabilizes TNBP. [6]

3.2. PLATELET

Different techniques are available to inactivate pathogen in cellular blood components suc as for platelets. The techniques include psorelans (Amotosalan) , methylene blue, porphyrins, UV light, Gamma irradiation and riboflavin (RB)

3.2.1 Psorelan

Amotosalen hydrochloride is synthetic psorelan compound that intercalates into helical region of DNA or RNA after illumination with ultraviolet ray light reacts with pyrimidine bases to form inter nucleic and intra nucleic acid stands crosslink. This is a fix bond and thus the strands of DNA cannot separate and replicate.

3.2.2 Riboflavin (RB)

UV light has been used as a pathogen inactivation method since it can damage nucleic acids. However, UV light alone has not proven to be an effective approach to pathogen inactivation of cellular components such as platelets. Therefore, RB in combination with UV light in the 265-370nm wavelength is being developed as a clinical method for pathogen inactivation of several blood components including platelets. It is believed that RB acts by intercalation with nucleic acids and when exposed to light causes damage to DNA by production of singlet's oxygen, electron transfer, production of hydrogen peroxide and hydroxyl radicals that lead to nucleic acid base damage and DNA strands breaks.[7]

3.2.3 PORPHYRINS

Porphyrins are "a large class of deeply coloured red or purple, fluorescent crystalline pigments, with natural or synthetic origin, having in common a substituted aromatic macrocyclic ring consisting of four pyrrole-type residues, linked together by four methine bridging groups". All porphyrin-like compounds have a strong absorption band around 400nm called band. Porphyrins have applications in a variety of novel chemical and medicinal procedures including the use of water-soluble porphyrins in photo dynamic theraphy. It was claimed that photosensitizers have been used for detection and treatment of cancer. It is also an effective modality against antibiotic resistant bacteria and cell free viruses.

Photodynamic interactions were described to take place wherever sensitizer, light and oxygen are simultaneously present. Inflammatory tissue was described to manifest similarities in porphyrin retention and therefore bacterial and viral infected tissues may become targets for photodynamic treatment. It is independent of the antibiotic sensitivity spectrum of the treated pathogen and it has an efficient and non-recovering anti-microbial killing effect upon illumination of Gram positive bacteria. Bacterial PDT is affected by the use of various sensitizers, as a general rule non-charged or positively charged molecules are effective in photoinactivation of Staphylococcus sp. In order to photosensitive Gram (-) bacteria such as Pseudomonas aeruginosa, it is necessary to introduce a small peptide polymyxin-B nona-peptide (PBNP) which stimulate the translocation of porphyrin through the outer membrane of these bacteria and makes PDT possible. Gram negative cell killing by the use of PBNP and DP broadens the antibacterial

spectrum of photodynamic inactivation and opens new horizons for this modality as a wide spectrum drug when antibiotic resistance is the main concern[8]

3.3. *Whole Blood and Red Blood Cells (RBC)*

3.3.1 S- 303

Pathogen Inactivation techniques used for RBC includes the S-303. This method is developed by the same manufacturer as amotosalen. S-303 is a part of class of compounds known as Frales (Frangible Anchor Linker Effectors). These tripartite molecules are composed of a nucleic acid anchor, an effector moiety, and a frangible linker. The effector moiety binds nucleic acids covalently, and the frangible linker breaks down forming an inactive negatively charged species (S-300). This prevents further binding to the nucleic acid, thus rendering the DNA or RNA non-functional. The completely light-independent reaction proceeds due to a shift in pH, which occurs as the S-303 is added to red blood cell concentrates. The process as developed requires the addition of S-303 to red cells at a concentration of 150 mg/mL, which is then incubated for 12 hours at room temperature. The red cells are incubated with a compound absorption device (CAD) for an additional 8 hours after transfer to a storage container to remove any residual S-303 and S-300. The CAD remains in the red cells throughout storage. [6]

3.3.1 PEN110

PEN110 is another pathogen inactivation compound that also disrupts nucleic acids. Like S-303, light is not required for the reaction and it can therefore be used to treat red cells. PEN110 is a compound chemically related to binary ethyleneimine and is known as an ethyleneimine oligomer. The altered molecule is a cation, selective for nucleic acids, and highly watersoluble. As the molecule is very small, it readily diffuses through cell membranes, which, the manufacturer claims, makes it more effective against non-lipid enveloped viruses, such as parvoviruses. PEN110 forms ionic bonds with nucleic acids, activating the molecule by protonation of the aziridino nitrogen. The active form can then alkylate a proximal nucleophilic center such as the N7 position of guanine in DNA. This results in the opening of the imidazole ring structure of guanine, which creates a break in the strand and creates a stop message. The nucleic acid is thus inactivated and becomes useless as a template. Binary ethyleneimines, like psoralens, have been used in nucleic acid research since the 1980s. The development and use of PEN110 for pathogen reduction of blood products has occurred only over the past 15 years. In the process known as INACTINE treatment, PEN110 is added to create a 0.1% (vol/vol) concentration and incubated at room temperature for 6 hours.

PEN110 is then removed by washing with unbuffered saline to levels below the limit of detection when using HPLC (30 ng/mL). The units are then ready for storage.[6]

4. METHODOLOGY

4.1 SEARCH METHODS

Literature were searched through electronic databases which included Medline, PubMed, Cochrane Database for Systematic Review, EBM Review HTA Database, INAHTA database and general databases such as Google and Yahoo.

The search strategy used the terms, which were either used singly or in various combinations: "Pathogen Inactivation", "white blood cells", "Pathogen Reduction", "Pathogen Inactivation AND Blood" ,"Blood products" platelets, plasma and "Red Blood Cells". The search was limited to articles on human. There was no language limitation applied in the search.

4.1.1 SELECTION OF STUDIES INCLUDED /EXCLUDED

All the studies pertaining to safety, efficacy, effectiveness and cost effectiveness of pathogen inactivation or pathogen reduction technology in donated blood were included in this review.

A critical appraisal of all relevant literature was performed using Critical Appraisal Skills Program (CASP) checklists and the evidence graded according to the US/Canadian Preventive Services Task Force (Appendix 1)

Data were extracted and summarized in evidence table as in Appendix 2. The data were not pooled and only non-qualitative analysis was carried out.

5. RESULTS AND DISCUSSION

This review was based on two Health Technology Assessment (HTA) reports, a World Health Organisation guideline, seven Randomised control trials (RCT), two laboratory experiment study design, two cost effectiveness studies, three narrative reviews and an abstract on pathogen inactivation or pathogen reduction technologies.

A. PLASMA

5.1 . A. SAFETY

Photochemical treatment (Amotosalen)

INAHTA briefs by Catalan Agency for Health Technology Assessment and Research-CAHTA, Spain (CAHTA), a systematic review revealed that pathogen inactivation technique using Amotosalen (photochemical treatment) is safe for plasma products.[9]

A phase III Randomised control trial (RCT) conducted by Mintz et al in 2006 was reviewed by Health Technology Assessment by Canadian Agency for Drugs and Technologies in Health (CADTH). A randomised, controlled, double-blind Phase III trial was conducted with Photochemical treatment of fresh-frozen plasma (FFP) with amotosalen and ultraviolet (UV) (PCT FFP) or control FFP for therapeutic plasma exchange (TPE) in patients with thrombotic

thrombocytopenic purpura (TTP). Thirty five patients were randomly assigned to receive plasma (n=17) or control plasma (n=18). These patients received plasma until a remission (defined as a platelet count of 150 x 10^9/L for two consecutive days) was achieved or for a maximum of 35 days. Those patients were observed for adverse events (AEs) for seven days after the last transfusion. This study found that there were no significant difference between groups in terms of the time to remission, relapse rate, time to relapse, total volume of plasma exchanged and number of plasma unit exchanged. The author concluded that the safety profile of PCT- treated FFP did not differ significantly from the control FFP. This study received funding from Cerus, the manufactures of INTERCEPT. [10 level 1]

Chemical Treatment (*Solvent/detergent-treated)*

World Health Organisation (WHO) guidelines reported that based on two small RCTs (Williamson LM et al. 1999 and Lerner RG et al. 2000) and two clinical trials (Inbal A et al. 1993 and Horowitz MS et al. 1998) showed that solvent/detergent (SD)-treated-plasma can replace FFP in all of its indications. These include the replacement of coagulation factors and in the treatment of thrombotic thrombocytopenic purpura. However, several deaths were reported in liver transplant patients who received a product provided by one manufacturer in the USA. Although the link with this product or with reduced levels of some anticoagulant proteins in SD-plasma is uncertain, the US manufacturer's product label has been amended to indicate that this product should not be used in patients undergoing liver transplant or in patients with severe liver disease and known coagulopathies. [11 Level III]

Methylene blue (MB)

A narrative review paper by Bryant BJ. et. al. 2007, indicated that millions of Methylene blue (MB) single units of plasma have been transfused in Europe without unexpected adverse outcomes. Methylene blue–treated plasma has replaced S-D plasma in Belgium and is the sole plasma product used in the United Kingdom for patients born after January 1, 1996. However, the long-term effects of exposure to even minute amounts of residual MB and its photo derivatives have not been studied in larger cohorts. To date, no adverse effects have been reported. Long-term studies of carcinogenicity and reproductive toxicity have not been conducted. [12 Level III]

5.2. A EFFECTIVENESS

PLASMA

Psorelan light treatment (Photochemical)

Baxter/ Cerus (INTERCEPT blood system) is a method applying amotosalen HCL (Formally known as S-59) and long wave length ultraviolet (UVA) for plasma pathogen reduction. Only two small randomised controlled trials were published as abstracts, have been performed comparing PLT-Plasma and FFP. One of these is the patients with acquired coagulopathy, including liver transplant and one involving exchange for thrombocytopenic purpura (TTP). They demonstrated a similar effect for platelet –plasma and traditional FFP. In patients with congenital coagulation deficiencies, recoveries were within the therapeutic range for FII, FVII, FIX and FX after transfusion of 15-20mL. PLT-plasma per kg, while $t_{1/2}$ was reduced for F1, FII and FXII; both PT and APTT values showed significant correction after transfusion.[5 Level III]

Riboflavin light treated plasma (RLT-Plasma)

Another method applies an essential natural vitamin (Vitamin B12 or riboflavin) that absorbs both visible and UV light(the Mirasol system). In this narrative review paper by Solheim BG, 2006, revealed that Riboflavin and UV light (280-360nm) could damage nucleic acids by direct electron transfer. The production of singlet oxygen and generation of hydrogen peroxide with formation of hydroxyl radicals hence damage to pathogen DNA/RNA. This process has been proven effective against a wide range of pathogens, including bacteria, intracellular HIV-1, West Nile virus (WNV) and porcine parvovirus in preclinical studies of platelets and plasma. However the clinical studies using the Mirasol PRT for plasma are still underway. [5] Level III

Pooled Solvent Detergent plasma (SD- plasma)

In vitro procedures have demonstrated that the SD method eliminates all lipid-envolped viruses, including West Nile virus except for vaccinia virus which demonstrates a relative resistance. The poxvirus family has unique structure which exhibits a general high physiochemical resistance. The SD- plasma production process also eliminates bacteria, protozoa cells and cellular fragments. It has no effect on nonlipid coated viruses, B19 and Hepatitis A virus (HAV), have been dispelled by screening of the strating material with Nuclear amplification technology. A reduction of the prion load which has been observed with SD production process is still under further investigation. The same SD method has been applied for all SD-plasma products. There are differences in in manufacturing processes which resulted in some important differences in product conmposition. In Europe, the production process patented by OctapharmaAG (Lanhen, Switzerland). In US, SD-plasma was produced under the brand name PLAS+SD by Vitex(Watertown, MA). Nine studies covered the indication for plasma examined the clinical efficacy and tolerance of SD-plasma. It was administered to 376 patients. Eight of the studies were European SD- plasma, while one observational study was with US SD-plasma. Four of the studies were prospective randomised trials, three SD-plasma versus Methylene blue light treatement- plasma(MBLT-plasma). It was concluded that SD-plasma was proved as effective as FFP or MBLT-plasma. [5] Level III

5.3. A COST EFFECTIVENESS

There was a cost effectiveness study to estimate the incremental cost/life year saved for SD-FFP compared with untreated FFP, having controlled for post-transfusion mortality and patient age. Various infective and non infective transfusion –related complication were considered. The findings showed that the discounted cost/life year saved for SD-FFP use in the UK was £22 728 [95%, CI: £22 604- 22853] for neonates and £98 465 (95%CI:£97 924-99 005) for patient age 70. The cost effectiveness ratio was below £50 000/life year saved for patients ≤ 48 years of age and below £30 000/life year saved for those ≤21 years of age. In transfusion recipients with no significant morbidity, the cost –effectiveness ratio was £12 335 for neonates and £61 692 for 70-years old. The most important driver of cost-effectiveness was transfusion-related acute lung injury (TRALI), on account of its relatively high incidence and mortality rate. Inclusion of non- infectious complications suggests that SD-FFP is cost effective in patients ≤48 years of age and in older patients with good clinical prognosis. [13]

The cost effective study by Pereri et al. 2000, investigated the costs and utilities of transfusing virus-inactivated plasma. Probability distributions for patients' age and sex and for the number of blood components transfused were determined in 924 plasma recipients in a tertiary-care hospital. Other values were obtained from the medical literature**.** Results of the baseline and sensitivity analyses are the mean (+/- SD) of 10 simulations with 10(7) patients per simulation.

In the baseline analysis, transfusing virus-inactivated plasma instead of standard plasma prolonged the quality-adjusted survival by 1 hour and 11 minutes per patient, at a cost-effectiveness ratio of $[redacted] +/- $[redacted] per quality-adjusted life year gained. Cost-effectiveness was most sensitive to the patients' mean age, the incremental cost per unit of virus-inactivated plasma, the HIV and hepatitis C virus transmission rates, and the short-term mortality of plasma recipients due to their underlying diseases. The finding showed that compared to most accepted medical procedures, the transfusion of virus-inactivated plasma produces little health benefit at a very high cost. This poor cost-effectiveness ratio is due to the low current risk of infection with transfusion-transmitted viruses and to the greater age and poor short-term prognosis of most plasma recipients. [14]

6.0. A CONCLUSION

PLASMA

Safety

i) Photochemical Treatment (Amotosalen)

Fair level of evidence on the safety aspect of photochemical treatment (Amotosalen) used for pathogen inactivation in plasma.

ii) Chemical treatment (Solvent/ detergent [SD-treated])

Evidence showed SD (treated) - plasma caused some deaths in liver transplant, severe liver disease and known coagulapathies patients

iii) Methylene Blue

Poor evidence on the safety aspect of Methylene Blue technology used in plasma products. There was no long term studies conducted on carcinogenicity and reproductive toxicity in Methylene blue treated plasma.

Effectiveness

i) Psoralen light treatment (Amotosalen- HCL)

Fair evidence on the effectiveness of INTERCEPT blood system when used on platelet-plasma.

ii) Riboflavin light treated (RLT)

Poor evidence on the effectiveness of Riboflavin light treated (RLT) technology when used in plasma. Clinical studies using Mirasol (riboflavin) pathogen inactivation technology is still underway.

iii) Solvent Deteregent (SD- plasma)

Fair evidence on the effectiveness of solvent detergent technology, when used for plasma and fresh frozen plasma.

Cost Effectiveness

i) SD- FFP transfusion was cost effective in patient's ≤ 48 years of age and in older patients with good clinical prognosis.
ii) In another baseline study on cost effectiveness of transfusing virus-inactivated plasma instead of standard plasma showed a cost-effectiveness ratio of $[redacted] +/- $[redacted] per quality-adjusted life year gained. The transfusion of virus-inactivated plasma produces little health benefit at a very high cost.
iii) There is no retrievable evidence on cost effectiveness for other pathogen inactivation technologies used for plasma.

7.0. A RECOMMENDATION

Based on the above review:

- Photochemical treatment (Amotosalen) and Solvent detergent (SD- plasma) may be recommended as pathogen inactivation technology for plasma.
- However, SD – treated plasma is not recommended for patients after liver transplant, severe liver disease and with known coagulopathies.
- Insufficient evidence to recommend Methylene Blue and Riboflavin light treated technologies as pathogen inactivation technologies for plasma. Hence, more clinical research is warranted before considering the technologies for plasma or fresh frozen plasma.

B. PLATELET

5.1.B SAFETY

INAHTA briefs by Catalan Agency for Health Technology Assessment and Research-CAHTA, Spain (CAHTA) also reported that pathogen inactivation treatment using Amotosalen (photochemical treatment) is also safe to be used in platelets concentrates. The results from active hemosurveillance subsequent to its commercialisation showed good patient (adult and pediatric) tolerance in 14 493 transfusions of platelet concentrations treated with amotosalen.[9]

Health Technology Assessment by Canadian Agency for Drugs and Technologies in Health (CADTH), reviewed the pathogen reduction technologies (PRTs) of INTERCEPT Blood System and Mirasol. INTERCEPT was licensed for use in Europe in 2006 and Mirasol received European approval in 2008. These technologies are currently not licensed in North America. Both systems used a photochemical treatment (PCT) approach which combines the blood products with photoactive chemical (amotosalen) for INTERCEPT and [riboflavin (vitamin B2)] for Mirasol. Both photochemical processes were claimed to inactivate pathogens without adversely affecting the quality or safety of blood products. [10 level 1]

The Randomised Controlled Trial (RCT) by Ambruso et al (2009) had compared Mirasol treated platelet with control platelets (no treatment with PRT). Patients involved were all had a confirmed diagnosis of thrombocytopenia due to chemotherapy or heamatopoetic stem cell transplantation. The serum of 44 patients received Mirasol- treated platelets and 22 patients received controlled platelets. Patients over 28-day study period was analysed for the presence of neoantigens. No patients in either group had antibodies to platelet neoantigens.

Therefore the author concluded that neoantigen formation is not a side effect of the Mirasol treatment. The immunereactivity of Mirasol-treated platelets was similar to that of control platelets. However, it was indicated that this study was funded by Mirasol manufactures.[10] level 1

CADTH also reviewed a prospective cohort study on the safety aspect of INTERCEPT-treated platelet (amotosalen +UVA) components in a broad patient population. Blood transfusion centres using the INTERCEPT Blood System for routine production of platelet components were invited to participate in the study. A total of 5,106 transfusions with INTERCEPT –treated platelets were performed in 651 patients over a period of approximately two years. Patients with heamatological or oncological conditions accounted for the majority (58.1%) of the participants. The mean number of transfusion per patients was 7.8 ±16.2 (SD) with a range of one to 156. Adverse events (AEs) were reported in 55 transfusions [1.1%; 95% CI; 0.81 to 1.40] corresponding to 42 patients (6.4%). AEs classified as related to transfusion included chills, fever, uticaria (hives), dyspenea (shortness of breath), nausea or vomiting, itching, flushing and hypotension. In this study, three AEs were reported as serious. The author reported that AEs occurred after a single transfusion or after multiple transfusions. Therefore, the authors suggested that repeated exposure to INTERCEPT-treated platelets did not increase the risk of transfusion- related reaction. INTERCEPT-treated platelets were well- tolerated and that the AEs profile of the patients receiving INTERCEPT – treated platelets was consistent with other studies evaluating conventional prepared platelets. However, this study did not have a control group receiving untreated platelets. This represents a limitation of the study. Furthermore this study received a funding from the manufactures (Cerus) and two of the authors were employed by Cerus. [10] level 1

Another RCT, double blind, intention to treat analysis conducted (in vivo phase II study) by Van Rhenen et. al. 2003, between June 1998 to 2000 (EURO SPRITE trial) on photochemical treatment (PCT) for platelets. One hundred three patients received either standard control platelets prepared by buffy coat method of buffy coat prepared platelets treated with amatosalen for pathogen inactivation. Fifty-two patients received 390 transfusions of amotosalen-treated platelets and 51 patients received 286 transfusions of control platelets. All patients were evaluated following platelet transfusion for transfusion-related symptoms and signs. Post transfusion events classified as acute transfusion reactions included fever, chills, nausea, skin rash, urticaria, bronchospasm, tachycardia, hypotension, hypertension, hemoglobinuria, hemolysis, and change in vital signs within six hours following platelet transfusion. In cycle 1, 6% of test transfusions were associated with acute reactions, compared with 5% of reference platelet transfusions ($p \geq 0.61$). A total of 147 types of adverse events were reported in 5% or more of the patient population evaluated during cycle 1 and cycle 2. Overall, there was no difference in the incidence of adverse events by system organ class between the two treatment groups. Serious adverse events were reported in 14 (27%) patients randomised to the test platelet treatment group and in 13 (25%) patients randomised to the reference platelet group. Adverse events reported as related to platelet transfusion were not statistically significantly different between the groups (p=0.20). No study transfusions demonstrated transfusion-associated bacteremia. Four test patients and five reference patients died while on study. No deaths were related to study transfusions

adverse events. Based on peritransfusion hemostatic assessments, 71% of test and 63% of reference patients had at least one episode of bleeding before transfusion (p=0.36). A high and equal proportion of patients had at least one hemorrhagic adverse event. The most frequent hemorrhagic adverse events were epistaxis (42% test vs 41% reference), gingival bleeding (17% test vs 12%reference), injection site hemorrhage (17% test vs 6% reference), purpura (15% test vs 14% reference), petechiae (13% test vs 16%reference), and hematoma (13% test vs 8% reference). Only 6% of patients in each group experienced severe hemorrhagic adverse events. Bleeding also was assessed indirectly by comparing the number of red blood cell units transfused during the transfusion periods. Based on this clinical trial, pooled platelet components prepared with PCT and stored for up to 5 days offer the potential to reduce transfusion-associated infections and inactivate residual contaminating leukocytes using a processing system that is compatible with the current method of preparing therapeutic doses of buffy coat platelets. [15 Level 1]

PLATELETS
5.2 B. EFFECTIVENESS

PHOTOCHEMICAL TREATMENT
A) Amotosalen system, *S-59* + UVA

HTA report by CADTH, included the SPRINT trial (randomised control phase III trial) which evaluated the clinical effectiveness of PCT (amatosalen+ UVA) treated platelets in patients with thrombocytopenia. In this RCT, the patients were randomised to receive either PCT-treated platelets (n=318) or control platelets (n=327). There were no significant differences in the baseline patient's characteristics. The patients received platelets until they became independent of transfusion (seven days without transfusions) or for a maximum of 28 days. Before receiving transfusion, platelet counts of the group did not differ significantly (PCT group = 15.1 x 10^9/L, control group = 15.2 x 10^9/L). Patients receiving transfusions with PCT- treated platelets had lower post- transfusion platelet counts than patients in the control group (36.5 x 10^9/L versus 49.5 x 10^9/L). Besides that patients in the PCT group had a shorter interval time between transfusions than the control group (8.4 versus 6.2). The author noted the mean dose of platelets per transfusion was lower in PCT group compared with the control group [3.7 x 10^{11} platelet per mililitre (mL) versus 4.0 x 10^{11} platelets/L]. Despite the differences in the secondary outcome the author concluded that the effectiveness of PCT platelets was similar to that of control platelets. This study was funded by Cerus, the manufactures of INTERCEPT. [10 Level 1]

In another RCT double blind, intention to treat analysis conducted by Van Rhenen et al 2003 between June 1998 to 2000 (euroSPRITE trial.) The study population was patients with thrombocytopenia or receiving therapy expected threshold of <20x10^9) gave informed consent and were randomised to receive transfusion support. A total of 103 patients (52 test and 51 references) received at least one study transfusion.The test platelets which was pooled concentrates were leukoreduced by filtration followed by photochemical treatment (PCT) with 150µM S-59 and 3 J/cm2, ultraviolet A (UVA) treatment (Helinx Technology; Cerus Corperation, Concord CA) for pathogen and leukocyte inactivation. The targeted platelet content of reference pooled components was 3.0 x 10^{11} platelets. During the cycle 1,

311(80%) of 390 test transfusion and 256(90%) of 286 reference transfusion were prepared according to protocol. The mean total platelet dose of on-protocol transfusion for both treatment groups and reference group was similar (test mean dose $21.3x10^{11}$ vs. reference mean total dose 21.2 $x10^{11}$). PCT– treated and non- PCT – treated platelets gave comparable 24-hour post transfusion platelet counts for equal doses in cycle 1 and post transfusion platelet counts for patients enrolled in cycle 2. Limited number of patients enrolled in cycle 2 (10 test and 2 reference patient). The treatment groups did not differ significantly with respect to the 1- hour platelet count (p=0.47). The estimated effect of PCT was an increase in the one- hour platelet count of $4x\ 10^9$/L. The interaction terms for PCT and dose were not significant (p=0.47). Similarly, the treatment groups did not differ significantly with respect to the 24-hour platelet count in cycle 2 (P =0 .90). The estimated effect of PCT was an increase in the platelet count of $1\ x10^9$/L (95% CI, -10 to 11 x 10^9/L). PCT treated and non-PCT-treated platelets provided comparable 1- hour and 24-hour platelet counts for equal doses in cycle 2. The data support the conclusion that pooled buffy-coat platelet components treated with the S-59 pathogen inactivation device and stored for up to 5 days were comparable to conventional platelet components used for transfusion in thrombocytopenic patients. [15 Level 1]

Kerikhoffs JL et. al. 2010, conducted a multicentre open label randomised and non-inferiority trial. This trial compared the clinical effectiveness of buffy-coat derived leucoreduced platelet concentrates (PC) stored for up to 7 days in plasma with platelets stored in platelet additive solution III (PASIII) without and with amotosalen HCI/ ultraviolet-A (UVA) photochemical pathogen reduction (PR-/PASIII).

Based on the abstract of this study, the primary endpoint evaluated was 1-h corrected count increment (CCI), secondary endpoint was 24-h CCI, bleeding, transfusion requirement on red cells and PC, platelet transfusion interval and adverse transfusion reactions. Compared to plasma-PC in the intention to treat analysis of 278 evaluable patients the mean differences for 1-h CCI of PR-PASIII-PC and PASIII-PC was -31% ($p<0.0001$) and -9%(P= n.s) respectively. Twenty-seven patients (32%) had bleeding events in the PR- PASIII arm, as compared to 19(19%) in the plasma arm and 14(15%) in the PASIII arm (p=0.034). Despite the potential advantages of pathogen (and leukocyte) inactivation of amotosalen-HCI/UVA-treated platelet products, their clinical efficacy is inferior to platelets stored in plasma, warranting a critical reappraisal of employing this technique for clinical use. [16 Level 1]

In vitro studies have found that after processing through the INTERCEPT Blood System, there is no insignificant drop (in the range of 8-10%) in the platelets present in the bag. This was due to the manipulation of platelets through three different bags, and agitation needed to mix the amotosalen with platelets and to expose amotosalen and photoproducts to the compound absorption device. In the Moog et al study, single-donor platelet concentrates contained mean platelet counts of $3.06\pm0.27x10^{11}$. On completion of the photochemical treatment, the mean count was $2.62\pm0.27\ x\ 10^{11}$, representing a loss of 9.7%. Also in the Moog study, significant decrease in pH was identified after PCT, with a mean drop to 6.98± 0.08.

Compared to the control, however this pH level was well above the required 6.8 limit required in Europe, and the pH remained above 6.8 until the end of the study, at 5 days of storage. [6 level III]

Another in Vitro study looked at PCT platelet survival following indium-III radiolabelling of the treated autologous platelets. The normal span of platelets survival is broad ranging from 5 to 7.3 days within 33-66% recovery. Recovery in PCT treated was 43%±8.7% and life span was 4.8±1.3 days. Although within the lower range of normal and significantly lower than controls, the findings were consistent with other in vitro studies. The author found that, in vitro studies, the label dissociation was higher in PCT platelets than in control platelets. [6 level III]

MIRASOL riboflavin (vitamin B2)

A multicenter, open-label, parallel-group noninferiority RCT was conducted in France by the Etablissement Francais du Sang and university hospitals (n = 6). This study compared PRT-PLTs (MIRASOL) and standard (reference) platelet products transfused to thrombocytopenic hematology and/or oncology patients. The aim of this clinical trial was to determine whether pathogen-reduced PLTs (PRT-PLTs) are as effective as standard untreated platelet products. The corrected count increment 1 hour post transfusion (CCI1hour) was evaluated in patients with chemotherapy-induced thrombocytopenia. Safety information of PRTPLTs was also documented on all adverse events. The primary efficacy outcome was the CCI 1 hour measured 30 to 90 minutes post transfusion for each of a maximum of eight on-protocol platelet transfusions per patient occurring within the 28-day treatment period. Six centers enrolled 118 patients into the study between December 2005 and September 2007: 60 patients received PRT-PLTs and 58 received reference PLTs.

The pre-specified primary outcome analysis for the CCI 1hour was based on a maximum of eight PLT transfusions per patient occurring in the 28-day treatment period: 258 for PRT-PLTs and 209 for the reference group (total 467). The test for homogeneity of treatment effects between sites for the CCI 1hour was not significant ($p = 0.1728$), indicating that data from all sites could be pooled to estimate the treatment effect. The Least square (LS) mean CCI 1hour in the PRT-PLT group was 11,725 (Standard error [SE], 1140) and in the reference group was 16,939 (SE, 1149), a difference of -5214 (95% CI, -7542 to -2887; $p < 0.0001$).

The secondary outcomes of CCI 24hour was analysed according to the time-compliant and extended time periods and adjusted for pre-transfusion platelet count as a continuous variable and site. The test for homogeneity of the effect of treatment between sites for the CCI 24hour was not significant ($p = 0.1336$) allowing for data to be pooled. The LS mean for time-compliant CCI 24hour was 6676 (SE, 883) for the PRT-PLTs and 9886 (SE, 915) in the reference group (difference, -3210; 95% CI, -5160 to -1260). The odds (OR, 0.284; 95% CI, 0.105 to 0.767; $p = 0.0130$) of achieving a successful response is significantly lower in the PRT-PLTs arm for the CCI 1hour among time-compliant transfusions but not significantly lower for the CCI 24hour among time compliant transfusions (OR, 0.481; 95% CI, 0.211 to 1.098; $p = 0.0822$). Similar results were found when considering transfusions within the extended time period although the 24-hour CCI result becomes significant in this analysis. Twenty-eight day treatment period was included in this analysis with the mean number of

days between transfusions was 2.16 (SD, 1.69) for PRT-PLTs and 2.30 (SD, 1.48) for the reference arm (p = 0.2903). The mean number of platelet transfusions per patient-day during the treatment period (includes on and off-protocol transfusions) was not significantly different: PRT-PLTs 0.24 (SD, 0.16) and reference group 0.20 (SD, 0.19; p = 0.2046). None of the differences observed were significant. RBC requirements were similar in the two groups.

In the PRT-PLT group 183 RBC units were transfused in the treatment and follow-up periods: 155 were given in the treatment period with a mean (SD) per patient of 2.8 (1.7). In the reference group 142 of 160 RBC units were given in the treatment group with a mean per patient of 2.6 (2.4; p = 0.7257). Overall PLT and RBC utilisation in the two study groups was not significantly different, suggesting that the lower CCIs with the PRT-PLTs did not translate into significantly higher blood product use. Therefore the author concluded further studies are needed to show whether the lower CCI observed with PRT-PLTs is associated with any change in the risk of bleeding the noninferiority of PRT-PLTs compared to reference platelets using the surrogate outcome measure of CCI 1hour. Safety data did not identify any major adverse effects associated with the transfusion of PRT-PLTs. [17 Level 1]

Goodrich et al looked at bacterial pathogen reduction in platelets in 2002. Riboflavin (50µM) was added, and the unit was spiked to 5-6log/mL titers with S. epidermidis, Escherichia Coli, S. areus, B. cereus, and K. pneumonia. Illumination time was with 6-7J/cm^2 of UV light. A low- titer experiment paralleled the above, spiking the units to 2 log/mL titers and using 7/ Jcm^2 of UV light. Significant reduction occurred from 3.1 to 5.5 log/mL reduction. Even the low titers were 100-1000 times higher than levels expected in platelets at the time of donation. Thus, the phoactivation of Riboflavin appears to be adequate for pathogen reduction in blood products. [6 level III]

Thionine/UV Light

A narrative review by Bryant BJ et. al. 2007, indicated that thionine (phenothiazine dye) can be safely used in place of MB with the same type low-pressure sodium UV light leading to a comparable spectrum of pathogen inactivation. Measurements of platelet function such as change in morphology, aggregation, and activation as well as biochemical parameters are just slightly affected by thionine/UV light treatment. There is no change in storage duration after treatment. Thionine with UV light treatment alone does not inactivate bacteria and leukocytes. Inactivation of bacteria can be accomplished with an additional step consisting of UV-B irradiation for approximately 2 to 4 minutes (1.2–2.4 J/cm2). The review claimed that an added advantage of the extra UV-B irradiation step is more effective for viral inactivation. However, the Thionine-based pathogen inactivation systems are currently under development and in clinical testing. [3 Level III]

5.4 B. COST EFFECTIVENESS

CADTH Health Technology Assessment report revealed information regarding the economy evaluations for pathogen reduction technology (PRT). The study by Janssen et. al. 2006, performed a cost –utility analysis which evaluated the cost- effectiveness of PRT (particular brand was not specified) compared to an untreated sample diversion pouch. The cost-effectiveness of these interventions was analysed after the introduction of the diversion pouch

during blood collection. The diversion pouch collects the first 20 to 30 ml of blood which contains the highest level of bacteria. A hypothetical population of 100,000 patients undergoing platelet transfusions was evaluated. This study took place in the Netherlands. The price year was 2002, the discounting rate was 4%, and costs were reported in US dollars. The estimation of quality –adjusted life years (QALYs) was derived using Markov model. The author reported that the additional cost per QALY gained was $[redacted] when using PRT with the sample diversion pouch compared to sample diversion pouch alone. The results obtained were most sensitive to the probability of sepsis, probability of death given sepsis, patients' quality – adjusted life expectancy, and probability of bacterial contamination. Therefore it was concluded that with the unknown probabilities, the cost effectiveness was uncertain.[10 Level 1]

Another study by Moeremas et. al. 2006, conducted a cost –utility analysis to evaluate cost effectiveness of INTERCEPT Blood system. The study compared a hypothetical population receiving INTERCEPT-treated platelets with a population received control platelets (prepared conventionally). The study population was people with haematological malignancies, breast cancer, and patients undergoing coronary artery bypass graft surgery. This study was conducted in Belgium and the costs were reported in Euros. The price year and the rate of discounting were not reported. It was indicated that with the assumption of an absence of an emerging virus, the incremental cost- effectiveness ratio (ICER) ranged from €[redacted] to €[redacted] per QALY. The author concluded that the implementation of INTERCEPT could be considered cost-effectiveness. [10 Level 1]

Similarly another study was by Postma et al, which was published in 2005. This study was conducted in Netherlands and the costs were expressed in Euros. The price year was 2003 and future costs were discounted at a rate of 4%. Two main assumptions were made, the PRT was 100% effective in eliminating pathogens and the PRT- treated platelets were not associated with AEs. Additional sensitivity analysis was performed taking in account various assumptions including risk of sepsis. The cost-effectiveness of PRT was €[redacted] per life year gained. The author concluded that PRT was cost- effective. [10 Level 1]

There was also a cost-utility analysis comparing the INTERCEPT Blood System with control single donor platelets. The study was conducted in Japan, by Staginnus and Corash, 2004. The price year was not stated; however, resource use data was taken from studies that were published between 2002 and 2004. The cost was presented in Japanese Yen. A one way sensitivity analysis was performed. The cost per QALY gained of using INTERCEPT-treated platelets compared with controlled platelet ranged from ¥ [redacted] (for hip arthroplasty) to ¥ 99,000 (for the treatment of acute lymphocytic leukemia with progenitor cell transplantation). The author concluded that the treatment of platelets with INTERCEPT Blood System was a cost- effective treatment strategy compared with treatment strategies in Japan including the use of nucleic acid testing to detect pathogens. [10 Level 1]

6.0 . B CONCLUSION

Safety

i) Amotosalen and Mirosal (Riboflavin)

Good evidence was obtained on the safety aspect of Amotosalen (photochemical treatment) and Mirosal (Riboflavin) used as pathogen inactivation technology for platelets. There was good patients tolerance for platelets treated with amotosalen. Both Amotosalen and Mirosol technologies did not affect the quality of platelets concentrates.

Effectiveness

i) Amotosalen and Mirosal (Riboflavin)

Fair evidence was obtained with regards to the effectiveness of Amotosalen (photochemical treatment) and Mirosal (Riboflavin) pathogen inacativation technology for platelets

ii) Thionine/UV Light

Low level of evidence on the effectiveness of Thionine/UV Light used as pathogen inactivation technology for platelets.

Cost effectiveness

i) Amatosalen

Sufficient evidence to show that Amatosalen (photochemical technology) is cost effective compared with non treated plaletets used for transfusions.

7.0. B RECOMMENDATION

Based on the above review:-

- Amotosalen and Mirasol (Riboflavin) pathogen inactivation technologies can be used for platelet concentrates.
- More research is warranted on Thionine /UV Light when used as pathogen inactivation on platelet concentrates.

RED BLOOD CELL (RBC)

5.1.C SAFETY

S-303

Jorge et. al. 2006, conducted a study which enrolled 42 subjects, in a two-arm, single blinded RCT. In this study, subjects were assigned to receive either S-303 RBCs or control RBCs. Subjects received a single transfusion of 10 to 15 mL of either 51Cr-labeled 35-day-old S-303-treated RBCs (test) or sham-treated (control) 51Cr-labeled 35-day-old RBCs. Radiolabeling and determination of 24-hour post transfusion recovery for all studies were performed with established methods Phase 1B design. The second study was a single-arm open-label trial to investigate whether repeated exposures to S-303-treated autologous RBCs would lead to immune-mediated destruction of S-303 RBCs. All of the subjects from Phase 1A were invited to participate in the second trial. Twenty-eight subjects were enrolled. Subjects donated whole blood that was treated with the same S-303 process used in Phase 1A and Phase 1C design. These studies were designed to examine several key aspects of RBCs function in vivo. The first two trials (1A and 1B) measured post transfusion recovery of S-303 RBCs after single and repeated exposures to assess viability and immune responses to potential neoantigens.

In the third study (1C), RBCs were prepared with a compound adsorption device (CAD), stored for 35 days, and median life span after transfusion was determined. Thirty-five days after donation, aliquots of the autologous study RBCs were removed for radiolabeling and transfused into subjects following the procedure of Moroff and coworkers. For all three studies, 24-hour post transfusion recovery was determined by collecting samples at 5, 7.5, 10, 12.5, 15, 20, 30, and 60 minutes after transfusion and 24 hours after transfusion.

In Phase 1C, blood samples were collected from the subjects on the day of transfusion, 24 hours after transfusion, and for 5 weeks after each transfusion to determine circulating life span based on the methods outlined by the International Committee for Standardization in Hematology (ICSH). All adverse events were recorded from the start of the first RBC transfusion through seven days after the last transfusion. The study found that in a Phase 3 trial of chronic transfusion support for patients with thalassaemia and sickle cell anemia, detected antibodies with specificity to RBC treated with S-303, prepared with the first-generation process, in two patients after repeated transfusions. Serum samples from these two patients were nonreactive in an in vitro monocyte phagocytosis assay, previously shown to correlate with RBC antibody physiologic activity. During the follow-up of patients transfused with S-303 RBCs for support of cardiovascular surgery, two patients who had not been exposed to S-303 RBCs were found to have transient low-titer antibodies with specificity for RBC treated with S-303. Both the test and control treatment groups exhibited mean post transfusion recovery greater than 75 percent. No evidence of immune responses to S-303 RBCs after repeated exposures were detected by in vitro crossmatch assays with autologous S-303 RBC, direct antiglobulin test (DAT) and antibody screen with a commercial cell pan. RBC life span was calculated by three different methods: a linear model, an exponential model, and a weighted mean linear-exponential model. RBC recoveries for test and control RBCs were weakly correlated with the life span measurements, correlation coefficients of 0.18 and 0.28, respectively. In preclinical studies, S-303 RBCs prepared with up to 1.0 mmol per L S-303 and 10 mmol per L Glutathione (GSH) demonstrated no toxicity in a wide range of in vitro and in vivo tests, including the absence of carcinogenicity with prolonged exposure in p53-deficient mice that are highly sensitive to carcinogens. It appeared that some subjects may form antibodies to S-303 RBC or have preformed antibodies cross-reactive with S- 303 RBCs. The mean 24-hour recovery of 35-day old S-303 RBCs was less than untreated RBCs, but greater than 75 percent. RBCs treated with S-303 and stored for 35 days exhibited median life span not different from that of conventional RBCs.[18 Level 1]

5.2 C. EFFECTIVENESS

Red Blood Cells (RBCs)

S-303

A randomised, double-blind trial evaluated the clinical efficacy of RBCs treated with pathogen inactivation with S-303, a synthetic labile alkylating agent. This was a phase III clinical trial evaluating the efficacy and safety of S-303–treated RBCs compared to conventional RBCs in the clinical setting of transfusion support for complex cardiac surgical procedure. A sample size of 100 patients per group was randomised in a one-to-one ratio to receive either S- 303–treated or control RBC transfusion during surgery and for 6 days thereafter. The trial was terminated prematurely owing to detection of antibodies to S-303

RBCs in a companion trial of S-303–treated RBCs administered in the setting of chronic transfusion support.

All transfused patients were asked to consent to a follow-up trial for further evaluation for safety and detection of antibodies to S-303–treated RBCs. Hundred forty eight transfused patients were equally distributed between the test and control groups in terms of demographics and indications for surgery. One-hundred forty-one patients (95%) completed the trial through Day 27; reasons for not completing the trial were death (3 patients), lost to follow-up (2 patients), and other reasons (2 patients): first-study RBC transfusion received after Day 6 (1 patient) and issues with transportation to study site (1 patient). Fifty-one (34.5%) patients who received transfusions participated in the follow-up study: 27 (36.5%) test patients and 24 (32.4%) control patients. Overall, 41 percent of all RBCs were transfused during surgery. The mean change in patients' heamoglobin (Hb) levels from baseline to the end of study was a decrement of 2.4 g per dL, and the mean change after each transfusion was an increment of 1.4 g per dL. Thirteen (8.8%) patients, seven in the test group and six in the control group, received off-study RBC transfusions owing to the difficulty in maintaining adequate inventory of study units at all sites and the unpredictability of RBC usage in this setting. The mean number of off-study RBC transfusions in these 13 patients was 1.0. No significant differences were noted between the test and control groups. The number of patients transfused with other blood products (PLTs, fresh-frozen plasma [FFP], and cryoprecipitate), and the mean number of units of other blood products transfused was similar between treatment groups. Serum samples from 127 patients (64 tests and 63 controls) were tested for antibodies to S-303–treated RBCs. One control patient had a positive result with S-303 RBC. The patient's serum sample was negative on day 32 but had a positive result 535 days after surgery; the reaction was 3+ positive and specific for S-303–treated RBCs in a PEG assay. A competitive inhibition assay with S-300, a nonreactive S-303 derivative, confirmed the specificity for S-303 RBC. A second follow-up sample taken on day 838 and tested with the same protocol in a different reference laboratory was negative for S-303–treated and conventional RBCs were equivalent with respect to clinical efficacy and safety in supporting the transfusion needs of cardiac surgery patients. Investigations are under way to ascertain the significance of S-303 RBC antibodies and to prevent their occurrence.[19 Level I]

PEN110

Extensive research has been conducted with regards to the pathogen inactivation capacity of PEN110. These studies were very specific in demonstrating the exact nature of the action of PEN110 on the virus and on the kinetics of inactivation and demonstrates the activity in the presence of high and low titers of viruses.

One of the initial studies evaluated the effect of PEN 110 on four enveloped viruses, six non-enveloped viruses, and cell-associated HIV. The viruses were chosen to include a wide array of physiological characteristics such as size, structure, biochemical composition, and whether the virus was cell associated or cell free. Of the enveloped types, Bovine Viral Diarrhea Virus (BVDV) and pseudorabies virus (PRV) are recognised models for HCV and herpes virus. Other enveloped viruses included in the study were sinbis (SV) virus and vesicularstomatitis Indiana virus (VSIV).

The non- enveloped viruses included porcine parvovirus (PPV), which is a model for B19 virus. Vesicular exanthema of swine virus (VESV), is a model for hepatitis E and Norwalk viruses. In these studies, the inactivation process was altered by using 1M sodium thiosulphate (STS) and 1M 3-morpholinopropanesulphonic acid (MOPS) to chemically stop the PEN 110 reaction (rather than washing) to ensure that the decreased viral cyctotoxic effect was due to PEN111 alone and not washing. In addition, red cell units were collected in three different additive solution storage media CPD/AS-1, CP2D/AS-3, and CPD/As-5. Virus titers were determined by tissue culture infectious dose 50% ($TCID_{50}$) assay and plaque-forming units assay. The kinetics of viral reduction was determined by collecting samples at 3, 6, 12, 18 and 22 hours during incubation with PEN111. Three of the non-enveloped (VESV, foot and mouth disease virus [FMDV], bluetongue virus [BTV] and two of the enveloped viruses (SV and VSIV) were reduced to the level of detection of the assay within 3 hours of incubation. These viruses were reduced by factors ranging from 5.4 to 7.5 $\log_{10}$ $TCID_{50}$ per milliliter. BVDV and PRV took longer 12 hours to be reduced to the level of detection. Three of the non-envoloped viruses PPV, reo-3 and Adeno-2 took 18 hours to be reduced to the level of detection. The reduction factors for these viruses were >6.2 $\log_{10}$ $TCID_{50}$ per milileter, >5.3 and >5.6 $\log_{10}$ PFU per milliliter, respectively. For cellular HIV the reduction to the level of detection took 6 hours. [20 Level II].

Another series of experiments investigating PEN110 inactivation of HIV. The effect of PEN110 on the structure of the virus by EM, the ability of virus to enter and the activity after the treatment of reverse transcriptase using PEN110 were investigated. The demonstration of the PEN110 treatment effect was estimated via the $TCID_{50}$ assay. The structure of the virus did not change and the ability of the virus to infect cells remained intact after PEN110. PEN110 effectively reduced HIV-1 to the limit of detection for a reduction factor of at least 5.57 log 50 percent tissue culture infectious dose per bulk test. The PEN110-treated virions maintained their morphology, protein integrity, and functionality However; the viral reverse transcriptase did not function, consistent with the alteration of nucleic acid by PEN110. The HIV reduction took place primarily in the first 6 hours and decrease to the level of detection after 12 hours. [21 Level II]

6.0. C. CONCLUSION

RED BLOOD CELLS (RBC)

Safety

i) S 303

Fair level of evidence to show the safety of S303 when using as pathogen inactivation technology for RBC.

Effectiveness

i) S 303

Fair evidence obtained on the effectiveness of S303 as a pathogen inactivation technology when used on RBC.

ii) PEN110

Poor evidence for the effectiveness of PEN110 as a pathogen inactivation technology when used on RBC.

Cost effectiveness

No retrievable evidence on the cost effectiveness of S303 and PEN110 pathogen inactivation technologies when used for RBC.

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9. APPENDIX

9.1 Appendix 1

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)