Joint UKBTS Professional Advisory Committee [1]
Summary Sheet

1. Paper for the JPAC meeting on:	09 March 2017
2. Date submitted:	03 March 2017
3. Title (including version no.):	Effect of irradiation on platelet function
4. Author(s):	Drs Rebecca Cardigan & Stanworth on behalf of the SAC on Blood Components
5. Brief summary:	Approximately 50% of platelets issued by NHSBT are irradiated, whereas all other UK Blood Services universally irradiated platelets. To simplify platelet stock management, reduce wastage and reduce the risk of issuing non-irradiated platelets to patients for whom irradiated platelets are indicated, NHSBT is considering irradiating all PC. The question has therefore arisen as to what effect irradiation has on platelet function and whether it is as benign as we have previously thought it to be, in light of more recent proteomic/metabolomic studies on platelets. SACBC were asked to review the literature on this subject.
6. Action required by JPAC: (What do you want JPAC to do in response to this paper?) e.g. • endorse a specific recommendation • advise where there is a choice of possible actions • advise on priorities within the work plan • provide a steer on policy	For information, but discussion of the wider considerations around the need to irradiate platelets at all, given universal LD in the UK.
7. Any other relevant information:	

(1) **J**oint **U**nited **K**ingdom **B**lood **T**ransfusion **S**ervices **P**rofessional **A**dvisory **C**ommittee

Effect of Irradiation on Platelet Function

Simon Stanworth, November 2016; updated from a paper prepared by Rebecca Cardigan, 22nd August 2011

Background

Platelet concentrates (PC) are irradiated to inactivate residual lymphocytes to prevent transfusion-associated graft versus host disease (TA-GVHD) in susceptible patients. Approximately 50% of platelets issued by NHSBT are irradiated, whereas all other UK Blood Services universally irradiated platelets. To simplify platelet stock management, reduce wastage and reduce the risk of issuing non-irradiated platelets to patients for whom irradiated platelets are indicated, NHSBT is considering irradiating all PC. The question has therefore arisen as to what effect irradiation has on platelet function. The purpose of this paper is to review the literature on this subject, particularly in view of two significant changes that have occurred within NHSBT: 1) X-irradiation is now used in some centres as an alternative to gamma irradiation and 2) the shelf-life of platelets is now 7 days.

The information from this paper needs to feed into other processes for determining the relative merits of universal irradiation of platelets for NHSBT. This will be achieved through the completion of the ABO Risk-Based Decision Making Framework and consultation with stakeholders.

There is a wider question as to whether there is a need to irradiate platelets at all, given the introduction of universal leucocyte depletion in 1998/1999 in the UK. This is beyond the scope of this paper. Given the severity of the risk of TA-GvHD, and that any such change would have to be widely accepted by hospitals, this would likely to have to be reviewed by SaBTO.

Studies examining the effect of irradiation on platelet function

The BCSH Guidelines on the Use of Irradiated Components (Treleaven et al, 2010) state that ‘gamma irradiation below 50 Gy has not been shown to produce significant clinical changes in platelet function’ and reference three studies to support this statement (Rock et al, 1988; Duguid et al, 1991; Sweeney et al, 1994). They therefore recommend that platelets may be irradiated at any point in their shelf-life and may be stored up to their normal shelf-life thereafter.

There are other published studies in the literature and these can be divided into three types of study:

- Laboratory studies
- Studies in healthy volunteers
- Studies in thrombocytopenic patients

A summary of clinical studies is shown in Table 1. These show that irradiation of platelets at doses of 15-30 Gy for up to 5 days does not appear to effect the recovery or survival of platelets in healthy volunteers. A small study in stable patients showed that there was no effect of irradiation on the 1 and 20 hour count increment (Duguid et al. An analysis of data from the multi-centre TRAP trial concluded that the effect of

gamma irradiation on platelets was small and dependent upon the type of platelets: there was no effect for apheresis platelets but a mean reduction in the 1 hour count increment for PRP platelets of 7 x 10^9/l from a mean control of 26.9 x10^9 (Slichter et al, 2005). In the latter study there was no effect of irradiation for any type of platelet on the 18-24 hour count increment or transfusion interval. Button et al showed that the effects on platelets are dose-dependent, as might be expected. The dose recommended by BCSH Guidelines and the Guidelines for UK Blood Transfusion Services is a minimum of 25 Gy with no part of the pack exposed to more than 50Gy. There are no clinical studies that have irradiated and stored platelets for 7 days.

A summary of laboratory studies is shown in Table 2. These studies suggest that gamma irradiation of platelets between days 0-5 of storage has limited effect on the in vitro function of platelets, even when these are stored for up to day 7.

All of the published studies have use gamma irradiation. Following a review of data and consultation with biophysicists, JPAC concluded that gamma and X-irradiation of blood components can be regarded as equivalent. The data reviewed included in vitro data on platelet function to day 7 of storage.

Pathogen inactivation of platelets would obviate the need for irradiation since the systems that are licensed have been shown to inactivate leucocytes.

Update. 27 October 2016. Simon Stanworth

A range of additional clinical and laboratory studies were identified by an update of the previous literature search (SRI, SS) and incorporated into Tables 1 & 2. The data would continue to support (very) limited effects of gamma irradiation on a range of measures of platelet function, but it should be noted that more recent novel techniques including proteomic analysis and studies of platelet microRNA's and mRNAs, suggest changes do occur by comparison to untreated platelets, the full clinical significance of which is unclear.

A number of laboratory studies were identified which were primarily evaluating pathogen inactivation of platelets, but which (variably) included a control group of irradiation – no consistent effects of changes by irradiation were reported (e.g. Van Aelst). Finally, it should also be recognised that policies of universal irradiation are applied in a number of hospitals in North America and in Japan, and no adverse consequences have been raised or reported.

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Table 1. Clinical Studies Assessing the Effect of Irradiation on Platelets

Type of Platelet	LD?	Source & Dose of Irradiation	Irradiated on	Stored until	Patient population	n=	Summary of findings	Reference
PRP	No	Gamma 50 Gy	Day 3	Day 3	Normal Volunteers Stable thrombocytopenic	5	No difference in survival, 30% reduction in recovery. Correction of bleeding time in donors given aspirin diminished and delayed. No effect on count increments or haemostasis following transfusion to thrombocytopenic patients.	Button et al, 1981
PRP	No	Gamma 30 Gy	Day 0	Day 5	Normal Volunteers	6	No significant difference in recovery or survival. Recovery 51%±13 control v 50±11 irradiated Survival 5.9d±0.5 control v 5.6±1.1 irradiated	Read et al 1988
Apheresis & PRP	No	Gamma 15 Gy	Point of transfusion (D1-5)	Day 5	Stable thrombocytopenic	26	No significant difference in count increments: 1 hour: 10.6 control v 10.6 irradiated 20 hour: 6.4 control v 6.9 iradiated	Duguid et al, 1991
Apheresis	?	Gamma 25 Gy	Day 1 or 3	Day 5	Normal volunteers?	10-12	No significant difference in recovery or survival. Day 1 irradiation: Recovery 52%±14 control v 51±7 irradiated Survival 146h±34 control v 147±36 irradiated Day 3 irradiation: Recovery 46%±12 control v 47±9 irradiated Survival 150h±60 control v 151±53 irradiated	Sweeney et al 1994
Whole blood	No	Gamma 15 Gy	<24 hours	<24 hours	Cardiac Surgery post CPB	24	No significant difference in platelet increments, or platelet aggregation to ECM following transfusion or 24 hour blood loss.	Lavee et al 1995
PRP & apheresis	Yes	Gamma 25-30 Gy	Not stated	Day 5	Stable thrombocytopenic	533	Irradiation reduced 1 hr CI by 7 x 10^9/l for PRP but not apheresis PC. No effect on 18-24 hour CI or platelet transfusion interval.	Slichter et al 2005
Platelets, including washed platelets with M-sol additive	Y	Gamma 15-50 Gy	Not stated				Guidelines (Japanese): “No distinct effect of irradiation of blood at the dose recommended on the life span or function of platelets”. Also applies to washed platelets. “Gamma irradiation is not associated with any changes in platelet properties”.	Asai et al, 2000; Hirayama et al, 2014; Katus et al, 2014

solution								
Single donor platelets apheresis	?	Gamma/ X-ray ? Gy	D1	Up to Day 7	Thrombocytopenia and haem malignancy	600	Study of functional characteristics of plts treated with riboflavin (mirasol) vs X-ray/G irradiated vs untreated. No differences between G irradiated vs untreated	Ignatova et al, 2016
Single donor platelets apheresis		Gamma 25 Gy	Varied	Day 5	Thrombocytopenia and haem malignancy (children)	144	Timing of irradiation: transfusion increment of platelts irradiated in advance than on day of transfusion was lower than when irradiated at the day of transfusion; otherwise well maintained characteristics.	Jilmy et al, 2014
Not clear	Y	Gamma 25 Gy	Not stated	Not stated	Broad surgical and medical	409	Transfusion associated micro-chimerism: persistence of MC not demonstrated in recipients of (mostly) irradiated blood components .	Sanchez et al, 2015
Single donor platelets apheresis	Y	Gamma 25 Gy	D1	Day 5	Haematology ward	44	Transfusion increments of amotosalen PR vs irradiation comparable; time to next transfsuions.	Sigle et al, 2013
Single donor platelets apheresis	Y	Gamma 25 Gy	D0	Day 3	Thrombocytopenia and haem malignancy	40	Markers of haemostatic function, count increments, bleeding in irradiated vs untreated, were comparable	Zhu et al, 2014

Table 2. Laboratory Studies Assessing the Effect of Irradiation on Platelets

Type of Platelet	LD?	Source & Dose of Irradiation	Irradiated on	Stored until	n=	Summary of findings	Reference
PRP	No	50 Gy	Day 1 or 5	Day 1 or 5	6	No significant difference v controls for morphology score, HSR, LDH, βTG release, thromboxane B2, PF3 activity, aggregation in response to collagen or ADP.	Moroff et al, 1986
PRP & Apheresis	No	Gamma 20 Gy	Day 0	Day 5	3 -5	No significant difference at day 5 v controls for aggregation to a wide range of agonists and serotin release/uptake. Also no effect on DEHP and MEHP levels at day 5 v control.	Rock et al, 1988
Apheresis	LD	Gamma 15 Gy	Day 0, 3 or 5	Day 5	15	No significant difference at day 5 v controls for resting or iduced CD62P, βTG release, glucose, lactate, pH. Irradiation of PC prior to storage increased aggregation to ADP and ADP/epinephrine throughout storage.	Zimmermann et al 2001
Buffy Coat	Yes	Gamma 25 Gy	Day 1 or 5	Day 8	12	Whether irradiated at day 1 or day 5 no significant diference v controls at day 8 for swirl, pH, blood gases, glucose, lactate, CD62P, morphology score.	Van der Meer et al 2005
Apheresis	Yes	Gamma 25 Gy	Day 0	Day 7	20	In irradiated units at day 7 v control: no significant difference in pH PO_2, glucose, LDH, GpIb, resting or TRAP induced CD62P, sCD62P, clot time or elasticity. Slight increase in PCO_2 and lactate.	Tynngard et al, 2008
Apheresis in 65% PASIII	Yes	Gamma 25-28 Gy	Day 1	Day 5	18	No significant difference in pH, blood gases, lactate, glucose, LDH, morphology score, HSR, CD62P. Small reduction in ESC at day 5 v controls.	Vassallo et al 2010
Buffy Coat (RT or cryopreserved)	Y	Gamma 25-50 Gy	Day 1	(Day 7)	24	Gamma irradiation has minimal impact on a range of in vitro marhers of the quality of cryopreserved platelets.	Crimmins et al, 20016
Single donor platelets apheresis	?	Gamma 30 Gy	D1	Up to Day 7	5?	Steady increment of IPF is suppressed by irradiation. Gamma irradiation supressed the increments during storage	Hong et al, 2014
Single donor platelets apheresis	?	Gamma 25 Gy	D1	Up to Day 5	400	Most in vitro functio9nal and biochemical parameters maintained – some effects on pH, glucose, lactate, selected markers of plt activation (eg CD62P)	Mallhi et al, 2015
Single donor platelets apheresis		Gamma 35 Gy	D1	Up to Day 5	15	Proteomic analysis: irradiation results in an acceleration of plt storage lesions	Marrocco et al, 2013

Single donor platelets apheresis	?	Gamma 25 Gy	D1	Up to Day 5	54	Micro-particle analysis: irradiation results in no effects, but small sample size	Maurer-Spurej et al, 2016
Single donor platelets apheresis	?	Gamma 30 Gy	D1	Up to Day 7	50	Platelet microRNA's, mRNAs, activation and function: Irradiation significantly reduced the level of only one micro-RNA (let-7e; one common family of proteins expressed in platelets)	Osman et al, 2015
Single donor platelets apheresis	?	Gamma 25 Gy	D1	Up to Day 5	30	Cytokine analysis: irradiation (control group) results in no effects	Sandgren et al, 2016
Single donor platelets apheresis	?	Gamma 25 Gy	D1	Up to Day 5	20	Cytokine analysis: irradiation results in no differential effects compared to non-irradiated	Shukla et al, 2015