

Extending Platelet Storage

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Current status

- 60% PC produced from BC method
- 40% from apheresis
- all stored in 100% plasma for up to 5 days

Why extend platelet storage?

- To aid implementation of systems to improve blood safety
 - screening for bacterial contamination
 - pathogen reduction technologies
- Improve the logistics of supply/use of components with a short shelf-life

Reducing Bacterial Contamination

- Bacterial contamination of PC causes significant morbidity/mortality (SHOT)
- Steps that might reduce this
 - Improved arm cleansing
 - Divert pouches
 - Screening of PC

Bacterial Contamination - screening

- Several options for testing PC
 - different test systems
 - different options for time of sampling/testing
 - whether to use as a release criteria
- Screening for bacterial contamination may take 2 days to produce a result
- If used as release criteria then shortens the shelf life of PC

Pathogen reduction technology

- 1 system now licensed in Europe for BC PC others in development
- Pre-storage pathogen reduction takes 1-2 days
- might decrease available shelf-life of component

Could we extend platelet storage?

- Do platelets still function?
- Are platelets stored in plasma or platelet additive solutions better for extended storage?
- What about accumulation of bioactive mediators during extra storage time?
- Is there any International experience with storing platelets beyond day 5?
- Taken as a given that PC would be tested for bacteria or treated if >day 5 storage considered

Assessing Platelet Function in PC

- **in vitro data**
- **animal models**
- **recovery and survival studies in healthy volunteers**
- **count increment studies in thrombocytopenic patients
PC for prophylaxis**

Relationship Between In Vitro tests and In Vivo Function

- very few tests in vitro correlate with results in vivo
- generally validated a long time ago with different storage containers and platelets in plasma
- only shown to correlate with ability of platelets to circulate (radiolabelled studies or CCI)- what about their function

In vivo studies on platelet function

- Healthy volunteers not the same as patients
- Stable thrombocytopenic patients not the same as those actively bleeding
- In patients actively bleeding platelets should be at the endothelial surface not in peripheral blood

Platelet Storage - in vitro data

- suggests that platelet metabolism is well preserved to day 7 in plasma
- as storage time increases so does platelet activation (not sure of clinical relevance)
- and cytokine accumulation
 - not WBC derived since all PC LD
 - TGF-B and RANTES are not higher than levels reported to be associated with allergic reactions

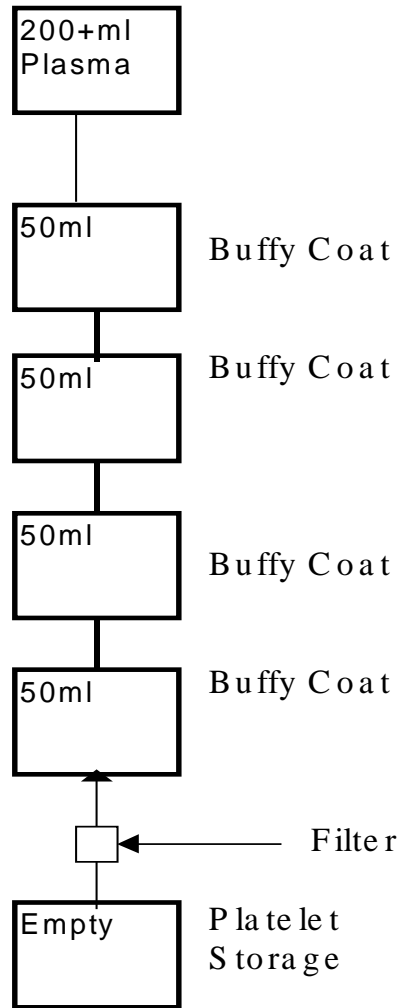
Recovery studies - normal volunteers

			% recovery			survival (days)			
Platelet Type	Storage Medium	N=	Day 0/1	Day 5	Day 7	Day 0/1	Day 5	Day 7	Reference
PRP?	CPD plasma	10		43±10	56±8		7.3±1.2	6.2±1.1	Heaton et al, 1990
PRP	plasma	8		59±17	46±8		6.4±3.0	5.4±1.0	Archer et al, 1982
PRP	CPDA1 plasma	10 9		46±8 43±9	46±8* 45±10*		7.2±1 6.8±1	6.8±1.0* 8.0±0.8*	Simon et al, 1987
PRP ^a	plasma PAS	5-10	55±10	41±11 45±12	37±11 51±8	7.9±1.0	6.1±1.7 6.7±1.3	4.5±1.6 6.0±0.7	Holme et al, 1990
Apheresis MCS	Plasma plasmalyte	10		79±20 79±22	53±21 64±14		6.0±1.1 5.9±1.4	5.0±1.6 5.9±0.6	Slichter ASH2001
Apheresis Spectra/Trima	ACD plasma	24		63±11	53.9±14		6.7±1.6	5.6±1.9	Dumont et al, 2002

CCI studies in thrombocytopenic patients

				1 hour CCI			18-24 hour CCI			
Platelet Type	Storage Medium	Patient type	N=	Day 0/1	Day 5	Day 7	Day 0/1	Day 5	Day 7	Reference
PRP	plasma	Clinically stable	16	20.1±8.4	Day 3 12.2±8.1	10.0±7.2 ^a	10.8±4.4	Day 3 7.5±5.6	7.0±5.5 ^a	Hogge et al, 1986
PRP?	CP2D plasma		14			21				Neurath et al ISBT 2002
Apheresis Spectra/M CS+	plasma		21			14.4±8.8				Aubuchon et al, 2002
Buffy coat?	Plasma	clinically stable Plt <20			19.6 n=45	19.0 n=39				Dijkstra-Tiesktra et al, 2004
Apheresis	plasma		9			16.0± 3.4				Rock 2004

most countries store platelet concentrates (PC) in plasma



synthetic solutions can replace 65-80% of plasma in PC

PAS V Plasma - normal volunteers

Slichter at al, 2001 ASH

- apheresis platelets (MCS+) in plasma or plasmalyte
- Only significant difference at day 7 of storage where PAS better
- recovery 64 ± 14 v 53 ± 21
- survival 5.9 ± 0.6 v 5.0 ± 1.6

PAS V Plasma - thrombocytopenic patients:

de Wildt-Eggen et al, 2000

- buffy coat platelets day 5 storage
- 1 hr CCI 20.7 ± 8.5 plasma v 17.1 ± 6.6 PASII, $p < 0.001$

van Rhenen et al, 2003

- control arm of Baxter Amotosalen multi-centre trial
- ns difference in 1 or 24 hr CCI between centres using PC in plasma or PASII (BC PC day 5)

Extended storage in PAS

- In vitro data shows that combination of type of PAS with storage pack important
- Some pack types give rapid reduction in pH past day 5 in PASII
- If we were to switch to PC in PAS this may limit the shelf life or restrict storage pack combinations
- Do we know how various PAS and PAS:plasma ratios effect bacterial growth or detection systems?

International Experience

Some European countries routinely store to 7 days if screened (e.g Netherlands, Sweden)

USA - 7 days storage permitted in 1980's, but in 1986 reduced to 5 days due to increased bacterial contamination at 7 days

USA - some centres apheresis PC in plasma to day 7 if screened

Platelet Shelf life & Pathogen Inactivation

- Amotosalen only system licensed (buffy coat and Amicus collected platelets only)
- All studies to date to day 5 only
- Clinical trials on day 7 platelets underway
- Therefore limited to day 5 currently

Summary of data

- In vitro and in vivo data on apheresis and buffy coat platelets in plasma suggest good function to day 7
- Probably not quite as good as at day 5
- How good is good enough? Any loss must be measured against benefit
- Don't really know if PAS will be better or worse than plasma at day 7

What is the NBS doing?

- Divert pouches now standard
- Improved arm cleansing in apheresis clinics now standard and being rolled out to mobile teams
- Operational assessment of bacterial screening
- Operational assessment of Amotosalen system

Extended storage

- Review of data from PC to day 7 in plasma
- Large in vitro study of 2 PAS v plasma underway
- recovery and survival studies in volunteers planned as part of an international collaboration

Alternatives

- Platelet substitutes - not much being developed internationally
- Frozen platelets
 - logistically difficult
 - effect on efficacy
- Storage of platelets at 4oC

Cold storage of platelets

- results in poor recovery and survival
- due to clustering of GPIb and removal by liver macrophages via complement receptors
- this interaction can be blocked by glycosylation and platelets stored at 4°C then circulate and function in animal models
- might we be able to store PC at 4°C?

See recent papers by Karin Hoffmeister

Conclusion

- The major drawback to extending platelet storage is a decrease in likely efficacy
- What loss is acceptable?
- Recent breakthroughs mean cold storage of platelets may be a reality but more data are needed