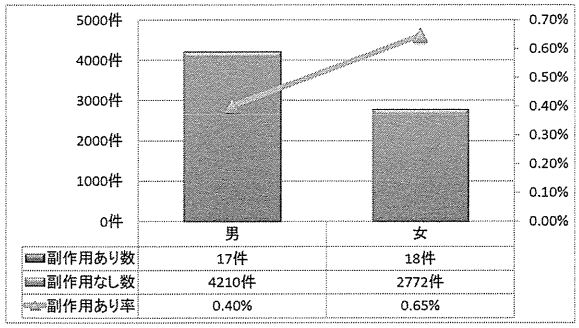
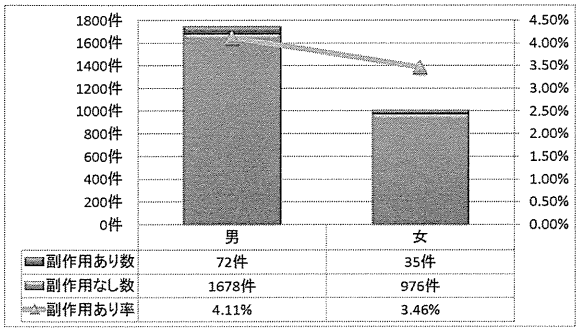
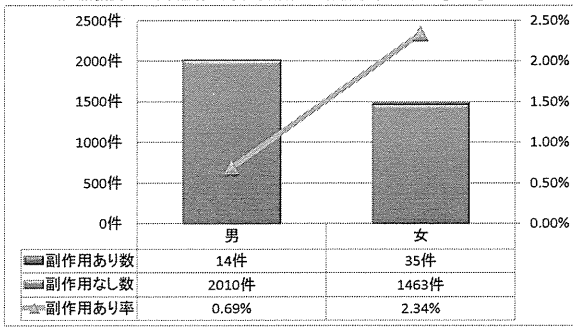
a．赤血球製剤



b．血小板製剤



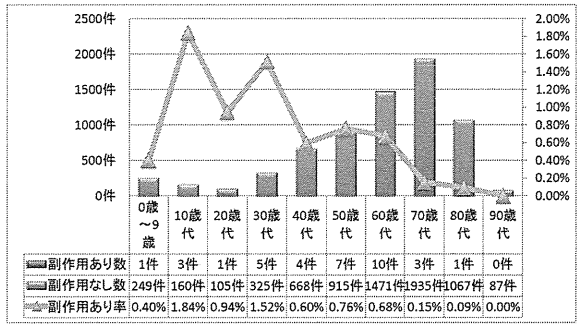
c．血漿製剤



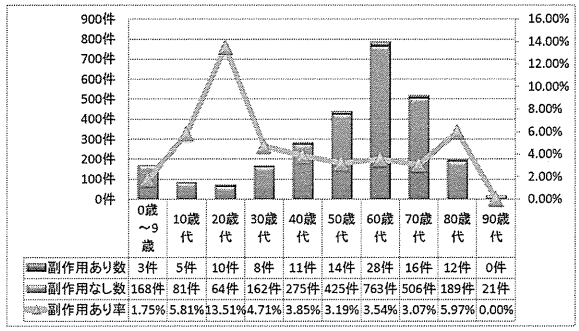
6）年齢と副作用発生率

患者年齢階級（病院側データ）別の副作用発生率は、0～9 歳で 0.67%（4/597）、10 歳代で 4.63%（15/324）、20 歳代で 4.53%（12/265）、30 歳代で 2.00%（18/899）、40 歳代で 2.43%（37/1,522）、50 歳代で 1.71%（23/1,961）、60 歳代で 1.69%（47/2,777）、70 歳代で 0.62%（20/3,245）、80 歳代で 0.96%（15/1,569）、90 歳代で 0%であった。製剤別・患者性別の副作用発生件数・頻度以下に示す。

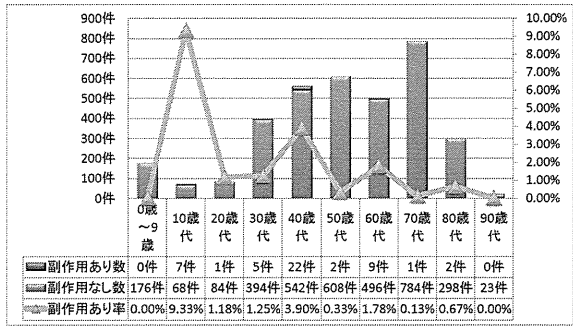
a．赤血球製剤



b．血小板製剤



c．血漿製剤

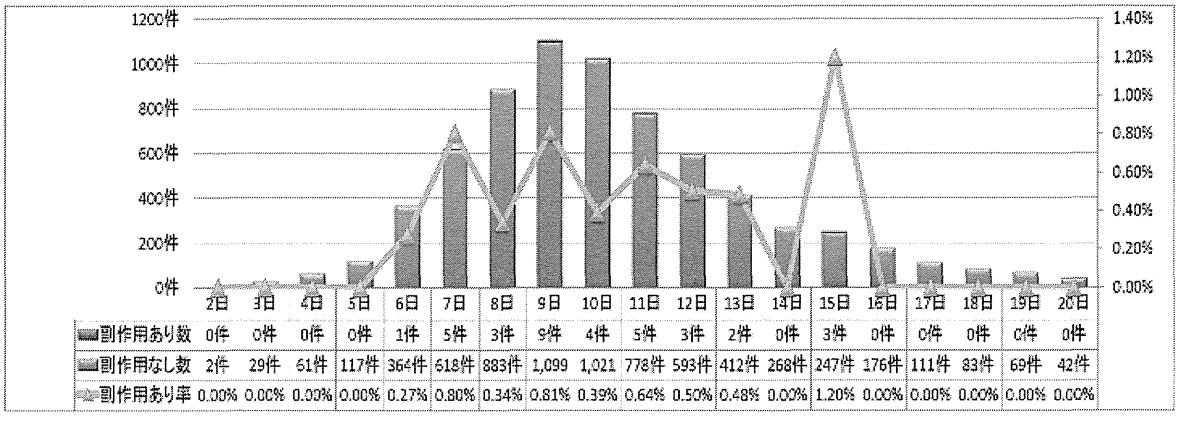


7）採血日から輸血日までの期間と有害事象発生率

輸血用血液の採血日から使用までの期間と有害事象発生率を検討した。赤血球製剤は、採血後使用までの期間が 10 日前後で使用される割合が高く、採血後の期間と有害事象発生率には明かな関係は見られなかった。血小板製剤で

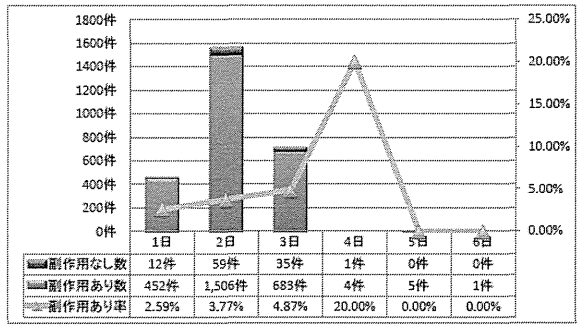
は採血後２日目で使用される割合が高く、採血後の日数が経過するほど有害事象発生率は増加する傾向を認めたが、有意であるかは今後の検討が必要である。血漿製剤は採血後８ヶ月から 10 ヶ月経過した製剤が使用される割合が高かったが、採血後期間と有害事象の発生率には明らかな関係を認めなかった。

a．赤血球製剤



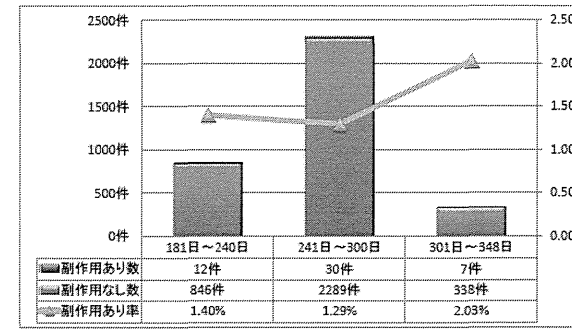
	2日	3日	4日	5日	6日	7日	8日	9日	10日	11日	12日	13日	14日	15日	16日	17日	18日	19日	20日
副作用あり数	0件	0件	0件	0件	1件	5件	3件	9件	4件	5件	3件	2件	0件	3件	0件	0件	0件	0件	0件
副作用なし数	2件	29件	61件	117件	364件	618件	883件	1,099	1,021	778件	593件	412件	268件	247件	176件	111件	83件	69件	42件
副作用あり率	0.00%	0.00%	0.00%	0.00%	0.27%	0.80%	0.34%	0.81%	0.39%	0.64%	0.50%	0.48%	0.00%	1.20%	0.00%	0.00%	0.00%	0.00%	0.00%

b．血小板製剤



	1日	2日	3日	4日	5日	6日
副作用なし数	12件	59件	35件	1件	0件	0件
副作用あり数	452件	1,506件	683件	4件	5件	1件
副作用あり率	2.59%	3.77%	4.87%	20.00%	0.00%	0.00%

c．血漿製剤



	181日～240日	241日～300日	301日～348日
副作用あり数	12件	30件	7件
副作用なし数	846件	2289件	338件
副作用あり率	1.40%	1.29%	2.03%

D. 考察

今年度は、日本赤十字社と１６医療施設にて１ヶ月間のパイロット・スタディを実施できた。実施施設数は、昨年より施設４倍、対象データ6.38 倍に拡大しながら、事前の打ち合わせにより不正データの割合は減少できた。ただし、データ収集時のエラーは、いまだに解消されていないので、入力するエクセルシートに物理的なチェックでエラーが入力出来ない仕組みをつけることが、さらなるエラー減少に有用と考えられた。

収集したデータを解析センターで紐付けし、副作用の発生数・頻度を製剤別に年齢・血液型・性別等で解析できた。今年度新たに採血日から使用までの日数による副作用の発生数・頻度を検討した。PC は1→４日で副作用発生頻度が上昇する傾向あり。RBC は古いものほど副作用の発生が多いという報告があるが、それとは異なる結果である。わが国の製剤は採血後の有効期限が諸外国に比し短いことがその要因かもしれない。

今後の検討課題としては以下のような点が上げられる。

① 病院情報システムに保存されているデータ項目とそれらの表示形式、定義の統一
② 日本赤十字社と医療機関のデータ紐付け精度の向上
③ 分析項目の検証と新規項目の設定
④ リアルタイムまたはオンタイムでデータの受け渡しが出来る環境の構築
⑤ データの受け渡し、保存分析および安全に管理する体制構築
⑥ マイナンバーによる情報の一元管理
⑦ 追跡期間の検討と電子カルテへの情報保存の在り方
⑧ インシデトおよびアクシデント、治療内容など想定される他の要因と連動
⑨ トレーサビリティにて得られた情報の有効活用（医療安全・継続医療・医療費適正化）

E. 結論

1)Transfusion chainに沿ったトレーサビリティに関する後方視的パイロット・スタディを行い、日本赤十字社がもつ血液製剤の情報と医療機関がもつ患者有害事象データを連結し、解析することが可能であった。

2) 今回開発したシステムを改良し、前向きなリアルタイム・トレーサビリティシステムを構築することで、血液製剤の安全対策が効率的に行えるようになると考えられる。

G. 研究発表

１．論文発表

1) 岩尾憲明、加藤栄史、小高千加子、高本滋、藤井康彦、米村雄士、田中朝志、岡崎仁、岡田義昭、大日康史、野村久子、松下明夫、北澤淳一、森宏、八十嶋仁、大隈和、山口一誠、大坂顕道、浜口功. 輸血副作用サーベイランスにおけるunderreporting. 日本輸血細胞治療学会誌、61(6)：561-566、2015.

2) 藤井康彦, 藤井　康彦, 田中　朝志, 小高千加子, 加藤栄史, 他：診療科別輸血製剤副作用発生率の調査, 日本輸血細胞治療学会誌, in press.

２．学会発表

第63回日本輸血・細胞治療学会総会にて、「システム搭載・輸血標準作成タスクフォース報告会－日本輸血・細胞治療学会が目指す輸血標準システムとは－」を開催

1）紀野修一．輸血標準を作成し病院情報システムに搭載するためのタスクフォースが誕生するまで
2）大谷慎一．タスクフォース誕生からの二年間の歩み－タスクフォース委員長より－
3）遠藤昌江．システム搭載・輸血標準作成タスクフォースに参加して
4）浜口功．ヘモビジランスからタスクフォースに期待すること

H．知的財産権の出願・登録状況

該当なし

別添1

データ定義書（for JRC）

Excelファイル共通仕様
・Excelファイルは、Excel2007以降のバージョンで作成されていること
・Excelファイルは、xlsx形式で保存されていること（xls形式は不可とする）　＊ファイル保存時に、xlsx形式を選択する
・Excelファイル名は、半角英数字であることとする。（スペース（空白）は含めないこと）
・Excelファイルの各項目には、改行コードを含めないこととする。
・データ項目の並び順は、以下に示す通りとし、順番を変更しないこと

Field-no	Field-name	型	桁数	固定値より選択する場合				個別の値を入力する場合		入力必須条件		その他仕様
				選択肢1	選択肢2	選択肢3	選択肢4	書式	書式例	必須	必須条件仕様説明	
J001	製剤番号	半角英数字	-	-	-	-	-	XX-XXXX-XXXX	ハイフン（半角）区切で、2桁-4桁-4桁のコードを設定 例：59-2023-6508	○	常に必須	<備考> ※病院データの製造番号・ロット番号に対応
J002	採血日	日付（半角数字・スラッシュ区切）	10桁					yyyy/mm/dd	2015年1月1日の場合は2015/01/01とする ※月・日が1桁の場合はゼロ埋めすること ※数値は半角で入力すること	○	常に必須	
J003	製造品	半角英字	2桁or3桁	RBC	FFP	FFP	PC	-	-	○	常に必須	<備考> ※病院データの製剤の種類に対応
J004	血液型	半角英字	1桁	A	B	O	AB			○	常に必須	
J005	RH型	半角英字	1桁	RH(+)	RH(-)	-	-			○	常に必須	
J006	性別	全角文字	1桁	男	女	女	-	-	-	○	常に必須	
J007	最終納品日	日付（半角数字・スラッシュ区切）	10桁	-	-	-	-	yyyy/mm/dd	2015年1月1日の場合は2015/01/01とする ※月・日が1桁の場合はゼロ埋めすること ※数値は半角で入力すること	○	常に必須	
J008	有効期限年月日	日付（半角数字・スラッシュ区切）	10桁	-	-	-	-	yyyy/mm/dd	2015年1月1日の場合は2015/01/01とする ※月・日が1桁の場合はゼロ埋めすること ※数値は半角で入力すること	○	常に必須	

データ定義書（for hospital）

別添2

Excelファイル共通仕様
・Excelファイルは、Excel2007以降のバージョンで作成されていること
・Excelファイルは、xlsx形式で保存されていること（xls形式は不可とする）　＊ファイル保存時に、xlsx形式を選択する
・Excelファイル名は、半角英数字であることとする。（スペース（空白）は含めないこと）
・Excelファイルの各項目には、改行コードを含めないこととする。
・データ項目の並び順は、以下に示す通りとし、順番を変更しないこと

項番	Field name	型			① 選択肢より選択する場合			② 仕様に基づき入力する場合			入力必須条件	
			入力例	入力方法	選択肢1	選択肢2	選択肢3	書式	桁数	書式例	必須	必須条件仕様説明
H001	施設内連番	半角数字	1	右記②（J列～L列）に従い入力	-	-	-	-	-	1から始まる連番とし、番号の重複は不可とする	○	常に必須
H002	製剤番号・ロット番号	半角英数字	59-2023-6508	右記②（J列～L列）に従い入力	-	-	-	XX-XXXX-XXXX	-	ハイフン（半角）区切で、2桁-4桁-4桁のコードを設定	○	常に必須
H003	製剤の種類	半角英字	RBC	右記①（G列～I列）から選択	RBC	FFP	PC	-	-	-	○	常に必須
H004	納品日	日付（半角数字・スラッシュ区切）	2015/09/03	右記②（J列～L列）に従い入力	-	-	-	yyyy/m m /dd	10桁	2015年1月1日の場合は2015/01/01とする ※月・日が1桁の場合はゼロ埋めすること ※数値は半角で入力すること	○	常に必須
H005	交差適合試験日	日付（半角数字・スラッシュ区切）	2015/09/03	右記②（J列～L列）に従い入力	-	-	-	yyyy/m m /dd	10桁	2015年1月1日の場合は2015/01/01とする ※月・日が1桁の場合はゼロ埋めすること ※数値は半角で入力すること	△	廃棄していない場合（廃棄日(H014)に値がセットされていない場合）は必須
H006	割付日	日付（半角数字・スラッシュ区切）	2015/09/03	右記②（J列～L列）に従い入力	-	-	-	yyyy/m m /dd	10桁	2015年1月1日の場合は2015/01/01とする ※月・日が1桁の場合はゼロ埋めすること ※数値は半角で入力すること	△	廃棄していない場合（廃棄日(H014)に値がセットされていない場合）は必須
H007	出庫日	日付（半角数字・スラッシュ区切）	2015/09/03	右記②（J列～L列）に従い入力	-	-	-	yyyy/m m /dd	10桁	2015年1月1日の場合は2015/01/01とする ※月・日が1桁の場合はゼロ埋めすること ※数値は半角で入力すること	△	廃棄していない場合（廃棄日(H014)に値がセットされていない場合）は必須
H008	受領日	日付（半角数字・スラッシュ区切）	2015/09/03	右記②（J列～L列）に従い入力	-	-	-	yyyy/m m /dd	10桁	2015年1月1日の場合は2015/01/01とする ※月・日が1桁の場合はゼロ埋めすること ※数値は半角で入力すること	△	廃棄していない場合（廃棄日(H014)に値がセットされていない場合）は必須
H009	接続前照合日	日付（半角数字・スラッシュ区切）	2015/09/03	右記②（J列～L列）に従い入力	-	-	-	yyyy/m m /dd	10桁	2015年1月1日の場合は2015/01/01とする ※月・日が1桁の場合はゼロ埋めすること ※数値は半角で入力すること	△	廃棄していない場合（廃棄日(H014)に値がセットされていない場合）は必須
H010	性別	全角文字	女	右記①（G列～I列）から選択	男	女	-	-	-	-	△	廃棄していない場合（廃棄日(H014)に値がセットされていない場合）は必須
H011	年齢	半角数字	40	右記②（J列～L列）に従い入力	-	-	-	-	3桁	-	△	廃棄していない場合（廃棄日(H014)に値がセットされていない場合）は必須
H012	終了時照合日	日付（半角数字・スラッシュ区切）	2015/09/03	右記②（J列～L列）に従い入力	-	-	-	yyyy/m m /dd	10桁	2015年1月1日の場合は2015/01/01とする ※月・日が1桁の場合はゼロ埋めすること ※数値は半角で入力すること	△	廃棄していない場合（廃棄日(H014)に値がセットされていない場合）は必須
H013	廃棄日	日付（半角数字・スラッシュ区切）	2015/09/03	右記②（J列～L列）に従い入力	-	-	-	yyyy/m m /dd	10桁	2015年1月1日の場合は2015/01/01とする ※月・日が1桁の場合はゼロ埋めすること ※数値は半角で入力すること	△	いない場合（製剤が使用されていない場合）は、必須
H014	副作用症状の有無	半角英字	YES	右記①（G列～I列）から選択	YES	NO	-	-	-	-	△	廃棄していない場合（廃棄日(H014)に値がセットされていない場合）は必須
H015	症状項目01：発熱	半角英字	YES	右記①（G列～I列）から選択	YES	NO	-	-	-	-	△	副作用症状の有無(H015)」がYESの場合
H016	症状項目02：悪寒・戦慄	半角英字	NO	右記①（G列～I列）から選択	YES	NO	-	-	-	-	△	副作用症状の有無(H015)」がYESの場合
H017	症状項目03：発熱・ほてり	半角英字	NO	右記①（G列～I列）から選択	YES	NO	-	-	-	-	△	副作用症状の有無(H015)」がYESの場合
H018	症状項目04：かゆみ	半角英字	NO	右記①（G列～I列）から選択	YES	NO	-	-	-	-	△	副作用症状の有無(H015)」がYESの場合
H019	症状項目05：発熱・顔面紅潮	半角英字	NO	右記①（G列～I列）から選択	YES	NO	-	-	-	-	△	副作用症状の有無(H015)」がYESの場合
H020	症状項目06：発疹・蕁麻疹	半角英字	NO	右記①（G列～I列）から選択	YES	NO	-	-	-	-	△	副作用症状の有無(H015)」がYESの場合
H021	症状項目07：呼吸困難	半角英字	NO	右記①（G列～I列）から選択	YES	NO	-	-	-	-	△	副作用症状の有無(H015)」がYESの場合
H022	症状項目08：吐気・嘔吐	半角英字	NO	右記①（G列～I列）から選択	YES	NO	-	-	-	-	△	副作用症状の有無(H015)」がYESの場合
H023	症状項目09：胸痛・腰痛	半角英字	NO	右記①（G列～I列）から選択	YES	NO	-	-	-	-	△	副作用症状の有無(H015)」がYESの場合
H024	症状項目10：頭痛・頭重感	半角英字	NO	右記①（G列～I列）から選択	YES	NO	-	-	-	-	△	副作用症状の有無(H015)」がYESの場合
H025	症状項目11：血圧低下	半角英字	NO	右記①（G列～I列）から選択	YES	NO	-	-	-	-	△	副作用症状の有無(H015)」がYESの場合
H026	症状項目12：血圧上昇	半角英字	NO	右記①（G列～I列）から選択	YES	NO	-	-	-	-	△	副作用症状の有無(H015)」がYESの場合
H027	症状項目13：動悸・頻脈	半角英字	NO	右記①（G列～I列）から選択	YES	NO	-	-	-	-	△	副作用症状の有無(H015)」がYESの場合
H028	症状項目14：血管痛	半角英字	NO	右記①（G列～I列）から選択	YES	NO	-	-	-	-	△	副作用症状の有無(H015)」がYESの場合
H029	症状項目15：意識障害	半角英字	NO	右記①（G列～I列）から選択	YES	NO	-	-	-	-	△	副作用症状の有無(H015)」がYESの場合
H030	症状項目16：赤褐色尿	半角英字	NO	右記①（G列～I列）から選択	YES	NO	-	-	-	-	△	副作用症状の有無(H015)」がYESの場合
H031	症状項目17：その他	半角英字	YES	右記①（G列～I列）から選択	YES	NO	-	-	-	-	△	副作用症状の有無(H015)」がYESの場合
H032	症状項目17：その他の内容	全角文字	（上記に無い副作用症状を記載）	②（J列～L列）に従い入力	-	-	-	-	1000桁	自由記述	△	H033がYesの場合は、症状を記述

別添3

〔 平成27年度 〕血液製剤のトレーサビリティ導入を目的としたパイロットスタディの分析をする上での不正データに対する修正及び取扱いについて

No	施設番号	項目	定義書との不一致内容など	提出されたデータの内容 (修正理由等も含む)	対象データ件数	修正内容	修正方法	データの取り扱い
1	H000001	製剤の種類	空白	RBC＋空白	9件	RBC	手修正	対象
2	H000003	納品日	14年前	2001/8/19	1件			対象外
3	H000005	交差適合試験日	未来日	2016/7/25	1件	修正せず		対象（分析項目外であり出庫日・受領日が該当月であるため）
4	H000016	性別	性別以外	0.0	1件			対象外
5	H000006	性別	同義語であるが定義以外	男性	535件	男	手修正	対象
				女性	440件	女		
6	H000012	性別	同義語であるが定義以外	男性	611件	男	手修正	対象
				女性	259件	女		
7	H000017	性別	同義語であるが定義以外	男性	151件	男	手修正	対象
				女性	107件	女		
8	H000005	年齢	定義以外「M」	1M	62件			対象外（副作用も空欄であるため）
				11M	12件			
			空欄	空欄	2件			対象外（廃棄日あり・副作用あり／データ内容不一致）
					3件			対象外（廃棄日なし・副作用なし／データ内容不一致）
9	H000016	年齢	空欄	空欄	7件			対象外
10	H000005	副作用	空欄	空欄	683件			対象外

※ 上記に記載した内容は、主となる(分析に影響を与える)ものでありデータ不正の全てではありません。

※ 分析データとしての取り扱い結果は、

	件数	割合
不正データ	2,884件	
対象データ	2,113件	73.27%
対象外データ	771件	26.73%

※ 日赤データの修正も実施しました。(製造品:WRC→RBC・血液型:大文字→小文字に修正)

※ 日赤データの製造品・血液型・Rh型・性別における12件の「NULL」は、日赤データを基準とする分析データの対象外としました。

＜ 分析方法の分類および分析データとしての取り扱い件数と割合について ＞

	件数	割合
提出データ	14,205件	
対象データ	13,434件	94.57%
対象外データ	771件	5.43%
① 副作用分析データ	13,300件	99.00%
② 廃棄血分析データ	134件	1.00%

分析対象データ数	医療機関基準	13,300件
	日赤基準	13,288件

Ⅲ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Kato H, Nakayama T, Uruma M, Okuyama Y, Handa M, Tomiyama Y, Shimodaira S, Takamoto S.	A retrospective observational study to assess adverse transfusion reactions of patients with and without prior transfusion history.	Vox Sang	108	243-250	2015
Kato H, Nakayama T, Uruma M, Okuyama Y, Handa M, Tomiyama Y, Shimodaira S, Takamoto S.	Repeated exposure rather than the total volume of transfusion components may influence the incidence of allergic transfusion reactions.	Transfusion	55	2576-81	2015
Ohsaka A, Kato H, Kino S, Kawabata K, Kitazawa J, Sugimoto T, Takeshita A, Baba K, Hamaguchi M, Fuji F, Horiuchi K, Yonemura Y, Hamaguchi I, Handa M, on behalf of the Japan Society of Transfusion Medicine and Cell Therapy Working Party on Safety Management of Blood Transfusions.	Recommendations for the electric pre-transfusion check at the bedside.	Blood Transfus	DOI 10.2450/2016.0184-15		2016

岩尾憲明、 加藤栄史、 小高千加子、 高本滋、 藤井康彦、 米村雄士、 田中朝志、 岡崎仁、 岡田義昭、 大日康史、 野村久子、 松下明夫、 北澤淳一、 森宏、 八十嶋仁、 大隈和、 山口一成、 大坂顕道、 浜口功	輸血副作用サーベイランスにおけるunderreporting.	日本輸血細胞治療学会誌	61	561-566	2015

Ⅳ. 研究成果の刊行物・印刷

VoxSanguinis
The International Journal of Transfusion Medicine

ISBT International Society of Blood Transfusion

Vox Sanguinis (2015) **108**, 243–250

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ORIGINAL PAPER

A retrospective observational study to assess adverse transfusion reactions of patients with and without prior transfusion history

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Vox Sanguinis

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Background and Objectives This study compares the frequency of adverse transfusion reactions (ATRs) after first transfusions with the frequency of ATRs for subsequent (non-first) transfusions.

Materials and Methods Five hospitals agreed to systematically collect and share 2 years of data. This was a retrospective observational analysis of data including the number of transfusion episodes and ATRs for red blood cells (RBCs), fresh frozen plasma (FFP) and platelet concentrates (PCs) given to first-time transfusion recipients and to those previously transfused.

Results First transfusion ATRs to RBCs, FFP and PCs were 1·08%, 2·84% and 3·34%, respectively. These are higher than ATR incidences to RBCs (0·69%), FFP (1·91%) and PCs (2·75%) on subsequent transfusions. Specifically, first transfusion incidences of febrile non-haemolytic transfusion reactions (FNHTRs) to RBCs (0·43%) and allergic reactions to FFP (2·51%) were higher than on subsequent transfusions (RBCs: 0·23%, FFP: 1·65%).

Conclusion There are risks of ATRs on the first transfusion as well as transfusions of patients with transfusion history.

Key words: adverse transfusion reaction, allergic reaction, first transfusion, haemovigilance, transfusion episode.

Introduction

Although blood transfusion is regarded as an essential and life-saving therapy, significant clinical risks are attributed to the allogeneic origin of blood components. Also, concerns have been expressed about adverse transfusion reactions (ATRs) attributed to cytokines that accumulate in stored autologous blood. As transfusion-transmitted infections decrease due to improved donor screening and blood testing [1], non-infectious ATRs attract greater concern. In fact, the risk of transfusion-transmitted infectious diseases has decreased approximately 10 000-fold [2], while deaths attributed to transfusion-related acute lung injury (TRALI) and haemolytic transfusion reactions now account for approximately 72% of all transfusion-related fatalities reported to the Center for Biologics Evaluation and Research (CBER) of the US Food and Drug Administration [3]. Although blood components in Japan – as elsewhere – can be considered as highly safe, transfusion-associated ATRs have not been eliminated. Indeed, the overall incidence of ATRs per transfused unit was 1·53% in Japan [4]. But, the incidences of ATRs per unique patient per year are still high: to red blood cells (RBCs), 2·61%; to fresh frozen

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plasma (FFP), 4·32%; and to platelet concentrates (PCs), 13·24% [4].

While the majority of ATRs are not serious, these reactions can lead to hospitalization for outpatients or prolonged hospital stays for inpatients. This is a burden to patients, their families and to healthcare under any system of delivery and reimbursement. For these reasons, preventive strategies should be embraced. To this end, it is prudent to quantify ATRs, search for causality and investigate mechanisms.

National haemovigilance systems began in France in 1994 [5] and in the United Kingdom in 1996 [6], although these two systems differ greatly. With the advent of Directive 2002/98/EC [7], the introduction of haemovigilance systems has become a priority throughout the European Community. The recently established US Biovigilance Network commenced data collection in 2008 [8]. Less well known, the Japanese Red Cross Society (JRCS), as a monopoly provider of allogeneic blood, recognized its duty to co-ordinate blood safety and established a haemovigilance system in 1993. In summary, the emergence of haemovigilance systems is a global phenomenon.

Although most of these systems report the incidence of ATRs on a per-transfused unit basis, the incidence of reactions from first vs. subsequent transfusions has not been published, even though some ATRs are associated with prior transfusion. Previous exposure to allogeneic blood may sensitize patients to foreign plasma proteins [9] as well as cell surface alloantigens. Even so, the impact of prior transfusion on subsequent ATRs is not well defined. Herein we report the incidence of first transfusion ATRs vs. subsequent (non-first) transfusion ATRs from five hospitals over 2 years and consider the factors that may account for any differences.

Patients and methods

Study set-up

Data from standardized records were collected by the Department of Transfusion Medicine, Aichi Medical University, from its own and four hospitals. The data covered January 2010 through December 2011 and were assembled in February 2012.

Study design

This was a retrospective observational analysis of data from standardized records in 5 Japanese hospitals with established haemovigilance systems (Aichi Medical University Hospital, Keio University Hospital, Osaka University Hospital, Shinshu University Hospital, and Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital) from January 2010 through December 2011, covering transfusions and associated ATRs for red blood cells (RBCs), fresh frozen plasma (FFP) and platelet concentrates (PCs). The study was approved by the Aichi Medical University Institutional Review Board, which is guided by local policy, national law and the World Medical Association Declaration of Helsinki. For each type of blood component, the data included the total number of first transfusion episodes on patients without any transfusion history and the total number of subsequent transfusion episodes for those with transfusion history, as well as the total number of transfusion-related ATRs per blood component with respect to both first and subsequent transfusions. We can identify first transfusions because physicians and nurses routinely solicit transfusion history from patients or family members and check hospital databases and medical records. We have defined a transfusion episode as any number of units of the same type administered within 24 h of each other. Therefore, if a patient with no transfusion history received more than one type of blood component within 24 h, a 'first transfusion' for each type of blood component was recorded. Any blood components thereafter would belong to a subsequent (non-first) transfusion.

Physicians and nurses monitored patients after the start of each transfusion for the occurrence of any ATRs and reported to the transfusion medicine service of each hospital whether or not an ATR had occurred. ATRs were investigated by a physician trained in transfusion medicine, and additional clinical and biological information was collected to facilitate diagnosis and assessment of severity. Adverse reactions were deemed ATRs according to professional assessment of imputability based on clinical and laboratory data.

A standard ATR assessment form included the following 16 items as shown in Table 1. A febrile non-haemolytic transfusion reaction (FNHTR) was diagnosed if fever, chills/rigours and feverishness (subjective feeling of warmth or glow) occurred during or within 4 h following transfusion without any other cause such as haemolysis, bacterial contamination or underlying disease. Allergic reactions consisted of skin symptoms or signs such as pruritus, skin rash and urticaria within 6 h of transfusion, after other potential etiologies of an allergic reaction were excluded. Any additional findings or comments, including suspected transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO) or transfusion-transmitted viral and bacterial infection, could be entered as free text, and were later analysed. The definitions of all signs, symptoms and specific clinical syndromes used by the Japan Society of Transfusion Medicine and Cell Therapy (JSTMCT) are based on

Table 1 Signs, symptoms and clinical diagnoses of ATRs

Signs/Symptoms	Clinical diagnoses
Fever (more than 38°C and more than 1°C increase after a transfusion)	Serious allergic reaction
	TRALI
Chills/Rigor	TACO
Feverishness (feeling of warmth or glow)	PTP
Pruritus	GVHD
Skin rash	Haemolytic transfusion reaction
Urticaria	Acute
Respiratory distress	Delayed
Nausea/Vomiting	Transfusion-transmitted infection
Headache	HBV
Chest/flank/back pain	HCV
Hypotension (a decrease of more than 30 mmHg after a transfusion)	HIV
	Bacteria
Hypertension (a increase of more than 30 mmHg after a transfusion)	Others
Tachycardia	
Vein pain	
Disturbance of consciousness	
Haemoglobinuria	
Others	

ATR, adverse transfusion reaction; TRALI, transfusion-related acute lung injury; TACO, transfusion-associated circulatory overload; PTP, post-transfusion purpura; GVHD, graft-versus-host disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

documents issued by the International Society of Blood Transfusion (ISBT) Working Party for Haemovigilance [10], which also defined the criteria for grading the severity of ATRs, as follows: grade 1, the absence of immediate or long-term consequences; grade 2, long-term morbidity; grade 3, immediate vital risk; and grade 4, death of the recipient. Serious ATRs were defined as grade 2 or higher according to documents issued by the ISBT Working Party for Haemovigilance.

Blood components

Blood collection, preparation and testing were performed according to protocols of the Blood Service Headquarters of the JRCS. Types of blood donation were 200 ml or 400 ml of whole blood and apheresis of platelets or plasma. Since January 2007, only prestorage leucoreduced blood components ($<1 \times 10^6$ leucocytes per unit) have been manufactured. After venipuncture, the first 25 ml of blood is diverted to decrease the risk of bacterial contamination, although not all units were tested for bacterial contamination. All blood components were screened using serological testing for infectious diseases. Furthermore, all blood components were screened using 20-minipool nucleic acid testing to reduce the risk of transfusion-transmitted infectious diseases (hepatitis B virus, hepatitis C virus and human immunodeficiency virus). RBCs are prepared with the additive solution MAP (mannitol adenine phosphate) and stored for up to 21 days at 5°C. All PCs are collected from single donors by apheresis, suspended in 200 ml of plasma and stored for up to 4 days at 22°C with agitation. FFP is prepared from whole blood plasma or by apheresis from single donors. Final volumes of FFP derived from 200 to 400 ml whole blood donations are approximately 120 and 240 ml, respectively, whereas the volume of FFP derived from single donor apheresis is around 450 ml. All blood components excluding FFP are irradiated with 15–50 Gy to prevent transfusion-associated graft-versus-host disease.

Statistical analysis

Data were analysed for first transfusion episodes and for subsequent transfusion episodes. To calculate the frequency of ATRs, the number of confirmed ATRs was correlated with the total number of first and subsequent transfusion episodes. All statistical analyses were performed by the chi-squared test, with Yates's correction for continuity and/or a Student's t-test. P values below 0·05 were considered statistically significant.

Results

Basic transfusion data set

During this study, there were 7594 RBC, 2469 FFP and 2127 PC first transfusion episodes (Table 2). As for the

Table 2 Number of transfusions

	First transfusion	Subsequent transfusion
No. of transfusion episodes		
RBC	7594	31 767
FFP	2469	6652
PC	2127	25 866
Gender ratio (female/male)		
RBC	0·8 (3380/4214)	0·6 (12 452/19 315)
FFP	0·7 (1031/1438)	0·6 (2463/4189)
PC	0·7 (896/1231)	0·6 (9533/16 333)
No. of units per episode[a]		
RBC	2·0	1·6
FFP	2·6	3·0
PC	1·2	1·1

[a]The values are averages.

gender distribution of first transfusion episodes, the female-to-male ratios for each blood component were at or near 0·7. On the subsequent transfusion episodes, the female-to-male ratios for each blood component were all 0·6. Thus, the gender distributions are quite similar for each blood component in both categories of transfusion episode. Furthermore, none of the differences in the number of units per episode for each blood component between first and subsequent transfusions was statistically significant.

ATRs following transfusion of blood components

As shown in Table 3, the incidence of ATRs to RBCs was significantly higher on first (1·08%) vs. subsequent (0·69%) transfusion episodes ($P = 0·0004$). Also, the incidence of ATRs to FFP was significantly higher on the first than on subsequent transfusion episodes: 2·84% vs. 1·91%, respectively ($P = 0·006$). Furthermore, although there was no significant difference in the incidence of ATRs to PC between first and subsequent transfusion episodes, the incidence of ATRs to PC trended higher on first vs. subsequent transfusion episodes (3·34% vs. 2·75%, respectively, but without statistical significance ($P = 0·10$).

When the incidence of ATRs to each blood component was investigated among males, the frequency of ATRs to RBCs on first transfusion episodes was found to be significantly higher than that on subsequent transfusion episodes ($P = 0·002$) (Table 3). The incidences of ATRs to FFP and PCs on first transfusion episodes were slightly higher than those on subsequent transfusion episodes. On the other hand, for females, the incidence of ATRs to FFP on first transfusion episodes was significantly higher than that on subsequent transfusion episodes ($P = 0·018$). Also, the incidences of ATRs to RBCs and PCs on first transfusion episodes were slightly higher than those on subsequent transfusion episodes among females.

Table 3 Incidence of ATRs on first transfusion and subsequent transfusion episode bases

	First transfusion		Subsequent transfusion		
	Number	Incidence (%)	Number	Incidence (%)	*P* value[a]
RBC					
Male	39	0·93	103	0·53	0·002
Female	43	1·27	117	0·94	0·08
Total	82	1·08	220	0·69	0·0004
FFP					
Male	34	2·36	75	1·79	0·18
Female	36	3·49	52	2·11	0·018
Total	70	3·24	127	1·91	0·006
PC					
Male	40	3·25	440	2·69	0·28
Female	31	3·46	271	2·84	0·30
Total	71	3·34	711	2·75	0·10

ATR, Adverse transfusion reaction.

[a]*P* values are for difference of incidences of ATRs between first transfusion and subsequent transfusion episodes.

Characteristics of clinical signs and symptoms associated with ATRs

When the incidence of various ATR types to RBCs was investigated, the frequency of FNHTR (0·43%) and other reactions (0·26%) on first transfusion episodes was found to be significantly higher than on subsequent transfusion episodes (FNHTR: 0·23%; $P = 0·001$, other reactions: 0·15%; $P = 0·03$) (Table 4). The first transfusion incidence of allergic reactions (0·47%) was slightly higher than for subsequent transfusion episodes (0·37%). Furthermore, first transfusion incidence of allergic reactions (2·51%) to FFP was significantly higher than that on subsequent transfusion episodes (1·65%, $P = 0·01$). On the other hand, there were no significant differences in the frequency of FNHTR, allergic reactions and others to PCs on first transfusion episodes vs. subsequent transfusion episodes (FNHTR: 0·33% vs. 0·23%, allergic reactions: 2·82% vs. 2·49%, others: 0·33% vs. 0·12%).

During the study, serious ATRs to RBCs and FFP were 3 (0·04%) and 4 (0·16%), respectively on first transfusion episodes (Table 4). On subsequent transfusion episodes, serious ATRs to RBCs, FFP and PCs were 5 (0·02%), 2 (0·03%) and 7 (0·03%), respectively. The proportions of serious ATRs among all ATRs to RBCs, FFP and PCs were low on first and subsequent transfusion episodes; thus, the majority of ATRs were not serious.

Discussion

One factor thought to influence the risk of ATRs is transfusion history. Despite this, previous reports about ATRs have not distinguished first from subsequent transfusions in their analysis. In the present study, incidences of ATRs to RBCs, FFP and PCs per first transfusion episode were 1·08%, 2·84% and 3·34%, respectively. On the other hand, the incidences of ATRs on subsequent transfusion episodes to RBCs, FFP and PCs were 0·69%, 1·91% and 2·75%, respectively. Thus, the risk of ATRs for patients with no transfusion history trended higher compared to patients who had already been transfused. In particular, the first transfusion incidences of ATRs to RBCs and FFP are significantly higher than those for subsequent

Table 4 Clinical characteristics of ATRs on first transfusion and subsequent transfusion episodes

	RBC			FFP			PC		
	First[a] *n* (%)	Subsequent[b] *n* (%)	*P* value[c]	First[a] *n* (%)	Subsequent[b] *n* (%)	*P* value[c]	First[a] *n* (%)	Subsequent[b] *n* (%)	*P* value[c]
FNHTR	33 (0·43)	73 (0·23)	0·001	7 (0·28)	6 (0·09)	0·07	7 (0·33)	60 (0·23)	0·35
Allergic reaction	36 (0·47)	108 (0·34)	0·09	62 (2·51)	110 (1·65)	0·01	60 (2·82)	643 (2·49)	0·31
Others	20 (0·26)	48 (0·15)	0·03	5 (0·20)	17 (0·26)	0·63	7 (0·33)	31 (0·12)	0·16
Serious ATR[d]									
Serious allergic reaction	2 (0·03)	5 (0·02)	0·28	4 (0·16)	2 (0·03)	0·18	0	7 (0·03)	0·46
TRALI	0	0	–	0	1 (0·01)	–	0	0	–
Delayed haemolytic reaction	1 (0·01)	0	–	0	0	–	0	0	–

ATR, Adverse transfusion reaction; FNHTR, Febrile non-haemolytic transfusion reaction.
The values are the number of ATRs (%).
[a]First transfusion episodes.
[b]Subsequent transfusion episodes.
[c]*P* values are for difference of incidences of ATRs between first transfusion and subsequent transfusion episodes.
[d]Serious ATRs were defined as grade 2 or higher according to documents issued by the ISBT Working Party for Haemovigilance and include serious allergic reaction, transfusion-related acute lung injury (TRALI) and haemolytic transfusion reaction.

transfusion episodes ($P < 0·01$). Furthermore, the first transfusion incidences of FNHTR to RBCs (0·43%, $P = 0·001$) and allergic reactions to FFP (2·51%, $P = 0·01$) were higher than those on subsequent transfusion episodes (RBCs: 0·23%, FFP: 1·65%). Therefore, the higher frequencies of ATRs to RBCs and FFP on the first transfusion vs. subsequent transfusions could be traced to the higher incidences of FNHTRs to RBCs and allergic reactions to FFP on the first transfusion.

Previous work has reported that the risk of ATRs for patients who had already been transfused trended higher compared to patients with no transfusion history [11]. In general, Japanese physicians and nurses must obtain transfusion histories from patients or their family members and the physicians in transfusion medicine check this history against hospital database records. Furthermore, they infer whether or not patients have received any previous transfusions based on the patients' diseases. Thus, in the present study, almost all patients in the first transfusion category are considered to be reliably categorized. Another possible reason for this discrepancy comes from a previous study that surveyed ATRs to only PCs and did not reach statistical significance in the incidences of ATRs for patients with no transfusion history vs. any transfusion history. Indeed, in the present study, although the first transfusion incidence of ATRs to PCs trended higher than for subsequent transfusions, the difference did not reach statistical significance ($P = 0·10$). It is suspected that although the data in this study were not analysed for the characteristics of transfused patients, such as underlying condition, age and pregnancy history, there are risks of ATRs on the first transfusion.

Heddle *et al.* [12, 13] have reported that FNHTRs to blood components are caused by white blood cell (WBC) antigen–antibody interaction and cytokines, such as interleukin (IL)-1β, IL-6 and tumour necrosis factor-α, released from WBCs and accumulated in blood components during storage. There is general agreement that prestorage leucoreduction will decrease the frequency of FNHTRs [14, 15]. However, leucoreduction dose not completely reduce the amount of CD154 (CD40 ligand), implicated in FNHTRs and elaborated by platelets. Thus, it is unlikely that leucocyte filtration by itself can completely eliminate the risk of FNHTRs. Furthermore, a recent study revealed that some cytokines start accumulating in stored whole blood within hours after donation [16]. In this study, although all blood components were leucocyte reduced before storage, a low rate of FNHTRs to blood components persisted both on first transfusion and subsequent transfusion episodes. In particular, the incidence of FNHTRs per first transfusion episode to RBCs, which contain relatively more WBCs than other blood components, was significantly higher than on subsequent transfusion episodes.

Furthermore, the number of RBC units per episode for the first transfusion was slightly more compared with that on subsequent transfusion episodes. In particular, the number of RBC units per episode for the first transfusion tended to be more than that on subsequent transfusion episodes for males (data not shown). Therefore, it is suspected that FNHTRs to blood components are not influenced by previous allogeneic exposure from transfusion and one risk of ATRs on the transfusion was correlated with the number of transfusion units per episode.

It is thought that allergic reactions to blood components are influenced by previous allogeneic exposure from transfusion. Tobian *et al.* [17] described that patients must be exposed to plasma multiple times before having an allergic reaction. In addition, the incidence of ATRs per patient was influenced by the number of transfusions per patient [4, 11]. However, in this study, the incidences of allergic reactions to RBCs, FFP and PCs were 0·47%, 2·51% and 2·82%, respectively on the first transfusion though these patients were not previously exposed to allogeneic transfusion (Table 4). Furthermore, there were 6 serious allergic reactions associated with first transfusions. Putative mechanisms underlying allergic reactions include biological response modifiers (BRMs) such as inflammatory cytokines and chemokines that accumulate during storage and enter the circulation during transfusion, leading to allergic reactions [18–22]. On the other hand, Savage *et al.* [23] showed that certain donors donated PCs that resulted in an allergic reaction rate of 5·8%, which was greater than the overall incidence of allergic reactions (1·72%). A recent study observed 1616 (1·72%) allergic reactions among 93 737 transfusions and found that 30% of recipients with an allergic reaction had allergic reaction rates of more than 5% [23]. Furthermore, in 630 instances where split PCs were given to two patients in whom one had a reaction, there were only six instances where the other patient also had a reaction [23]. On the other hand, Ahmed *et al.* [24] reported that pregnancy history directly correlates with the risk of allergic reaction on initial transfusion. Indeed, although the data analysis in this study did not consider pregnancy for female patients, the incidence of ATRs (3·49%) per first transfusion episode to FFP was significantly higher than on subsequent transfusion episodes (2·11%, $P = 0·018$, Table 3). Thus, it is suspected that blood component factors, donor factors and patient factors including pregnancy may contribute to allergic reactions. Therefore, as the present study shows, risks of allergic reactions to blood component exist in patients without previous allogeneic exposure from transfusion.

The incidences of allergic reactions to blood components on the first transfusion were higher or almost the same compared to subsequent transfusion episodes. In particular, the frequency of allergic reactions to FFP (2·51%) on the first transfusion was significantly higher compared to subsequent transfusion (1·65%, $P = 0·01$). It is possible that this pattern is due to an increased use of premedication among patients with reactions to a previous transfusion. However, most studies performed to date have failed to demonstrate that premedication is effective in preventing allergic transfusion reactions [25–28]. Furthermore, in the present study, although most patients receiving RBCs and PCs were premedicated, the first transfusion incidences of allergic reactions to RBCs and PCs were not significantly higher than for subsequent transfusions. Another possibility is that serial exposure to blood components may desensitize recipients. A recent study revealed that recurrent exposure to PCs caused recipients to become less likely to experience allergic reactions [29]. Furthermore, experiments show a desensitization effect on repeat exposure to reconstituted donor serum [30]. It is thought that desensitization is mediated by two mechanisms, the suppression of proallergic innate effectors and the upregulation of regulatory T-cell activity. Proallergic innate effectors could undergo rapid desensitization against allergens [31]. In addition, functional allergen-specific regulatory T cells can attenuate allergic responses through suppression of mast cells, basophils and eosinophils; suppression of allergen-specific T cells; and reduction of IgE production [31]. Indeed, Jo *et al.* [32] showed the acquisition of tolerance to cow's milk allergens during childhood is associated with the suppression of proallergic innate effectors' activity and activity of regulatory T cells. Taken together, these findings help explain why the incidence of allergic reactions to blood components on first transfusions could exceed that of subsequent transfusions.

We conclude that there are risks of ATRs on the first transfusion as well as transfusions of patients with transfusion history. It is suspected that FNHTRs are not so much provoked by previous allogeneic transfusion exposure as by the number of transfusion units per episode. On the other hand, with regard to allergic reactions, although both atopic susceptibility in the recipient as well as particular donor and component characteristics are risk factors, the first transfusion itself appears to be an important risk. Thus, despite the limitations of this study, it suggests the need for more elaborate analyses of patient data to further improve transfusion therapy. In particular, ATR risk factors elucidated here and elsewhere might refine clinical indications for washing PCs.

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Conflict of interest

The authors declare no conflict of interests.

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Repeated exposure rather than the total volume of transfused components may influence the incidence of allergic transfusion reactions

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BACKGROUND: The plasma fraction of blood components has an essential role in the etiology of allergic transfusion reactions (ATRs). The difference of incidences of ATRs between fresh-frozen plasma (FFP) and platelet concentrates (PCs), in which plasma is the main component, is not clearly understood. This study compares the frequency of ATRs to FFP versus PCs on both first and subsequent (nonfirst) transfusions and considers the factors influencing the risk of ATRs.

STUDY DESIGN AND METHODS: Five hospitals agreed to systematically collect and share 2 years of data (January 2010 through December 2011). This was a retrospective observational analysis of data including the number of transfusion episodes and ATRs for FFP and PCs on first-transfusion patients (without transfusion history) and previously transfused patients.

RESULTS: The incidence of ATRs to PCs (2.51%) was significantly higher than to FFP (1.68%) on subsequent transfusions ($p < 0.001$). On the other hand, there were no significant differences in the incidences of ATRs to FFP (2.67%) and PCs (2.82%) on first transfusions. This discrepancy was most pronounced among males: FFP versus PCs on first transfusions, 2.02% versus 2.60% ($p = 0.30$); and on subsequent transfusions, 1.58% versus 2.46% ($p = 0.0007$). Among females, FFP versus PCs on first transfusions was 3.59% versus 3.13% ($p = 0.61$) and on subsequent transfusions was 1.87% versus 2.61% ($p = 0.029$).

CONCLUSION: Repeated exposure rather than the total volume of transfused components may influence the incidence of ATRs.

Although blood transfusion is regarded as an essential and life-saving therapy, significant clinical risks are attributed to blood components' allogeneic origin. In particular, adverse reactions (ARs) are frequent in patients receiving transfusions of platelet concentrates (PCs).[1] We have previously demonstrated that the incidence of ARs to PCs per transfused unit was 3.8%.[2] It was also shown that the incidence of ARs to PCs per patient was 13.2%. Furthermore, most ARs to PCs were allergic transfusion reactions (ATRs).

ABBREVIATIONS: AR(s) = adverse reaction(s); ATR(s) = allergic transfusion reaction(s); PC(s) = platelet concentrate(s).

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