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Patient outcomes and amotosalen/UVA-treated platelet utilization in massively transfused patients

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Background Amotosalen/UVA-treated platelet concentrates (PCs) have demonstrated efficacy for treating and preventing bleeding in clinical trials and in routine use; however, most studies were performed in haematology/oncology patients. We investigated efficacy during massive transfusion (MT) in general hospitalized patients.

Methods Universal amotosalen/UVA treatment (INTERCEPT Blood System) of platelets was introduced at a large Austrian medical centre. We performed a retrospective cohort analysis comparing component use, in-hospital mortality and length of stay after MT that included platelet transfusion, for two periods (21 months each) before and after implementation.

Results A total of 306 patients had MT. Patients were mostly male (74%) and ≥18 years old (99%), including 93 liver transplant, 97 cardiac or vascular surgery and 51 trauma patients. There were no differences in demographics between the periods. Component use on the day and within 7 days of the MT event was unchanged post-IBS implementation, except trauma patients received fewer RBCs on the day. The mean ratio of RBC:platelets:plasma on the day of the MT was close to 1:1:1 in both periods, except for liver transplants with MT who received more plasma components. Overall, in-hospital mortality (preimplementation = 27·6% vs. postimplementation = 24·0%; $P = 0{\cdot}51$) and median time to discharge (preimplementation = 27 vs. postimplementation = 23 days; $P = 0{\cdot}37$) did not change, except for cardiac and vascular surgery patients who were discharged earlier.

Conclusion The introduction of amotosalen/UVA-treated, pathogen-reduced PC did not adversely affect clinical outcomes in massively transfused patients in terms of blood product usage, in-hospital mortality and length of stay for a range of clinical indications for platelet transfusion support.

Key words: amotosalen, INTERCEPT Blood System, massive transfusion, pathogen reduction, platelets.

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Introduction

In early 2013 the University Hospital, Innsbruck (UHI), Austria introduced universal pathogen reduction in whole blood (WB) buffy-coat (BC) and apheresis platelets with amotosalen/UVA light (INTERCEPT Blood System, Cerus Europe BV, Amersfoort, Netherlands) (IBS) to mitigate bacterial and other infectious risks and to replace gamma irradiation for prevention of transfusion-associated graft-versus-host disease (TA-GVHD) [1–3]. Pathogen-reduced plasma was already in routine use. Amotosalen/UVA treatment is designed for the *ex vivo* preparation of pathogen-reduced whole blood-derived and apheresis PC, suspended either in plasma or plasma with platelet additive solution (PAS), and is intended to reduce the risk of transfusion-associated transmission of viruses, bacteria

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and parasites and prevent TA-GVHD. Amotosalen/UVA-treated PCs have demonstrated efficacy for treatment and prevention of bleeding in large randomized controlled clinical trials [4–6]. Efficacy and safety were confirmed under routine-use conditions, as reported to large national haemovigilance programmes and in industry-sponsored postmarketing comparative effectiveness studies [7–14].

A recent commentary highlighted that most clinical studies for pathogen-reduced platelets have focused on haematology/oncology patients in which patients were primarily transfused to prevent rather than to treat active bleeding, raising the question whether amotosalen/UVA-treated platelets were effective at treating bleeding in acutely haemorrhaging patients [15]. This would be especially important for the trauma setting where the rapid transfusion of plasma, platelets and RBC is advocated [15]. The recently published PROPPR study [16], a large randomized controlled trial that compared rapid transfusion of plasma, platelets and RBC in a 1:1:1 ratio versus a 1:1:2 ratio in trauma patients receiving MT, found no significant differences in mortality at 24 h or at 30 days. Exsanguination, which was the predominant cause of death within the first 24 h, was significantly decreased in the 1:1:1 group, and more patients in the 1:1:1 group achieved haemostasis than in the 1:1:2 group. Hess *et al.* hypothesized that the use of pathogen-reduced platelets and plasma in the trauma setting would cause patient harm from haemorrhage, due to an inferred decrease in component potency. In support, they quote an open-label, randomized controlled trial comparing the clinical effectiveness of BC-derived PC that found a lower corrected count increment (CCI) and increased, mostly low-grade, bleeding events in patients receiving amotosalen/UVA-treated PC [17].

In response to this hypothesis, we evaluated whether the implementation of amotosalen/UVA-treated PC was associated with increased component usage, in-hospital mortality or delayed patient discharge for patients who received massive transfusions (MT), in a hospital where amotosalen/UVA-treated platelets were the only available type of PC.

Materials and methods

Amotosalen/UVA treatment of all PCs was implemented between January and March 2013 at the University Hospital, Innsbruck (UHI), a large Austrian academic medical centre, which supports active trauma, transplant and cardiac surgery programmes [1]. In a retrospective, two-treatment period, observational study, we analysed transfusion data for all patients who received a massive transfusion (MT), defined as ≥1 PC and ≥10 red blood cell concentrates (RBCs) on a single calendar day, for 21 months before (pre-IBS: 1 April 2011–31 December 2012) and after (post-IBS: 1 April 2013–31 December 2014) full implementation of amotosalen/UVA treatment of PC. In general, an MT event was defined within a single calendar day; however, 11 patients received MT on 2 consecutive days and their component use was totalled and analysed as a single MT event. Twelve patients had MT events on 2 or 3 non-consecutive days, and only the first MT event was considered in the subsequent analysis; however, for two patients these separate events occurred within 7 days and so their component use data are included in the 7-day component usage statistics (Table 1).

Physicians ordered blood components according to the institutional guidelines, which were the same in both periods. In general, clinical transfusion triggers did not change over the two periods of the study, except that thromboelastometry (ROTEM, Tem International GmbH, München, Germany) was increasingly used as a basis for evaluating coagulation status and the need for transfusion in cardiac surgical patients during the second study period.

All recipients of blood components were included for analysis in both observation periods. Patient demographics and component characteristics were extracted from the blood bank electronic medical records. Patient

Table 1 Patient demographics of all patients receiving ≥1PC and ≥10 RBC components on a single day in the 21 months before (pre-IBS) and 21 months after (post-IBS) implementation of amotosalen/UVA treatment of all platelets. There were no significant differences in the patient populations pre- and post-IBS implementation ($P > 0{\cdot}05$)

Demographics	Pre-IBS	Post-IBS
Total patients	156	150
Male	115 (73·7%)	111 (74·0%)
Female	41 (26·3%)	39 (26·0%)
Patient age		
Mean (SD)	58·3 (14·6)	59·5 (14·5)
Median (IQR)	59·5 (49·0–69·5)	60·5 (50·0–70·0)
Min	10	16
Max	90	86
1–18 years	1 (0·6%)	1 (0·7%)
19–64 years	99 (63·5%)	92 (61·3%)
≥65 years	56 (35·9%)	57 (38·0%)
1 Episode	150 (96·2%)	144 (96·0%)
2 Episodes	5 (3·2%)	5 (3·3%)
3 Episodes	1 (0·6%)	1 (0·7%)
Liver transplant	45 (28·8%)	48 (32·0%)
Cardiac & vascular surgery	53 (34·0%)	44 (29·3%)
Trauma	27 (17·3%)	24 (16·0%)
Other	31 (19·9%)	34 (22·7%)

IQR, interquartile range.

outcomes for date of in-hospital death or discharge were extracted from the hospital electronic medical records by two local investigators (WN, MA). Plasma was prepared as quarantined plasma, methylene blue-treated plasma (Macopharma, Tourcoing, France) or solvent detergent plasma (Octaplas, Octapharma, Wien, Austria) in both study periods. The mean content of a dose of both apheresis and WB-derived platelets was ~3·0 × 10^{11}/component for both periods, although the actual transfused platelet dose was not recorded. Average PC counts before amotosalen/UVA treatment and changes in the proportion of apheresis and BC PC transfused are described in Amato *et al.* [1].

Collection and preparation of PC

Platelet components were collected on Trima (Terumo BCT, Zaventem, Belgium) or Amicus (Fresenius Kabi, Bad Homberg, Germany) apheresis separators or prepared from pools of five BC concentrates separated from WB collections after room temperature overnight storage. All final components were leucocyte-reduced and suspended in approximately 35% plasma and 65% SSP+ PAS (Macopharma, Tourcoing, France) during both periods. During the first period, apheresis and BC platelet pools were subjected to gamma irradiation when requested by clinical care physicians and universally screened for bacterial contamination using the BacT/ALERT culture system (bioMerieux, Marcy-I'Etoile, France). For PC still in inventory on day 4, shelf life was extended following BacT/ALERT reculture, allowing for relabelling with a 7-day shelf life on day 5.

For amotosalen/UVA treatment in the second period, PCs containing 2·5–8·0 × 10^{11} platelets were treated with amotosalen (nominal final concentration 150 μM) and 3 J/cm^2 UVA according to the manufacturer's instructions for use, followed by incubation on a compound absorption device (CAD) for 6–16 h depending on production schedules. Apheresis components were generally treated on the day of collection (day 0), and products were released into inventory the next day on receipt of the viral testing results. For BC pools, amotosalen/UVA treatment was performed immediately after BC pool preparation on the day after collection and the PC could be released into inventory after CAD incubation on day 2 or 3. Amotosalen/UVA-treated PCs were stored for up to 7 days before transfusion [5]. Gamma irradiation and bacterial culture screening were not performed during the second period. Viral marker testing was not changed after amotosalen/UVA implementation.

Statistical analysis

Data were summarized descriptively by mean, standard deviation, median and interquartile (IQR) range for continuous data or by frequencies and proportions (%) for categorical data, using SAS® version 9.4 (SAS Institute, Cary, NC, USA). Fisher's exact test was used to test for the difference between the two cohorts for non-ordinal categorical variables, and the Cochran–Mantel–Haenszel (CMH) row mean scores differ statistic were used for ordinal categorical data. For time to in-hospital mortality and time to discharge, Kaplan–Meier estimates and the log-rank test were utilized.

Results

Three hundred and six patients had 331 MT episodes, 156 patients in the 21 months pre-IBS and 150 patients in the 21 months post-IBS implementation (Table 1). A total of 217 of 331 (65·6%) MT events that occurred on the day of admission or the next day were related to emergent admission or scheduled elective surgery. Patients were mostly male (226/306: 73·9%) and over 18 years old (304/306: 99·3%). Ninety-three (30·4%) patients underwent liver transplantation (including five-second liver transplants); 97 (31·7%) patients had cardiac or vascular surgery procedures, including cardiac transplantation (11), aortic or mitral valve replacement (19), or emergent or elective aortic aneurysm repair (34), while 51 (16·7%) patients were treated for trauma. The remaining 65 (21·2%) patients were admitted for a variety of medical and surgical conditions. There was no difference in the patient demographics comparing the pre-IBS and post-IBS implementation populations (Table 1).

Component use on the day of the MT event was similar pre- and post-IBS implementation, except that trauma patients used fewer RBC post-IBS (Table 2a). The mean ratio of RBC: platelets: plasma was close to 1:1:1 in both periods [16], except for liver transplant patients who used a disproportionate amount of plasma components compared with RBC and PC in both periods. Considering component usage in the 7 days following the MT event, there were again no differences in blood component usage, with the exception that 'other medical or surgical patients' utilized significantly fewer RBCs in the pre-IBS period (Table 2b).

The proportion of patients with in-hospital mortality (%) or median time to discharge from the first MT event did not change after implementation of IBS, except for cardiac and vascular surgery patients who were discharged earlier in the post-IBS period (Table 3). Likewise, Kaplan–Meier survival analysis showed no difference in time to in-hospital mortality after the implementation of IBS for all (Fig. 1a; $P = 0·58$) or any subset of patients (Table 3). Indeed, the trend favoured a decrease in in-hospital mortality in the post-IBS implementation period (Fig. 1a). Similarly Kaplan–Meier analysis showed no

Table 2 Component use on the day of the massive transfusion event (a) and within 7 days (b) shown as mean, standard deviation, median and interquartile range values [mean ± SD; (median; interquartile range)]

		Pre-IBS	Post-IBS	*P* Value
(a) Day(s) of MT event				
All patients (*N* = 156/150)	RBC	16·4 ± 7·4; (14·0, 12·0–19·0)	16·2 ± 7·3; (13·0, 11·0–19·0)	0·78
	Platelets	3·0 ± 2·1; (2·0, 2·0–4·0)	3·3 ± 2·0; (3·0, 2·0–4·0)	0·33
	Plasma	24·2 ± 20·9; (19·5, 10·0–38·0)	23·5 ± 19·7; (16·5, 10·0–35·0)	0·75
	Mean ratio RBC: platelets: plasma	1·0: 0·9: 1·2	1·0: 1·0: 1·3	
Liver transplant (*N* = 45/48)	RBC	16·7 ± 7·4; (15·0, 12·0–19·0)	16·5 ± 7·7; (12·5, 11·0–20·0)	0·88
	Platelets	3·2 ± 2·0; (3·0, 2·0–4·0)	3·6 ± 2·0; (3·0, 3·0–5·0)	0·30
	Plasma	45·4 ± 20·3; (45·0, 33·0–60·0)	42·8 ± 20·0; (45·0, 30·0–54·5)	0·55
	Mean ratio RBC: platelets: plasma	1·0: 0·9: 2·4	1·0: 1·1: 2·5	
Cardiac & vascular surgery (*N* = 53/44)	RBC	16·7 ± 8·1; (15·0, 12·0–19·0)	16·9 ± 8·8; (13·0, 12·0–19·0)	0·91
	Platelets	3·3 ± 2·4; (3·0, 2·0–4·0)	3·8 ± 2·6; (3·0, 2·0–5·0)	0·30
	Plasma	19·7 ± 14·6; (16·0, 10·0–29·0)	18·0 ± 11·9; (15·0, 10·0–24·0)	0·53
	Mean ratio RBC: platelets: plasma	1·0: 0·9: 0·9	1·0: 1·1: 0·9	
Trauma (*N* = 27/24)	RBC	18·3 ± 7·8; (17·0, 12·0–24·0)	14·6 ± 4·7 (13·0, 11·0–17·5)	0·05
	Platelets	2·6 ± 1·2; (2·0, 2·0–3·0)	2·4 ± 1·3; (2·0, 2·0–3·0)	0·63
	Plasma	13·8 ± 10·9; (10·0, 5·0–20·0)	9·7 ± 7·6; (10·0, 1·0–14·5)	0·13
	Mean ratio RBC: platelets: plasma	1·0: 0·8: 0·7	1·0: 0·8: 0·7	
Other medical & surgical (*N* = 31/34)	RBC	13·9 ± 5·1; (13·0, 10·0–15·0)	16·0 ± 6·4; (13·5, 12·0–19·0)	0·16
	Platelets	2·7 ± 2·2; (2·0, 2·0–3·0)	2·6 ± 1·3; (2·0, 2·0–3·0)	0·79
	Plasma	10·5 ± 13·1; (6·0, 0·0–16·0)	13·1 ± 10·9; (13·0, 5·0–20·0)	0·39
	Mean ratio RBC: platelets: plasma	1·0: 0·9: 0·7	1·0: 0·8: 0·8	
(b) Within 7 days of the MT event				
All patients (*N* = 156/150)	RBC	18·9 ± 8·2; (16·0, 13·0–23·0)	19·1 ± 9·3; (16·5, 13·0–24·0)	0·79
	Platelets	5·4 ± 4·0; (4·0, 3·0–7·0)	6·0 ± 4·1; (5·0, 3·0–8·0)	0·26
	Plasma	30·6 ± 28·2; (22·0, 10·0–44·0)	29·9 ± 22·8; (22·5, 12·0–45·0)	0·80
Liver transplant (*N* = 45/48)	RBC	18·5 ± 8·6; (16·0, 13·0–23·0)	17·9 ± 7·9; (15·0, 12·0–22·5)	0·73
	Platelets	7·7 ± 4·6; (6·0, 5·0–9·0)	7·6 ± 3·9; (7·0, 4·5–10·0)	0·96
	Plasma	61·2 ± 29·5; (55·0, 43·0–72·0)	53·2 ± 16·4; (50·0, 42·5–65·0)	0·11
Cardiac & vascular surgery (*N* = 53/44)	RBC	19·4 ± 8·3; (17·0, 14·0–23·0)	20·0 ± 9·7; (18·0, 13·0–23·5)	0·76
	Platelets	5·2 ± 3·6; (4·0, 3·0–7·0)	5·8 ± 4·2; (5·0, 3·0–7·5)	0·48
	Plasma	22·0 ± 15·5; (20·0, 10·0–31·0)	21·8 ± 15·9; (19·0, 10·0–28·5)	0·93
Trauma (*N* = 27/24)	RBC	22·2 ± 8·4; (22·0, 15·0–27·0)	18·9 ± 7·9; (16·0, 13·0–24·0)	0·16
	Platelets	4·1 ± 3·2; (3·0, 2·0–4·0)	3·8 ± 1·9; (3·5, 2·0–5·5)	0·70
	Plasma	15·3 ± 10·9; (14·0, 6·0–21·0)	11·1 ± 8·4; (10·0, 3·5–16·0)	0·13
Other medical & surgical (*N* = 31/34)	RBC	15·6 ± 5·7; (14·0, 12·0–16·0)	20·0 ± 11·4; (17·0, 13·0–22·0)	0·05
	Platelets	3·7 ± 2·8; (3·0, 2·0–5·0)	5·3 ± 4·5; (3·5, 2·0–8·0)	0·09
	Plasma	14·2 ± 17·2; (10·0, 5·0–19·0)	20·7 ± 19·1; (16·0, 10·0–25·0)	0·15

Table 3 In-hospital mortality and median time to hospital discharge (days) before (pre-IBS) and after (post-IBS) implementation of amotosalen/UVA treatment of platelet concentrates

		Pre-IBS	Post IBS	*P* Value
All patients (*N* = 156/150)	In-hospital mortality (%)	43 (27·6%)	36 (24·0%)	0·51
	Median (IQR) time to discharge (days)	27 (9·0–35·0)	23 (13·0–33·0)	0·37
Liver transplant (*N* = 45/48)	In-hospital mortality (%)	1 (2·2%)	3 (6·3%)	0·62
	Median (IQR) time to discharge (days)	22·5 (17·0–34·0)	21 (16·5–28·5)	0·55
Cardiac & vascular surgery (*N* = 53/44)	In-hospital mortality (%)	20 (37·7%)	13 (29·5%)	0·52
	Median (IQR) time to discharge (days)	33 (7·0–35·0)	21 (4·5–27·5)	0·03
Trauma (*N* = 27/24)	In-hospital mortality (%)	12 (44·4%)	8 (33·3%)	0·57
	Median (IQR) time to discharge (days)	32 (1·0–34·0)	29 (11·5–33·0)	0·48
Other medical & surgical (*N* = 31/34)	In-hospital mortality (%)	10 (32·3%)	12 (35·3%)	1·00
	Median (IQR) time to discharge (days)	27 (6·0–37·0)	34 (6·0–53·0)	0·17

IQR, interquartile range.

difference in the overall time to patient discharge for surviving patients (Fig. 1b; $P = 0{\cdot}37$).

Discussion

The UHI implemented universal pathogen reduction in all PCs in 2013, using the amotosalen/UVA treatment process. A previously reported comparative effectiveness analysis of overall blood component usage in the entire hospital for 21 months before (pre-IBS) and after implementation (post-IBS) showed that the mean numbers of PC transfused per patient (4·8 vs. 4·5, $P = 0{\cdot}44$) were not different, but days of PC support (5·9 vs. 5·0, $P = 0{\cdot}05$) decreased in the second period [1]. Most patients who received PC also received RBC (86·8% pre-IBS vs. 84·8% post-IBS, $P = 0{\cdot}10$) with similar mean numbers transfused (10·8 vs. 10·2 RBC, $P = 0{\cdot}22$), and fewer patients (55·4% pre-IBS vs. 44·7% post-IBS, $P < 0{\cdot}01$) received plasma and less plasma units per patient (mean 9·9 vs. 7·8, respectively, $P < 0{\cdot}01$) after implementation of amotosalen/UVA treatment. Analysis of haematology–oncology (522 pre-IBS, 452 post-IBS), cardiac surgery (739 pre-IBS, 711 post-IBS), paediatric (157 pre-IBS, 130 post-IBS) and neonate (23 pre-IBS, 20 post-IBS) patients revealed no increase in PC, plasma and RBC utilization, or adverse events [1].

In the same clinical centre, we now demonstrate that the implementation of amotosalen/UVA-treated PC did not adversely affect rates of transfusion in 1 and 7 days, length of stay and mortality in patients who received MT, defined as ≥1PC plus ≥10 RBCs on a single calendar day. MTs were most frequently related to liver transplantation and cardiac and vascular surgeries in both periods. Liver transplants are usually elective procedures in patients with an underlying coagulopathy related to liver dysfunction. While most liver transplants do not require MT [13], the major vascular anastomoses necessary and the unavoidable exacerbation of coagulopathy related to the anhepatic phase of transplantation surgery cause these patients to be at high risk of excessive bleeding. While plasma transfusion is critical to replace coagulation factors synthesized in the liver, platelets also play an important role in achieving haemostasis. The low overall in-hospital mortality rate [4/93 patients (4·3%)] despite the need for MT is reflective of the elective nature of liver transplant surgery, and speaks to the effectiveness of massive transfusion strategies that now include pathogen-reduced PC. A similar study previously showed that plasma treated with the amotosalen/UVA process was equivalent to conventional plasma in the liver transplantation setting [13].

Cardiac and vascular surgeries, likewise, included elective, urgent and emergent surgery; however, the overall in-hospital mortality of 33/97 (34·0%) patients for both periods who received MT is indicative of the mostly emergent nature of the MT events. Similar mortality rates were evident for the trauma (20/51 patients; 39·2%) and 'other medical and surgical' (22/65; 33·8%) patients. While we observed no clinically significant differences in blood component usage, in-hospital mortality or time to discharge before or after implementation of amotosalen/UVA-treated PC, these data are consistent with the expected high mortality associated with MT in general, outside of the liver transplantation setting.

Recent experiences with MT for combat trauma have highlighted the need for aggressive resuscitation with a combination of plasma, platelets and RBC, with a minimization of the use of crystalloids [18–23]. Multiple retrospective analyses have reinforced the notion of the use of 'massive transfusion protocols' (MTP) that incorporate

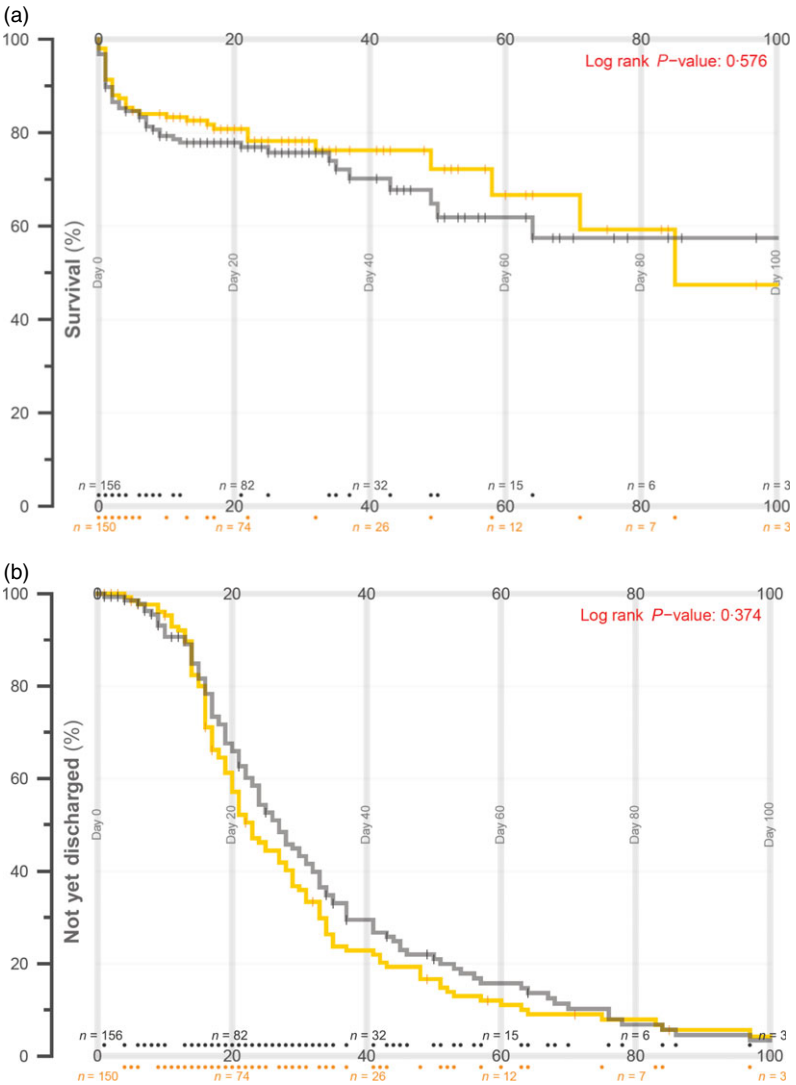

Fig. 1 (a) Kaplan–Meier survival statistic of in-hospital mortality for all patients. Patients were censured on day of hospital discharge. (b) Kaplan–Meier survival statistic of hospital discharge for all patients. Patients were censured on day of in-hospital fatality. Orange: post-IBS, grey: pre-IBS.

the ready availability of thawed or liquid plasma and platelets in the emergency room, or even during prehospital ambulance or helicopter transport. These findings have been encapsulated in the recommendation for the use of a balanced ratio of plasma, platelets and RBC early in the treatment of trauma requiring MT. Although the PROPPR randomized controlled clinical trial did not find a difference in 24-h and 30-day mortality when comparing a 1:1:1 with a 1:1:2 ratio, it did support the efficacy of the 1:1:1 protocol for prevention of early exsanguination and effective haemostasis [16]. Hess *et al.* extrapolated from these findings and hypothesized that the potency of platelet and plasma components – measured by surrogates such as CCI – is critical to patient outcomes in MT associated with trauma, further suggesting losses due to pathogen reduction treatment may reduce component potency and compromise patient safety [15]. Our clinical observations reported here for amotosalen/UVA-treated platelets in the MT setting argue strongly against this hypothesis and instead support the safety and efficacy of these components in patients requiring MT. Furthermore, the comparative effectiveness studies of amotosalen/UVA-treated and conventional plasma in general liver transplantation, including those that required MT, similarly suggested that pathogen reduction in plasma did not adversely affect outcomes [13]. While our study included only a small number of trauma patients, the high mortality in all non-liver transplant patients with MT supports a similar haemorrhagic risk profile as is seen in trauma.

Comparative effectiveness studies with a retrospective cohort design have inherent limitations, as they cannot fully describe all potential confounding factors that may have changed over the duration of the study, including

disparities in the patient populations between the two time periods or individual physician practice. Changes in clinical practice such as reduced crystalloid use, as well as possible increased use of fibrinogen concentrates and tranexamic acid in massive bleeding, could not be accounted for. Nevertheless, the two time periods were contiguous, likely minimizing the risk of changes in clinical practice. Ordering clinicians may have been aware of the change in the nature of the PC being transfused in the second period; however, there is no indication that they ordered more or fewer components on that basis.

Ours was a single institution study of modest size that needs to be confirmed in more patients at multiple institutions, but did include all physicians treating MT patients within our institution, allowing for variation in practice. To avoid selection bias, we arbitrarily defined MT by calendar day and not by a running 24-h period; nevertheless, the same rigorous definition was used in both time periods. Massive transfusions are challenging to study in a prospective fashion and few randomized studies have compared blood products utilization in this setting, making our study unique. In conclusion, our analysis suggests that amotosalen/UVA-treated PCs are efficacious in the MT setting, while also providing the added advantage of helping to protect patients from transfusion-transmitted infections who by definition receive many donor exposures.

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References

1 Amato M, Schennach H, Astl M, *et al.*: Impact of platelet pathogen inactivation on blood component utilization and patient safety in a large Austrian Regional Medical Centre. *Vox Sang* 2016; doi:10.1111/vox.12456 [Epub ahead of print].

2 Lin L, Dikeman R, Molini B, *et al.*: Photochemical treatment of platelet concentrates with amotosalen and long-wavelength ultraviolet light inactivates a broad spectrum of pathogenic bacteria. *Transfusion* 2004; **44**:1496–1504

3 Lin L, Hanson CV, Alter HJ, *et al.*: Inactivation of viruses in platelet concentrates by photochemical treatment with amotosalen and long-wavelength ultraviolet light. *Transfusion* 2005; **45**:580–590

4 McCullough J, Vesole DH, Benjamin RJ, *et al.*: Therapeutic efficacy and safety of platelets treated with a photochemical process for pathogen inactivation: the SPRINT Trial. *Blood* 2004; **104**:1534–1541

5 Lozano M, Knutson F, Tardivel R, *et al.*: A multi-centre study of therapeutic efficacy and safety of platelet components treated with amotosalen and ultraviolet A pathogen inactivation stored for 6 or 7 d prior to transfusion. *Br J Haematol* 2011; **153**:393–401

6 van Rhenen D, Gulliksson H, Cazenave JP, *et al.*: Transfusion of pooled buffy coat platelet components prepared with photochemical pathogen inactivation treatment: the euroSPRITE trial. *Blood* 2003; **101**:2426–2433

7 Osselaer JC, Cazenave JP, Lambermont M, *et al.*: An active haemovigilance programme characterizing the safety profile of 7437 platelet transfusions prepared with amotosalen photochemical treatment. *Vox Sang* 2008; **94**:315–323

8 Osselaer JC, Messe N, Hervig T, *et al.*: A prospective observational cohort safety study of 5106 platelet transfusions with components prepared with photochemical pathogen inactivation treatment. *Transfusion* 2008; **48**:1061–1071

9 Osselaer JC, Doyen C, Defoin L, *et al.*: Universal adoption of pathogen inactivation of platelet components: impact on platelet and red blood cell component use. *Transfusion* 2009; **49**:1412–1422

10 Cazenave JP, Waller C, Kientz D, *et al.*: An active hemovigilance program characterizing the safety profile of 7483 transfusions with plasma components prepared with amotosalen and UVA photochemical treatment. *Transfusion* 2010; **50**:1210–1219

11 Cazenave JP, Isola H, Waller C, *et al.*: Use of additive solutions and pathogen inactivation treatment of platelet components in a regional blood center: impact on patient outcomes and component utilization during a 3-year period. *Transfusion* 2011; **51**:622–629

12 Knutson F, Osselaer J, Pierelli L, *et al.*: A prospective, active haemovigilance study with combined cohort analysis of 19 175 transfusions of platelet components prepared with amotosalen-UVA photochemical treatment. *Vox Sang* 2015; **109**:343–352

13 Cinqualbre J, Kientz D, Remy E, *et al.*: Comparative effectiveness of plasma prepared with amotosalen-UVA pathogen

inactivation and conventional plasma for support of liver transplantation. *Transfusion* 2015; **55**:1710–1720
14 Corash L, Benjamin RJ: The role of hemovigilance and postmarketing studies when introducing innovation into transfusion medicine practice: the amotosalen-ultraviolet A pathogen reduction treatment model. *Transfusion* 2016; **56**(Suppl 1):S29–S38
15 Hess JR, Pagano MB, Barbeau JD, *et al.*: Will pathogen reduction of blood components harm more people than it helps in developed countries? *Transfusion* 2016; **56**:1236–1241
16 Holcomb JB, Tilley BC, Baraniuk S, *et al.*: Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA* 2015; **313**:471–482
17 Kerkhoffs JL, van Putten WL, Novotny VM, *et al.*: Clinical effectiveness of leucoreduced, pooled donor platelet concentrates, stored in plasma or additive solution with and without pathogen reduction. *Br J Haematol* 2010; **150**:209–217
18 Borgman MA, Spinella PC, Perkins JG, *et al.*: The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. *J Trauma* 2007; **63**:805–813
19 Holcomb JB, Jenkins D, Rhee P, *et al.*: Damage control resuscitation: directly addressing the early coagulopathy of trauma. *J Trauma* 2007; **62**:307–310
20 Holcomb JB, Spinella PC: Optimal use of blood in trauma patients. *Biologicals* 2010; **38**:72–77
21 Holcomb JB, Zarzabal LA, Michalek JE, *et al.*: Increased platelet: RBC ratios are associated with improved survival after massive transfusion. *J Trauma* 2011; **71**:S318–S328
22 Holcomb JB, Donathan DP, Cotton BA, *et al.*: Prehospital transfusion of plasma and red blood cells in trauma patients. *Prehosp Emerg Care* 2015; **19**:1–9
23 Hess JR, Holcomb JB: Resuscitating PROPPRly. *Transfusion* 2015; **55**:1362–1364