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Day or overnight transfusion in critically ill patients: does it matter?

Running head: Day and night transfusion in intensive care unit

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Abstract

Background and objectives: The timing of blood administration in critically ill patients is first driven by patients' needs. This study aims to define the epidemiology and significance of overnight transfusion in critically ill patients.

Materials and methods: This is a *post hoc* analysis of a prospective multicentre observational study including 874 critically ill patients receiving red blood cells, platelets, fresh frozen plasma (FFP) or cryoprecipitate. Characteristics of patients receiving blood only during the day (8 am up until 8 pm) were compared to those receiving blood only overnight (8 pm up until 8 am). Characteristics of transfusion were compared and factors independently associated with major bleeding were analyzed.

Results: The 287 patients transfused during the day only had similar severity and mortality to the 258 receiving blood products overnight only. Although bleeding-related admission diagnoses were similar, major bleeding was the indication for transfusion in 12% of patients transfused in daytime only versus 30% of patients transfused at night only ($p < 0.001$). Similar total amount of blood products were transfused at day and night (2856 versus 2927); however, patients were more likely to receive FFP and cryoprecipitate at night compared with daytime. Overnight transfusion was independently associated with increased odds of major bleeding (odds ratio, 3.16, 95% confidence interval, 2.00-5.01).

Conclusion: Transfusion occurs evenly across day and night in ICU; nonetheless, there are differences in type of blood products administered that reflect differences in indication. Critically ill patients were more likely to receive blood for major bleeding at night irrespective of admission diagnosis.

Key words: Transfusion, red blood cells, critically ill patient, major bleeding, outcome, timing of care

Introduction

Transfusion is a common therapy in intensive care units (ICU), where up to 30% of patients receive red blood cell (RBC) transfusion [1, 2]. Blood products, including RBC, platelets (PLT) and fresh frozen plasma (FFP) can be lifesaving; however their administration has also been associated with an increase in morbidity and mortality in critically ill patients [3-5]. A better understanding of transfusion epidemiology in critically ill patients may identify strategies to reduce exposure to blood products and potentially improve patient management and outcome.

In most hospital settings, 'after hours' transfusion is strongly discouraged [6, 7] due to reduced staffing for blood administration and monitoring, and fewer resources to respond in the event of an adverse reaction. In ICU, unlike other clinical settings, the timing of administration of blood products is based more on patient requirements, as a constant nurse-to-patient ratio over 24 hours facilitates safe blood

administration. Therefore, transfusion of blood products would be expected to occur more evenly across the day in ICU. However, the timing and clinical indications for transfusion is not routinely analyzed in haemovigilance reports [8, 9], and no data on time of blood administration are available in the setting of critically ill patients. This question is of importance, as some authors have found that ICU admission at night is associated with a poorer prognosis, suggesting that critical care delivered after hours may be in some way different to care given during normal working hours [10, 11]. Whether differences in care in critically ill patients extend to transfusion practice has not been investigated previously.

To investigate whether there are differences in blood product administration after hours in ICU, we studied the time of blood product administration across 47 Australian and New Zealand ICUs to compare patient and transfusion characteristics according to the time of day during which patients were transfused. We hypothesized that there would be differences in administration of blood products for planned transfusions (e.g. prior to a scheduled procedure), but there would be no difference for other indications, such as major bleeding.

Materials and methods

Study design and study population

This study is a *post hoc* analysis of a prospective observational study which described Australian transfusion practice [12]. In brief, the primary observational study was conducted in 47 Australian and New Zealand ICUs over 5 weeks. All patients hospitalized in ICU and receiving at least one bag/unit of RBC, PLT, FFP or cryoprecipitate, were included. Patient demographic characteristics, primary diagnosis, comorbidities, hospital admission and discharge dates and status at hospital discharge were recorded. Laboratory data collected included hemoglobin before RBC transfusion, international normalized ratio (INR) before FFP, platelet count before PLT and fibrinogen level prior to cryoprecipitate administration. Date and time of transfusion were documented. There was no system for transfusion review in the study centers.

Transfusion indications and classifications

Blood component transfusion indications were categorized into major bleeding (defined by ongoing bleeding associated with a decrease in hemoglobin of at least 3g/dL in the preceding 12 hours or the requirement for at least 3 RBC units in 12 hours), minor bleeding, and unknown. To improve oxygen delivery was also an indication for RBC, while PLT, FFP and cryoprecipitate administration were also categorized into prophylaxis against spontaneous bleeding, invasive procedure and disseminated intravascular coagulation (DIC). Admission diagnoses that were considered likely to be associated with bleeding events were trauma, gastrointestinal bleeding (GI), ruptured abdominal aortic aneurysm and intra-peritoneal bleeding based on the APACHE (Acute Physiology Age Chronic Health Evaluation) III codes.

Patients were classified according to the time/s of day in which they received a transfusion: day transfusion was defined as those who received blood products only between 8 am and 8 pm; night

transfusion was defined as those who received blood products only between 8 pm and 8 am; and both day and night was defined as those who received at least one transfusion over both time periods.

The study was approved by the human research ethics committees of each participating institution.

Statistical Analysis

All statistical analyses were performed using Stata version 12 (StataCorp, College Station, Texas, USA). Categorical variables were described as frequency (%) and compared using Pearson's Chi-Square and continuous variables were described as median [interquartile range, IQR] and compared using a Kruskal-Wallis test when non-normally distributed and Student's t-test when normally distributed. Univariate analysis was performed to compare: 1) demographic and transfusion characteristics of patients transfused in daytime only versus night only, and 2) characteristics of transfusion occurring at daytime only and at night only. Multiple logistic regression was performed to identify factors independently associated with transfusion for major bleeding. Multivariate models were constructed using both stepwise selection and backwards elimination techniques before undergoing a final assessment for clinical and biological plausibility. Parameters included in this model were those associated with transfusion for major bleeding in univariate analysis with a p value less than 0.20. A two-sided, *p*-value less than 0.05 was regarded as statistically significant.

Results

Characteristics of patients transfused in daytime only and at night only

During the study period, 874 patients received 5783 blood products. Of these 874 patients, 258 (29.6%) were transfused at night only, 287 (32.8%) at daytime only and 329 (37.6%) were transfused across both time periods. There was no difference in patient severity as defined by the APACHE III score between the night only and day only groups (median 60 [IQR 47-77] vs. 65 [IQR 45-82], p=0.4), however patients who received transfusion across both day and night were of higher illness severity (median 74, IQR 56-94, Table 1) and received more transfusions (Table 2). Patients transfused at night only were more often male (168 [65%] vs. 159 [55%], p = 0.02) and were younger (65 [53-75] years vs. 68 [55-78] years, p = 0.04) than patients transfused in daytime only. Comorbidities were similar between day only and night only patient groups except for coronary artery disease, which was more frequent in the night only group (77% *vs*. 70%, p = 0.065) (Table 1). There was no significant difference in patients admitted for a bleeding-related diagnosis, although the numbers were small (Table 1). There was no significant difference in mortality between groups (65 [20%] in day/night patients vs 48 [17%] in day only and 33 [13%] in night only groups, p=0.08).

Transfusion occurring in patients transfused in daytime only and at night only

When considering the indications for transfusion, 78 patients (30%) had at least one transfusion for major bleeding in the group of patients transfused at night only versus 33 patients (12%) in the group of patients transfused in daytime only (p <0.001). Patients transfused in daytime only received blood

products more often for improvement of O_2 delivery (51% *vs*. 32%, p<0.001) and for invasive procedures (13% *vs*. 7%, p = 0.016) (Table 1).

In 119 (46%) patients who were transfused at night only, RBC transfusion was given in conjunction with non-RBC blood products compared with 82 (29%) of patients during the day (p <0.001). Patients transfused at night only were more likely to receive one or more FFP (100 [39%] vs. 60 [21%], p<0.001), one or more PLT (55 [21%] vs. 31 [11%], p=0.001) and one or more cryoprecipitate (19 [7%] vs. 9 [3%], p=0.026) than patients transfused during the day only (Table 2).

Day versus night transfusion for the whole study population

When considering all blood products transfused to the 874 patients, 2856 units were administered in daytime and 2927 at night (Table 3). Major bleeding was the most common indication for transfusion regardless of the time of the transfusion. However, significantly more blood products were given for major bleeding at night than during the day (43% versus 30%, p<0.001) while improvement of O_2 delivery (21% versus 14%, p<0.0001) and invasive procedures (8% versus 5%, p<0.0001) were significantly more common in daytime. When considering blood products separately, RBC were more often transfused at day time (52% versus 48%, p=0.001), while FFP was more often transfused at night. Major bleeding was the indication for RBC administration in 39% of cases at night versus 23% in daytime (p<0.001). Major bleeding was also more often the indication for PLT (36% versus 23%, p<0.0001) and for FFP (46% versus 36%, p<0.0001) but not for cryoprecipitate (56% versus 57%, p = 0.834) (Table 3).

There were differences in the triggers for blood product administration at night compared with day transfusion (N = 5783), including significantly higher platelet count pre-PLT transfusion at night (median 62 $x10^9$/L [IQR 33-110] versus median 49 $x10^9$/L [IQR 23-79], p = 0.002), and lower pre-RBC hemoglobin at night (median 77 g/L [IQR 70-83] versus 78 g/L [IQR 72-84], p=0.010). There was no difference in fibrinogen pre-cryoprecipitate or INR pre-FFP administration in day versus night transfusion (Table 3). When considering only patients with major bleeding, Hb level prior to RBC, platelets count prior to PLT and fibrinogen level prior to cryoprecipitate were not different between patients transfused at night only versus day only; however, INR prior FFP administration was lower in patients with major bleeding transfused only at night versus at day (median 1.6 [IQR 1.4-1.9] versus median 1.7 [IQR 1.6-2], p < 0.001).

Risk factors for major bleeding

Although the proportion of patients admitted with a bleeding-related diagnosis was similar in both groups (6% vs. 9%, p = 0.135), transfusion was more frequently given for major bleeding in the group of patients transfused only at night compared to those transfused only during the day, suggesting that ICU care overnight may be a risk factor for requiring transfusion for major bleeding in critically ill patients. To determine whether care overnight was independently associated with transfusion for major bleeding, after adjusting for admission diagnosis and patient characteristics, multivariate analysis was performed. This found that transfusion at night only (odds ratio [OR], 3.16, 95% confidence interval

[CI], 2.00-5.01, p<0.001) and transfusion during both day and night (OR, 6.24, 95% CI, 4.03-9.66, p<0.001) were independently associated with major bleeding. Trauma (excluding head injury) was the second greatest risk factor (OR, 3.99, 95% confidence interval [CI], 2.27-7.00, p<0.001) for major bleeding after day and night transfusion. Other factors independently associated with transfusion for major bleeding were other bleeding-related admission diagnoses, unstable current angina and treatment with aspirin (Table 4).

Discussion

The overall number of blood products transfused was approximately equal across night and day in critically ill patients. Nonetheless, patients who were transfused only at night received more blood products overall per patient and were more likely to receive FFP and cryoprecipitate compared with patients transfused during the day only. The different pattern of blood product use was likely due to differences in indications for transfusion between day and night, with major bleeding more likely to be an indication for transfusion overnight compared with during the day, and improvement of O_2 delivery more likely to be an indication for blood products during the day. Indeed, transfusion at night remained independently associated with transfusion for major bleeding after adjusting for confounders. Given that bleeding-related admissions were evenly distributed over the two time periods, our results suggest that there may be differences in the management of major bleeding at night compared to day hours.

To our knowledge this is the first study describing the timing of transfusion in ICU patients. The higher rate of transfusion for major bleeding, while pre transfusion Hb triggers were comparable between day and night time, and higher use of non-RBC support at night in our study suggests a difference in the management of major bleeding. These differences may include access to hemostatic interventions or variations in triggers for transfusion. Schwartz et al recently reported that patients admitted for pelvic trauma after hours had a significant increase in time to embolization compared to those admitted during day time [13] and after-hours admissions were independently associated with mortality. In a cohort of 22,720 patients with GI bleeding undergoing a colonoscopy, there was an independent beneficial effect of an early colonoscopy (<24hours) on blood transfusion requirement [14]. These findings highlight: 1) the importance of timely access to hemostatic procedures to prevent exposure to high volume of blood products 2) the positive impact of hemostatic procedures on patient outcome and 3) the potential association between bleeding overnight and delayed access to hemostatic procedures. In keeping with these findings, our study found that patients were more likely to be transfused overnight for major bleeding after adjusting for admission diagnosis, raising the possibility that access to embolization, colonoscopy or surgery for bleeding may be delayed over-night.

There were also differences in triggers for blood product administration between day and night, and although these differences were not clinically meaningful for all triggers, the findings raise the possibility that at night there may be different hemostasis objectives as shown by the differences in blood product triggers [15]. These differences may also suggest differences in transfusion strategy in actively bleeding patients. Recently, Matsushima et al. reported similar transfusion ratio in trauma

patients requiring massive transfusion at night between advanced practitioners and resident physicians [16].

The differences in blood components administered between day and night time may reflect, as mentioned above, differences in access to hemostatic interventions or in transfusion strategy between day and night time. They may also reflect difference in bleeding severity that led to a greater transfusion of plasma and platelets at night time and that could not be evaluated in our study.

This is the first study to analyze transfusion characteristics according to the circadian time in critically ill patients. If overnight bleeding events in ICU are associated with an increased in blood product exposure secondary to delayed access to hemostasis procedures, then changes in bleeding management and timely access to definitive care would be a priority.

Strengths and limitations

This study addresses an original question about the significance of the timing of transfusion in critically ill patients using prospectively collected data from 47 hospitals across Australian and New Zealand, thus ensuring the reliability of the data and the generalizability of the findings. However, our study has limitations, including that the original study was not designed to answer this study question. Subsequently, there are small numbers of patients with transfusion for major bleeding, which precluded a meaningful comparison of transfusion practice for specific indications. No information was available on the management of major bleeding in terms of haemostatic procedures, and therefore we can only hypothesize about possible explanations for our findings, including whether there were differences in access to haemostatic procedures between day and night. The definition of night transfusion (transfusion occurring between 8 pm and 8 am) differs from other definitions, including afterhours being between 5.30 pm and 7.30am and weekends [13]. However, in Australia the day and night ICU shifts typically change at 8 pm and 8 am and the ratio of ICU registrars does not change on the weekends. This study only accounted for the time each individual unit was administered and did not take into account the time when blood product was prescribed. Finally, while audits report that overnight transfusion is associated with a low rate of post-transfusion observation, information related to adverse events secondary to transfusion was not available, preventing any analysis of transfusion safety between day and night time [7].

Further research is required to test the hypothesis that management for major bleeding is different during the day compared with night-time and to investigate the clinical context (cause of bleeding, access to blood product support and hemostatic interventions) and human factors associated with these differences. Prospective observational studies comparing the delay between bleeding onset and hemostatic procedures when required during weekdays and after-hours are warranted to define the need for transfusion at night and impact of night management (in ICUs and blood services) on patient outcome.

In conclusion, in critically ill patients, the volume of blood products transfused in daytime is similar to those transfused at night. Nonetheless, variations in types of blood products, transfusion

indications and triggers may reflect variations in bleeding management between these circadian periods. Our results show that patients transfused for major bleeding were more likely to be transfused overnight, independent of the admission diagnosis, raising the possibility of delayed access to hemostatic procedure at night. Prospective studies designed to address this issue are warranted.

CONFLICT OF INTEREST

The authors attest that they have no conflict of interest to declare.

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TABLE 1 Characteristics n (%) of patients (n=874) who received blood products at daytime only and night time only

	Patients transfused in daytime only N=287	Patients transfused at night only N=258	Patients transfused both day and night N=329	p value
Gender, male	159 (55%)	168 (65%)	217 (66%)	0.01
Age, years	68 [55-78]	65 [53-75]	63 [52-74]	0.01
APACHE III score[a]	65 [45-82]	60 [47-77]	74 [56-94]	<0.01
Admission diagnosis				
Trauma	9 (3%)	7 (3%)	15 (5%)	0.20
Bleeding-related admission (not trauma) [b]	14 (5%)	20 (8%)	30 (9%)	
Conditions and therapy prior to transfusion				
Aspirin	110 (38%)	99 (38%)	113 (34%)	0.49
Clopidogrel	28 (10%)	30 (12%)	33 (10%)	0.74
Oral vitamin K antagonist	28 (10%)	38 (15%)	33 (10%)	0.12
Past history of coronary artery disease	201 (70%)	198 (77%)	215 (65%)	0.09
Liver insufficiency	20 (7%)	18 (7%)	31 (9%)	0.43
Cardiogenic shock	5 (2%)	5 (2%)	21 (6%)	0.02
Cardiac arrest	13 (5%)	7 (3%)	19 (6%)	0.13
Current active ischemic heart disease	84 (30%)	87 (34%)	86 (26%)	0.26
Malignant arrhythmia	15 (5%)	11 (4%)	12 (4%)	0.63
Bone marrow failure	4 (1%)	5 (2%)	17 (5%)	0.01
Platelet function abnormalities	10 (3%)	13 (5%)	25 (8%)	0.08
Indication for transfusion (at least 1 transfusion[c])				
Major bleeding	33 (12%)	78 (30%)	143 (44%)	<0.001
Minor bleeding	56 (20%)	51 (20%)	138 (42%)	<0.01
Improvement of O_2 delivery	147 (51%)	82 (32%)	174 (53%)	<0.01
Invasive procedure	38 (13%)	18 (7%)	68 (21%)	<0.01
DIC	2 (1%)	7 (3%)	4 (1%)	0.13
Prophylaxis	25 (9%)	33 (13%)	100 (30%)	<0.01
Patient outcomes				
ICU length of stay	3.3 [1.8-6.9]	2.7 [1.3-4.8]	6.1 [2.9-12.2]	<0.001
Hospital mortality	48 (17%)	33 (13%)	65 (20%)	0.08

Data are reported as number (%) or median [IQR].

APACHE III, Acute Physiology Age Chronic Health Evaluation III score; ICU, Intensive Care Unit; DIC, disseminated intravascular coagulopathy.

[a] Data were missing in 195 patients – 95 in “day only” group and 100 in “night only” group

[b] Included:, gastrointestinal bleeding, intra-peritoneal bleeding and rupture of abdominal aortic aneurysm

[c] Percentage of patients who received at least one blood component for the indication considered

TABLE 2 Blood transfusion characteristics in patients (n=874) according to time of administration: day and night times only

	Patients transfused at day time only N=287	Patients transfused at night time only N=258	Patients transfused both day and night N=329	P value
Median number of total transfused products per patient	2 [1-3]	2 [2-4]	7 [4-13]	<0.01
RBC transfusion				
Proportion of transfused products that were RBC	482/748 (64%)	465/939 (50%)	1951/4096 (47%)	<0.01
Patients receiving at least one RBC unit	234 (82%)	209 (81%)	320 (97%)	<0.01
RBC unit per patient	2 [1-2]	2[1-2]	4[3-7]	<0.01
RBC only	205 (71%)	139 (54%)	106 (32%)	<0.01
FFP transfusion				
Proportion of transfused products that were FFP	176/748 (23%)	293/939 (31%)	1080/4096 (26%)	<0.01
Patients receiving at least one FFP unit	60 (21%)	100 (39%)	181 (55%)	<0.01
FFP per patient	2 [2-4]	2 [2-4]	4 [2-8]	<0.01
FFP only	31 (11%)	26 (10%)	3 (1%)	<0.01
PLT transfusion				
Proportion of transfused products that were PLT	45/748 (6%)	76/939 (8%)	516/4096 (13%)	0.10
Patients receiving at least one PLT bag	31 (11%)	55 (21%)	145 (44%)	<0.01
PLT bag number per patient	1 [1-2]	1 [1-2]	2 [1-3]	<0.01
PLT only	14 (5%)	10 (4%)	3 (1%)	0.01
Cryoprecipitate transfusion				
Proportion of transfused products that were Cryo	45/748 (6%)	105/939 (11%)	549/4096 (13%)	<0.01
Patients receiving at least one unit	9 (3%)	19 (7%)	50 (15%)	<0.01
Cryoprecipitate bags per patient	2 [2-9]	5 [3-8]	8.5 [5-14]	0.02
Cryoprecipitate only	1 (<1%)	0 (0%)	0 (0%)	1.00

Data are reported as number (%) or median [IQR].

RBC, red blood cells; PLT, platelets; FFP, fresh frozen plasma; Cryo, cryoprecipitate.

TABLE 3 Characteristics of transfusion occurring at daytime and at night where all units of blood products (n=5783) are considered

	Blood products transfused at day time N=2856	**Blood products transfused at night time N=2927**	**P value**
Transfusion indication for all blood products, N (%)			
Major bleeding			
Minor bleeding	853 (30%)	1265 (43%)	<0.01
Improvement of O_2 delivery	390 (14 %)	407 (14 %)	0.78
Invasive procedure	606 (21%)	401 (14%)	<0.01
DIC	222 (8%)	145 (5%)	<0.01
Prophylaxis	41 (1%)	79 (3%)	<0.01
Unknown indication	376 (13%)	352 (12%)	0.19
	368 (13%)	278 (10%)	<0.01
Biological values before transfusion			
Hemoglobin pre-RBC, g/L	78 [71-84]	76 [69-83]	<0.01
INR pre-FFP	1.7 [1.5-2.0]	1.7 [1.4-2.1]	0.48
Platelet count pre-PLT, $x10^9$/L	44 [18-78]	59 [31-108]	<0.01
Fibrinogen pre-Cryoprecipitate, g/L	1.6 [1.3-1.9]	1.4 [1.1-1.7]	0.03
Main indications per blood product			
RBC units, *N* (%)*	1494/2898 (52%)	1404/2898 (48%)	<0.01
Major bleeding	337 (23%)	553 (39%)	<0.01
Minor bleeding	257 (17%)	237 (17%)	0.82
Improve O_2 delivery	597 (40%)	401 (29%)	<0.01
Unknown	207 (14%)	109 (8%)	<0.01
PLT units, *N* (%)[a]	320/637 (50%)	317/637 (50%)	0.65
Major bleeding	72 (23%)	113 (36%)	<0.01
Minor bleeding	36 (11%)	47 (15%)	0.18
Prophylaxis	133 (42%)	82 (26%)	<0.01
Invasive procedure	48 (15%)	28 (9%)	0.02
DIC	8 (3%)	21 (7%)	0.01
FFP bags, *N* (%)[a]	731/1549 (47%)	818/1549 (53%)	0.04
Major bleeding	266 (36%)	380 (46%)	<0.01

Minor bleeding	69 (9%)	87 (11%)	0.43
Prophylaxis	170 (23%)	184 (23%)	0.72
Invasive procedure	114 (16%)	60 (7%)	<0.01
Cryoprecipitate units, N (%)[a]	311/699 (44%)	388/699 (56%)	0.01
Major bleeding	178 (57%)	219 (56%)	0.83
Minor bleeding	28 (9%)	36 (9%)	0.90
Prophylaxis	39 (13%)	44 (11%)	0.63
DIC	16 (5%)	32 (8%)	0.11

Data are reported as number (%) or median [IQR].

RBC, red blood cells; PLT, platelets; FFP, fresh frozen plasma; DIC, disseminated intravascular coagulopathy; INR, international normalized ratio.

[a] Percentage of blood products given at night and at day respectively

TABLE 4 Variables independently associated with transfusion for major bleeding

	Adjusted OR	**95% confidence interval**	**p value**
Time of transfusion			
Day only (reference)	1.0		
Night only	3.16	2.00 - 5.01	<0.001
Day and night	6.24	4.03 - 9.66	<0.001
Age	0.99	0.97 - 0.99	0.02
Admission category			
No bleeding (reference)	1.0		
Bleeding non-trauma	3.42	1.08 - 10.8	0.04
Trauma (excluding head)	3.99	2.27 - 7.00	<0.001
Treatment with aspirin	1.57	1.08 - 2.27	0.02
Current angina	1.94	1.19 - 3.15	0.008
Bone marrow failure	0.22	0.06 - 0.78	0.02

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