Original article

To formulate baseline thresholds for the initiation of RBC transfusion in elective surgical patients: an observational study at a tertiary care center

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Abstract:

Introduction: *A wide discrepancy exists in terms of transfusions in elective surgical procedures. An 'evidence based' institutional recommendations hence is needed to prevent procedure-based mortality.* ***Objective:*** *This present mixed cohort study was conducted at a tertiary health care center to propose a safe threshold for RBC transfusion in elective surgical patients.* ***Materials and Methods:*** *Elective surgical patients (n = 793) were categorized into 12 surgical groups and evaluated for pre-transfusion hemoglobin (Hb), red cell (RBC) units transfused, length of stay (LOS) and mortality.* ***Results:*** *We analyzed significant differences within surgical subgroups as per objectives and survival, mortality comparisons using the Kaplan Meyer Log-rank survival curve KM(LR) for differences in evaluated parameters. We found that in elective surgical patients, malignancy and general surgical patients had lower Hb than other groups. ($p < 0.05$). There were significant differences in gender (male vs female) included Hb and LOS. Male patients had significant differences in survival with Hb > 7.0 g/dL compared to ≤ 7 g/dl, KM (LR) ($p < 0.05$) and higher survival with Hb > 7 g/dL than ≤ 7g/dL after 15 days of hospital stay. In addition, increased RBC units usage was associated with lower survival but without significant survival benefit between 1U and > 1U transfusion. Hb had a small effect size of only 0.6% in overall survival in patients.* ***Conclusion:*** *A Hb threshold of > 7g/dL is beneficial only after 7-15 days of hospital stay. An increase in RBC units does not provide a survival benefit. Hb level has an overall low 'effect size' in patient outcomes. Hb thresholds provide baseline data for evidence-based institutional surgical transfusion management.*

Keywords : ● *Evidence-based recommendations* ● *Pre-surgical Hb* ● *Length of Hospital Stay*

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Introduction

The variations observed in current transfusion practice in elective surgeries despite transfusion recommendations from observational studies or clinical trials are due to a difficulty in institutional implementation[1,2]. The safe threshold for transfusion for elective surgical patients should hence be evidence-based locally relevant, and with minimal variations. Presurgical tools for rational transfusions include maximum allowable blood ordering schedule (MSBOS) and patient specific or risk-factor based predictive scoring system which has low predictive probability within diverse presurgical diagnosis[3-6]. This observational study at a tertiary care center was aimed towards safe hemoglobin (Hb) threshold for RBC transfusions upon different elective surgical patients. We studied the correlation of the Hb threshold for transfusion with the number of RBC units, length of hospital stay (LOS), and mortality among these patients to provide an institutional recommendation for transfusion to elective surgical patients.

Materials and Methods

The data of elective surgical patients with transfusion between 2016-2019 were sub-grouped into respective surgical categories. The data for the length of stay (LOS), and mortality (M) of the patients were retrieved from the Medical Records Department (MRD). This study had ethical institutional approval IEC AIIMSRPR/IEC/2018/204.

Pre-transfusion Hb (g/dL) was obtained at the blood bank by cell counter 'Sysmex S-100' and patients MRD records. The elective surgical patient parameters are listed in Table 1.

Inclusion criteria: elective surgical patients admitted at multi-speciality tertiary hospital requiring general or spinal anaesthesia and received RBC transfusions.

Exclusion Criteria: we did not include surgical patients without transfusion, referred patients and emergency surgeries in this study.

We classified surgical patients (n = 793) into 12 Surgical categories ranked from the diagnosis or the departments listed in the requisition forms or discharge summaries (Table 2). The studied patients were evaluated according to the study algorithm as shown in Figure 1. The surgical patients were evaluated for significant differences under the following categories, gender (M vs F); hemoglobin stratified (HBS) (< 7 g/dL vs > 7 g/dL) across length of stay (LOS); overall HBS (< 7 g/dL vs > 7 g/dL); length of stay period (P) (0-7 d; 8-14 d; ≥ 15 d); RBC units (1U vs > 1U) and mortality. (Mann Whitney U test; Chi-square test; Table 2).

The outcome measures were, evaluation of significant variations within surgical groups; recommendations of safe transfusion based upon gender (M:F); HBS (< 7 g/dL; > 7 g/dL); number of RBC units transfused; RBC unit (1U or > 1U) transfusion; LOS (in days); LOS (P) (0-7 d; 8-14 d; ≥ 15 d) and mortality (ANOVA T test).

All the statistical calculations were performed by SPSS version 26. We created a flowchart of the study and study algorithm using an online software https://online.visual-paradigm.com (Figure 1). The missing values were coded and not included in the final calculations. We included the outliers in the present study for each parameter in the final analysis, with final statistical calculation as parametric or non-parametric depending upon the available data. We adhered to the

Table 1 Descriptive patient information

No.	Variable	N	Mean	SE Mean	St Dev	Minimum	Median	Maximum	IQR
1	Age (years)	793	41.5	0.613	17.16	0.160	42.0	88.0	25.0
2	Hb (g/dL)	767	9.5	0.106	2.93	1.500	9.5	16.5	4.7
3	Unit used	787	1.3	0.0230	0.64	1.0000	1.0	5.0	1.0
4	Length of stay (d)	695	15.5	0.458	12.0	1.000	13.0	82.0	12.0

Table 2 Hb, RBC unit used and LOS across elective surgical procedures

	Summary of surgical procedures				
	Department		**Hb***	**Unit used**	**Length of stay (d)**
1	Malignancy (38)	Mean	8.1*	1.29†	15.0
		Std. Deviation	2.9	0.61	9.0
		Median	8.1	1.0	14.0
2	CTVS (18)	Mean	11.0	1.47†	14.5
		Std. Deviation	3.01	0.800	7.4
		Median	11.7	1.00	13.0
3	ENT surgery (48)	Mean	11.1	1.24	14.0
		Std. Deviation	2.40	.529	11.8
		Median	11.7	1.00	11.0
4	Female genital procedures (40)§	Mean	9.4	1.30	14.4
		Std. Deviation	2.35	.516	10.7
		Median	9.3	1.00	11.5
5	General surgery (154)	Mean	8.4*	1.34	16.7
		Std. Deviation	2.63	.670	10.74
		Median	8.3	1.00	15.0
6	Gynaecology obstetrics surgery	Mean	8.0	1.32	9.5
		Std. Deviation	2.85	.587	7.5‡
		Median	8.1	1.00	8.0
7	Head and neck carcinoma (66) ‖ §	Mean	10.7	1.32	21.6
		Std. Deviation	2.72	.531	15.7
		Median	11.1	1.00	17.5
8	Neurosurgery space occupying lesions § (75)	Mean	11.6	1.57	17.2
		Std. Deviation	2.46	.760	15.6
		Median	12.0	1.00	12.0
9	Neurosurgery vertebral surgery (25)	Mean	10.9	1.60	20.2
		Std. Deviation	2.89	.645	18.3
		Median	11.70	2.00	16.0
10	Orthopaedics benign lesions (49)	Mean	10.2	1.35	16.7
		Std. Deviation	2.23	.812	11.7
		Median	10.1	1.00	13.0
11	Orthopaedics fractures (98) ‖	Mean	9.9	1.24	17.5
		Std. Deviation	2.68	0.61	11.07
		Median	9.7	1.0	15.5
12	Paediatric surgery (24)	Mean	8.6	1.3	17.4
		Std. Deviation	2.44	0.71	13.7
		Median	8.30	1.00	14.5
	Total	Mean	9.51	1.35	15.5
		Std. Deviation	2.93	0.64	12.0
		Median	9.50	1.00	12.5

Important significant variations ($p < 0.05$) *, †, ‡, §, ‖

* Hb significantly different (≥ 4 surgical procedures); † Blood unit used; ‡ Length of stay (days)

§ Hb thresholds (≥ 7 g/dL; > 7g/dL); ‖ Survival blood unit used : LOS (d)

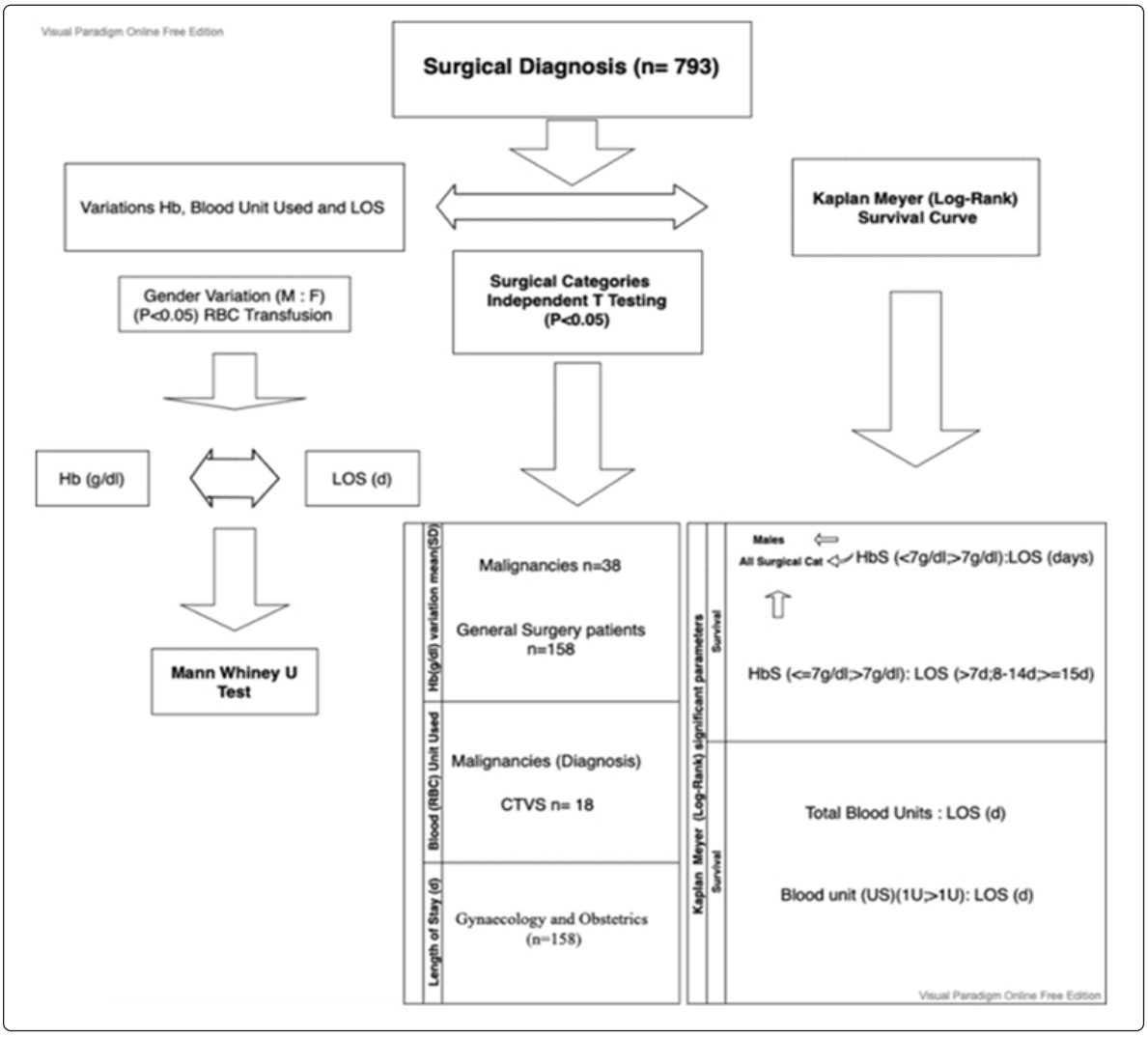

Figure 1 Flow-chart depiction elective surgical patients

STROBE checklist for cohort (observational) studies for methodology review (Annexure). We performed the statistical analysis and 'effect size estimation for the study. We conducted statistical tests using reference guidance from YouTube videos http://www.how2stats.net/p/home.html and Kaplan Meier analysis accessible URL: https://www.youtube.com/watch?v=Tw1WVxiXHsk. *We* tested the normal distribution of parameters using independent T testing and Mann Whitney test for non-normally distributed parameters and Chi-square testing for gender variation and comparison of Hb, the number of RBC units transfused and LOS for statistical significance ($p < 0.05$). Kaplan Meier (Log rank) testing for survival and mortality correlation. Sample size was adequate to provide recommendations ($p < 0.05$; the power of 80%). An effect size estimation for a significant p-value of the parameters was evaluated for survivors and non-survivors to know the extent of influence the parameters had on ultimate survival.[7]

Results

In 793 elective surgical patients, an overall Hb g/dL (SD) at transfusion was 9.5 g/dL (2.9); unit used 1.3 U (0.64); LOS 15.5 d (12.08) and mortality (n = 14) (Table 1). A comparison within the surgical groups is depicted in Table 2. Mean (SD) of Hb at transfusion (HbS) for ≥ 7 g/dL and > 7 g/dL range was 5.6 g/dL (1.2) and 10.7 g/dL (2.1). One unit transfusion (1 U) was transfused in 72.6% and > 1 U in 27.4% of all patients. Mean (SD) of blood units transfused (> 1 U) were 2.2 (0.59) units. The Mean (SD) LOS up to 7d (23.6%) was 4.6 d (1.9); 7-15 d (35.5%) 10.6 (2.0) days and > 15 d (40.9%), 25.8 (12.4) days, respectively.

Table 3 Statistical significance of survival distribution curves

Overall survival comparisons			
Log rank (mantel-cox)	**Chi-square**	**df**	**Sig**
HBS; LOS (d) (males)	6.04	2	0.049
HBS; LOS (d) (females)	2.5	1	0.11
HBS; LOS (d)	7.79	2	0.02 [a]
HBS; LOS (P)	8.03	2	0.018
Blood unit transfused; LOS (d)	9.077	3	0.03 [b]
RBC unit (1u; > 1u); LOS (d)	0.302	2	0.86 [c]

a. Test of equality of survival distributions for the different range of Hb

b. Test of equality of survival distributions for the different levels of unit used

c. Test of equality of survival distributions for the different range of blood units

HbS: Hb (≤ 7 g/dL; > 7 g/dL); LOS(d): length of stay (days); LOS(P): length of stay period (0-7 d; 8-14; ≥ 15 d)

Table 4 Patient characteristics based upon unit used

S no.	Variable	US	Total count	Mean	Median
1	Hb	1	570	9.76	9.90
		2	216	8.84	8.60
2	Age	1	570	41.96	42.00
		2	216	40.67	40.00
3	Length of stay	1	570	14.82	12.00
		2	216	17.04	13.00

US: Blood unit stratified 1 = single unit transfused 2 = > 1 unit transfused

The important significant variations within the surgical categories included malignancies (n = 38) and general surgical patient's (n = 154) for pre-transfusion Hb, blood units used in malignancy patients (n = 38) and cardiothoracic and vascular surgery (n = 18) and LOS in gynaecology and obstetrics (n = 158) (one way ANOVA) ($p < 0.05$) (Table 2). The overall gender differences for surgical procedures included (M:F) Hb (g/dL) at transfusion Hb median (IQR) males 10.1 (3.0) g/dL: females 9.1 (2.7) g/dL and LOS males 18.6 (14) days (n = 292); females 13.3 (10.0) days (n = 404) ($p < 0.05$) (significance 2-sided test) Mann Whitney U test. An overall (M:F) survival across LOS(d) was not significantly different (Chi-square 0.083; df = 1; sig $p = 0.77$). Males admitted under general surgery and females in neurosurgery showed a difference in Hb (g/dL) from mean gender Hb g/dL (-2.4 g/dL and +2.8 g/dL); however, blood unit; LOS were not significantly different within surgical subgroups of males and most subgroups in females. Females had better survival at Hb > 7g/dL, (KMLR) ($p = 0.11$) (Table 3). Overall (M:F) did not show survival difference. Males showed a significant difference in survival at Hb ≤ 7 g/dL compared to a Hb > 7 g/dL with better survival with > 7 g/dL. KM (LR) ($p = 0.049$) (Table 3).

All-surgical diagnosis survival HBS (≤ 7 g/dL; > 7 g/dL) across the LOS (in days) showed differences in survival to be statistically significant. KM-LR (Mantel-Cox) with Hb ≤ 7 g/dL showed lower survival than Hb > 7 g/dL ($p = 0.02$) (Table 3). The difference in survival with Hb > 7 g/dL was most evident after 15 days of hospital admission (Table 4). Total blood units transfused evaluated for survival across the LOS (days) (all diagnosis) had significantly different survival across the number of RBC unit KM-LR ($p = 0.03$) (Table 3). Three red cell units transfused (n = 26; 3.3% of total transfusions) showed a lower survival when compared to

the 1U (n = 571; 72.6%), 2U (n = 175; 22.2%) or 4 units (n = 14; 1.8%). An overall survival (unit stratified) (1U over > 1U) across LOS (days) was however non-significant (p = 0.86) (Table 3). Mean Hb, unit used, and LOS of deceased subjects (n = 14) was 8.0 (2.2) g/dL: 1.57 (0.6) units and 16.7 (7.4) days, respectively. An 'all diagnosis' 'elective surgical patient', only Hb (g/dL) was significantly different between patients who expired during surgery and the survivors (one way ANOVA) (p = 0.04). Overall Hb at transfusion had a small 'effect size' of only 0.6% as a cause of mortality in the deceased subjects (Eta square test for effect size).

Discussions

Blood transfusions are 'at risk' of indiscriminate transfusion practices due to lack of safe and evidence-based RBC threshold for transfusion. WHO definition of anemia is a Hb of < 13 g/dL in men and < 12 g/dL in women; this definition is further modified according to ethnicity, age and gender, for example, Hb value of 12.0 g/dL for both sex in the elderly western population.[4,8,9]

In this study, a safe transfusion threshold in elective surgery patients was suggested by observing the Hb threshold for transfusion, length of stay (LOS), blood units consumed and mortality among patients. Across the 12 surgical categories, the mean Hb 9.5 (2.9) g/dL was significantly different only in malignancy and general surgical patients, indicating a lower threshold of transfusion within these two categories than the remaining diagnosis (Table 2). Patient demography (surgical cases) had significant gender (M:F) differences of Hb (g/dL) at transfusion and LOS. We found no significant better survival in males compared to the females across LOS Kaplan Meier (Log-rank) (p = 0.774) (Table 3).

Survival Hb range (< 7 g/dL; > 7 g/dL) when evaluated against the LOS(P) stay[(0-7 d; 8-15 d; > 15 d); (all diagnoses)] a significant difference in mortality between transfused patients (< 7 g/dL; > 7 g/dL) was observed. Table 3; KMLR (p = 0.018). The Hb ≤ 7 g/dL presurgical patients showed higher mortality with an increase in LOS (d) than > 7 g/dL. An increased survival with Hb > 7 g/dL is more evident after 15 days of hospital stay (Table 2). The overall survival blood units (1U; > 1U) across the LOS (days) out of 12 surgical categories was non-significantly different (p = 0.86) (Table 3).

An analysis of all RBC Blood Units (BU) and LOS showed significant survival differences within the blood units (p = 0.028) during the LOS. This difference in survival of RBC units across LOS was more after the median duration of hospital stay (13 days). Survival of patient transfused 3 units was lower than the patient transfused with 1 unit, 2 units or 4 units (p = 0.028). An individual diagnosis analysis showed significant differences of Hb range in survival HBS (≤ 7 g/dL; > 7 g/dL) within female genital procedures (n = 40); head and neck carcinoma (n = 66) and neurosurgery SOL (n = 75) with higher mortality with Hb ≤ 7 g/dL in comparison to Hb > 7 g/dL (p < 0.05) (Figure 2).

In this study, head and neck CA (n = 66) and orthopedic fracture group (n = 98) showed an increase in mortality with 3-units blood transfusion as compared to 1-2 units for RBC transfusion (p < 0.05) (Figure 2). None of the surgical categories showed a survival advantage of > 1 unit over 1 unit transfusion. An increase in the number of blood units associated with better survival in certain elective surgical category of patients, which needs to be correlated with surgical diagnosis, as observed in CTVS procedures of this present study (p = 0.165). Safe transfusion threshold in a clinical trial setting (FOCUS) has been evaluated in elective surgical procedures with observational studies targeted towards finding the difference between restrictive and liberal transfusion thresholds.[1,10,11]

In this present study, specific patient parameters were missing due to non-availability, which could potentially confound result findings; the missing values are unlikely to be significant in adequately powered study for each analysis. We did not remove the outliers in the Hb, unit used, and LOS before analysis. This analysis is subject to variation in a different population of subjects for any surgical category; however, the

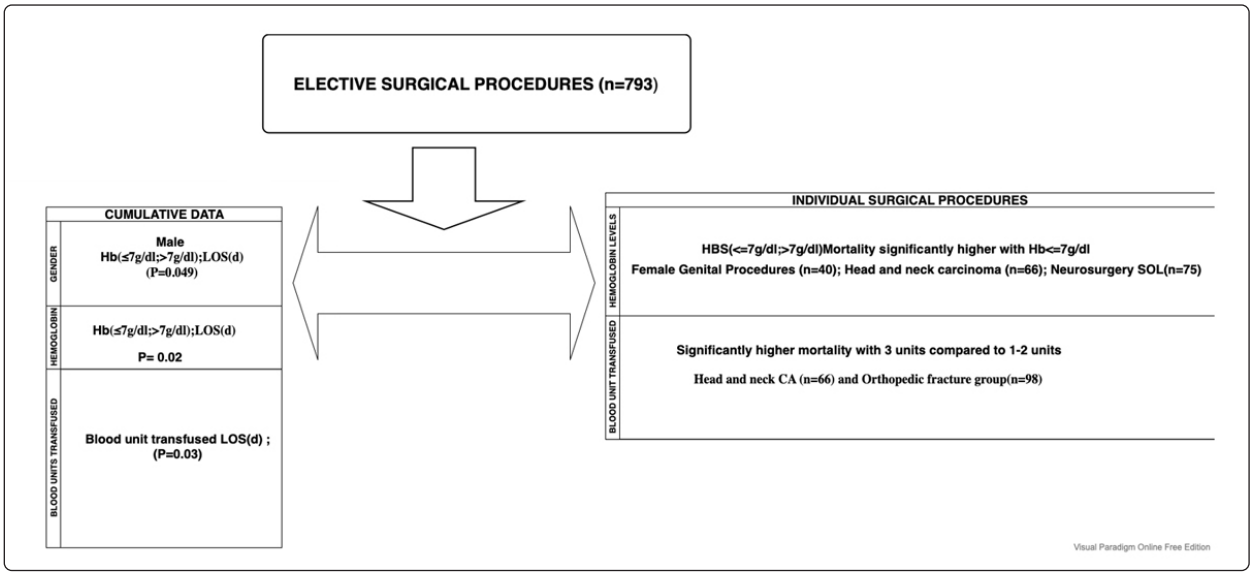

Figure 2 Flowchart of significant differences in evaluated parameters

pattern followed would be similar to present study for an evidence-based presurgical Hb for transfusion based recommendations for any institution.

Conclusion

The present study included gender comparison (M:F), pre-transfusion Hb and overall length of stay, and number of blood units transfused in elective surgical patients. Male patients had significantly better survival at Hb > 7 g/dL than ≤ 7 g/dL. A general effect of Hb in elective procedure had a small effect size. Higher mortality among patient Hb ≤ 7 g/dL as opposed to Hb > 7 g/dL is evident after the first 15 days of hospital stay favour the hemoglobin of > 7 g/dL. Increasing number of blood units transfused among surgical patients was not associated with higher survival. Overall, 3U had higher mortality than 1U, 2U or 4U transfusion; however, this parameter needs further individualization according to the surgical procedure.

Increased RBC transfusion (1U; > 1 Unit) in elective surgeries may not lead to a reduction in mortality. Institutional recommendations for a transfusion to surgical patients should be evidence-based, with a periodic review, and modifications depending on changes in surgical procedures or new surgical procedures requiring modified transfusion requirements.

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