Original article

Challenges in perioperative blood transfusions in kidney transplantation and the need for Patient Blood Management

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Background - Anemia is highly prevalent in end-stage chronic kidney disease patients, increasing their risk of receiving blood transfusions during and on the days after a kidney transplant (KTx) surgery. However, there is currently a lack of data that thoroughly describes this phenomenon in this population, the associated risk factors, and how they could benefit from the application of Patient Blood Management (PBM) guidelines.

Materials and methods - Observational study. All adult patients who received a KTx between January 1st, 2020, and December 31st, 2021, were included and followed up to six months after transplantation. Those who received a multiorgan transplant, whose data was missing in the electronic health records, and who had primary non-function were excluded. We recorded donor and recipient characteristics, cold ischemia time, preoperative hemoglobin concentration, iron status deficiency biomarkers, incidence of delayed graft function and biopsy-proven graft rejections, and graft function at discharge and 6 months after transplantation.

Results - We found that a high amount (39%) of KTx recipients required at least one blood transfusion during the perioperative period. And that 1) most of these patients had anemia at the time of transplantation (85.4%), 2) iron status upon admission was associated with the transfusion of more blood units (3.9 *vs* 2.7, p=0.019), 3) surgical reintervention (OR 7.28, 2.35-22.54) and deceased donor donation (OR 1.99, 1.24-3.21) were associated with an increased risk of transfusion, and finally, 4) there was an association between a higher number of blood units transfused and impaired kidney graft function six months after hospital discharge (1.6 *vs* 1.9, p=0.02).

Conclusions - In conclusion, PBM guidelines should be applied to patients on the KTx deceased donor waiting list and especially those scheduled to receive a transplant from a living donor. This could potentially increase the utilization efficiency of blood products and avoid transfusion-related severe adverse effects.

Keywords: *blood transfusions, kidney transplant, anemia, patient blood management.*

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INTRODUCTION

Anemia is one of the most common complications in patients with chronic kidney disease (CKD), and its causes are multifactorial[1]. In CKD, there is inadequate erythropoietin

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synthesis by interstitial cells in the peritubular capillary bed of the renal cortex, and the accumulation of uremic toxins reduces the myeloid response to the already low erythropoietin levels. In addition, CKD anemia is also associated with an iron-deficiency state secondary to chronic inflammation, blood loss, and malnutrition, which can also generate folic acid and vitamin B12 deficiency[2].

The appearance of erythropoiesis-stimulating agents (ESA) has significantly reduced blood transfusions in stable patients with advanced CKD or on dialysis[3]. Nevertheless, given that hemoglobin normalization with ESA is associated with increased morbidity and mortality, the Kidney Disease Outcomes Quality Initiative (KDOQI) and the Kidney Disease Improving Global Outcomes (KDIGO) guidelines state that the target for CKD patients treated with ESAs should be hemoglobin levels of 10 to 11.5 g/dL, while not intentionally surpassing 13 g/dL[4,5]. Therefore, most patients with advanced CKD who receive kidney transplants (KTx) are anemic at the time of the surgical intervention, potentially increasing their risk of requiring blood transfusions during the perioperative period[6].

While recent data show that blood transfusions received within the first month after KTx are not associated with antibody sensitization or rejections[7], the description of transfusion patterns, rate and number of packed red blood cells (PRBC), and factors associated with the risk of transfusion in this population (e.g., hospital stays, cardiovascular events, surgical reoperations, hemoglobin levels at discharge, kidney graft function) are scarce. More knowledge on this topic may help us understand our current practice and identify factors that could reduce KTx units' expenditure on blood products.

Blood products are scarce, given their availability relies on voluntary donations[8]. Moreover, optimizing their prescription would help avoid potentially severe side effects such as infections, transfusion-related lung injury, transfusion-related circulatory overload, and hyperkalemia, which, although rare, have significant clinical consequences[9]. Therefore, the transfusions of PRBC needs to be more carefully and efficiently managed by health specialists[10].

In this sense, the Patient Blood Management (PBM) guidelines suggest three pillars as the central methodology required to reduce the needs and avoid unnecessary PRBC transfusions[11]. The first is based on optimizing hematopoiesis, which focuses on repleting patients' iron deposits and optimizing ESA treatment in CKD patients. The second requires minimizing blood losses that may occur during surgery while remaining aware of transfusion risk factors. Finally, the third pillar proposes increasing patients' tolerance to anemia by improving their physical condition and treating comorbidities. In addition, these guidelines promote the one-at-a-time (single unit) transfusion of PRBC in stable patients to reduce the risk of undesired complications.

This study aims to describe the percentage of KTx recipients who require blood transfusions during their admission, the rate of PRBC administered per patient, and the proportion of single units prescribed. As secondary outcomes, we aimed to describe the association between factors related to KTx recipients and donor grafts, the need for transfusion, and the association between blood transfusions and postoperative kidney graft function.

MATERIALS AND METHODS

Study design

This observational single-center study was performed at the Hospital Clínic of Barcelona, Spain, between January 1st, 2020, and December 31st, 2021. This study adhered, as applicable, to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies[12].

Participants

Adult patients who received a KTx were included. Those who received a multiorgan transplant or a dual kidney transplantation, were missing data in the electronic health records, were transplanted in another hospital, and had primary non-function of the organ (i.e., permanent lack of graft function from the time of transplantation[13]) were excluded from the study.

Variables collected

Demographic and baseline medical treatment and medical history of KTx recipients and donors were retrieved from the electronic health records. The kidney disease stage at the time of transplantation was classified as pre-dialysis (for those who had not started kidney replacement therapy), hemodialysis (HD), and peritoneal dialysis (PD). Hemoglobin levels were measured at hospital admission and discharge. Anemia was defined as hemoglobin inferior to 13 mg/dL in adult men and 12 mg/dL in adult females[1] or treatment with ESA. Creatinine levels were measured at discharge and six months after transplantation. Ferritin and transferrin saturation index (TSAT) were measured upon admission and categorized as suboptimal if lower than 500 ng/mL and 30%, respectively, according to the

KDIGO anemia guidelines[5]. Length of hospital stay (LOS) and the use of antiplatelet agents and/or anticoagulation after surgery were registered.

Kidney donors were classified as donation after brain death (DBD), and donations after circulatory death (DCD) as uncontrolled or type 2 (patients who have already died before consideration of organ donation) and controlled or type 3 (the retrieval of organs is planned before death occurs) according to the Maastricht classification[14]. Donors were further categorized as extended criteria if they were older than 60 years, had a history of or died from cardiovascular disease[15]. Cold ischemia time (the time from cold perfusion of the kidney to the start of the venous anastomosis) was registered. Delayed graft function (DGF) was defined as the need for dialysis during the first seven postoperative days. The most recent calculated panel reactive antibody (cPRA) before transplantation and the one obtained during protocol or for-cause biopsies 3 to 12 months later were recorded. Induction immunosuppressive therapy consisted of either rabbit antilymphocyte thymoglobulin (rATG) or basiliximab, and the prescribed maintenance immunosuppression was either a mammalian target of rapamycin inhibitor (mTORi) (i.e., everolimus and sirolimus) or mycophenolic acid (MPA) in combination with tacrolimus and prednisone.

Blood transfusions were indicated in any patient with a Hb lower than 7 g/dL, in those with a Hb above 7 g/dL but lower than 8-9 g/dL who had a medical history of cardiovascular disease, peripheral arterial disease, or stroke, and in those with acute ongoing bleeding; although, the final indication of a blood transfusion was decided by the attending physician during their hospitalization. The number and timing of PRBCs prescribed per patient were recorded. A single-unit transfusion was defined as the dosing scheme of one unit of red blood cells followed by an assessment of the patient. The administration of ESA and intravenous iron were also registered. Rejection episodes were registered as biopsy-proven rejections (BPAR) and classified according to the 2019 Banff score. Every variable collected was performed following clinical practice standards. No additional procedure was performed for this study.

Statistical analysis

If normally distributed, quantitative variables are shown as mean and standard deviation, or as median and interquartile range otherwise. Qualitative variables were described as absolute and relative frequencies. The normal distribution of the quantitative variables was tested with the Shapiro-Wilk test and Q-Q plots. The quantitative variables' analysis between the two groups was made with the U-Mann Whitney test when non-normal or the independent Student's t-test when normally distributed. One-way ANOVA or the Kruskal-Wallis tests were used for analysis between more than two groups when variables were normally or non-normally distributed, respectively. Differences in qualitative variables were analyzed with the χ^2 or Fisher's exact test when a field had less than five events.

The multivariate analysis estimated the associations between receiving blood transfusions and demographic, donor-related variables, and practice patterns factors. A two-sided p-value inferior to 0.05 was considered statistically significant. Analyses were performed with IBM (Armonk, NY, USA) SPSS® Statistics 26th version.

RESULTS

Three hundred KTx were performed in our unit from January 2020 to December 2021. A total of 240 were finally included (**Figure 1**). The mean recipient age was 57±13 years, most were males 165 (69%), median baseline hemoglobin was 11.6 g/dL (11.6-12.8), most patients had anemia upon admission 205 (85.4%), and 67 (28%) had a history of cardiovascular disease. The mean age of the donors was 59.6±13 years, and 105 (44%) of them fulfilled the criteria of expanded criteria donors. Although non-significant, patients on predialysis had higher Hb levels than their counterparts on hemo- or peritoneal dialysis (13 *vs* 11.6 g/dL *vs* 11.4 g/dL, respectively, p 0.19). Other demographic and baseline data are shown in **Table I**.

Ninety-four patients (39%) received at least one blood transfusion unit during their hospital stay, with 393 PRBC units administered. The median transfusion rate was two PRBC units per patient, with a minimum of one and a maximum of eleven (**Table II**). Patients' median

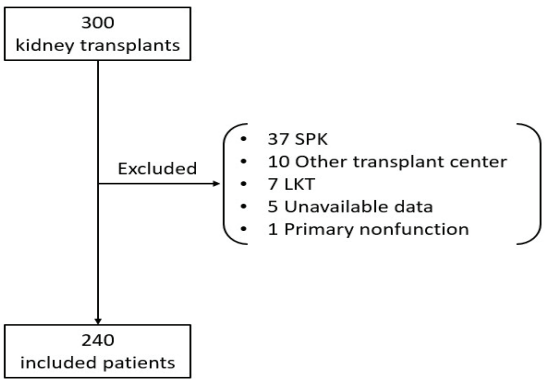

Figure 1 - Flowchart of the kidney transplant recipients included in the study
LKT: liver and kidney transplant; SPK: simultaneous pancreas and kidney transplant.

Table I - *Recipients' and donors' characteristics during kidney transplant hospitalization*

Variable	Total kidney transplant recipients No.=240	Transfused No.=94	Not transfused No.=146	p-value
	Recipient characteristics			
Age (years), mean ± SD	57±13	59.7±12.7	55.6±13.6	0.019
Male sex, No. (%)	165 (68.8)	59 (62.8)	105 (72.4)	0.116
Cardiovascular disease, No. (%)	69 (28.8)	37 (44.6)	32 (31.1)	0.058
cPRA baseline (%), median (IQR)	0 (0-51)	0 (0-66)	0 (0-47)	0.167
Anticoagulated, No. (%)	23 (9.6)	12 (12.8)	11 (7.6)	0.001
Hemoglobin baseline (g/dL), mean ± SD	12.1±8	11.1±1.9	12.7±10.1	0.050
Ferritin (ng/mL), mean ± SD	406±323	469±338	369±311	0.029
TSAT (%), median (IQR)	25.1 (11.4-38.8)	25.1 (10.4-39.9)	25.3 (11.4-39.2)	0.426
CKD stage, No. (%)				0.009
Predialysis	49 (20.42)	11 (11.7)	38 (26.2)	
Hemodialysis	160 (66.66)	73 (77.7)	86 (59.3)	
Peritoneal dialysis	31 (12.92)	10 (10.6)	21 (14.5)	
	Donor characteristics			
Donor age (years), median (IQR)	61 (53-70)	63.5 (45.5-81.5)	60 (40-80)	0.002
Donor type, No. (%)				0.013
Living donor	67 (27.92)	15 (16)	51 (34.9)	
DBD	95 (39.58)	41 (43.6)	54 (37)	
DCD 3	72 (30)	35 (37.2)	37 (25.3)	
DCD 2	7 (2.92)	3 (3.2)	4 (2.7)	
Expanded criteria, No. (%)	106 (44.17)	51 (82.3)	49 (62)	0.009
Cold ischemia time (min), median (IQR)	300 (250-894)	690 (337.5-921)	328 (89-891)	0.012
	Other factors			
Surgical reoperation, No. (%)	21 (8.75)	16 (17)	4 (2.7)	<0.001
Immunosupressive induction, No. (%)				0.673
rATG	110 (45.8)	45 (47.9)	64 (45.1)	
Basiliximab	127 (52.92)	49 (52.1)	78 (54.9)	
Immunosuppressive maintenance, No. (%)				0.392
Mycophenolic acid	125 (52.08)	52 (55.3)	72 (49.7)	
mTORi	115 (47.92)	42 (44.7)	73 (50.3)	

CKD, chronic kidney disease; cPRA, calculated panel reactive antibody; DBD, dead brain donor; DCD, donation after circulatory death; IQR, interquartile range; mTORi, mTOR inhibitors; rATG, rabbit antithymocyte globulin; TSAT, transferrin saturation.

Table II- *Anemia parameters and transfusion habits*

Variable	Results
Preoperative Hb (g/dL), median (IQR)	11.6 (11.6-12.8)
Anemia at admission, No. (%)	205 (85.4)
Total PRBC units, No.	393
PRBC units per patient, median (IQR)	2 (1-4)
PRBC prescribed as single units (%), median (IQR)	81.5 (33-100)
PRBC units prescribed with Hb <8 g/dL, No. (%)	85 (90.4)

Hb: hemoglobin; IQR: interquartile range; PRBC: packed red blood cells; TSAT: transferrin saturation.

hemoglobin was 11.1 g/dL (9.5-12.5) at baseline, 7.3 g/dL (7-7.6) at the time of transfusion, while the median hemoglobin drop from baseline to transfusion was 3.6 g/dL (2.2-5.3). There were no significant differences between the mean baseline hemoglobin and its reduction with the donor type. A longer cold ischemia time was significantly associated with the probability of transfusion (p=0.012). Twenty-one patients were reoperated due to surgical complications and were more likely to receive at least one transfusion of PRBC than their counterparts [76.2%, OR 7.23 (2.3-22.4), p<0.001]. The causes for surgical reintervention were bleeding (12, 57.14%), urinary fistulas (6, 28.57%),

incisional hernias (2, 9.5%), and graft thrombosis (1, 4.76%). Among transfused patients, nine patients (9.6%) received a PRBC with hemoglobin levels above 8 g/dL; this transfusion threshold was unrelated to the recipients' history or symptoms of cardiovascular disease.

Fourteen (6%) of patients had low TSAT upon admission, and they required significantly more PRBC when transfused (3.9 *vs* 2.7, p=0.019). Only 45 (48.4%) and 65 (73.9%) patients of those transfused received treatment with intravenous iron and ESA, respectively. However, there was no correlation between the number of PRBC transfused per patient and the administration of iron or ESA during admission.

There was no association between the type of surgery (robotic *vs* open), type of donation (living *vs* deceased), or the kidney receptor's or donor's ages with the number of PRBC units received. However, the number of PRBC administered in patients requiring surgery was associated with the need for blood transfusion (4.6 *vs* 2.7, p 0.043; OR 7.28 [2.35-22.54]). Fewer living-donor transplant recipients received blood transfusions compared to DCD and DBD (living: 22.7%, DBD: 43.2%, DCD type 3: 48.6%, DCD type 2: 42.9%, p=0.013), with a significant difference when comparing cadaveric and living donors overall [OR 1.99 (1.24-3.21)].

Those who required at least one blood transfusion had a significantly worse kidney graft function (measured by serum creatinine) and lower hemoglobin levels at discharge, than those who did not, and among this group, those with higher creatinine also required more PRBC units. Kidney replacement therapy with hemodialysis before transplantation was significantly associated with the need for blood transfusion (p=0.003). Creatinine, at discharge and six months after transplantation, was lower in non-transfused patients (2.2 *vs* 3 and 1.6 *vs* 1.9, respectively, p=0.02). Moreover, the number of PRBC administered also significantly correlated with a worse kidney graft function six months after transplantation (**Table III**). However, the latter inferential result lost significance when adjusted for the recipient and donor age and expanded criteria donors.

There were no differences between pre-transplant cPRA, prior antiplatelet or anticoagulant medications, kidney disease etiology, or cardiovascular disease history. Similarly, recipient sex was unrelated to transfusion risk, though once transfused, males received significantly more PRBC than females (3.44±2.6 *vs* 2.26±1.11, p=0.003). KTx recipients who received a blood transfusion, as well as the number of the administered PRBC, were associated with longer hospital stays (19.2±14.2 *vs* 8.4±4.9 p≤0.001) (**Table III**).

Table III - *Association between kidney transplant function, anemia, and hospitalization length with blood transfusions*

Variable	Transfused No.=94	Not transfused No.=146	p
Hospital-stay length (days) median (IQR)	17 (9-22)	7.5 (6-8)	<0.001
Creatinine at discharge (mg/dL), median (IQR)	2.29 (1.39-3.7)	1.7 (1.1-2.21)	<0.001
Creatinine 6 months post-transplant (mg/dL), median (IQR)	1.67 (1.26-2.3)	1.4 (1.13-1.77)	0.008
Hemoglobin at discharge (g/dL), median (IQR)	9.1 (8.6-10)	9.5 (9.2 -10.7)	<0.001

IQR: interquartile range.

Regarding immunological outcomes, there were 49 BPARs during follow-up. The measured cPRA levels at six months post-transplantation did not significantly differ from baseline, and the incidence of BPAR was not significantly increased in transfused patients.

DISCUSSION

In this study, we described PRBC transfusion practices and risk factors of KTx recipients. The main finding of this study is that a high percentage of KTx recipients require at least one PRBC unit transfused during the perioperative period. In addition, we found that:

1. most of these patients have anemia at the moment of transplantation;
2. a low TSAT upon admission was associated with the administration of more PRBC units;
3. surgical reintervention is associated with an increased risk of receiving a PRBC transfusion and more PRBC units, and, finally;
4. there is an association between the number of PRBC units administered and a worse kidney function six months after hospital discharge.

The incidence of patients receiving PRBC in our cohort is similar to previously reported KTx data (40%)[16,18], although the reported number of recipients who require blood transfusions varies between different centers, ranging from 18%[19] to 79.3%[20]. In contrast, the percentage of blood transfusions in other solid organ transplants is significantly greater-around 90% in liver[21], 49% in lung[22], and virtually in all heart transplant recipients[23]. Despite the wide range of transfusion incidence, most of the available data coincides with ours in that older donors and older recipients have an increased risk of severe or symptomatic anemia, as well as the latter usually have lower hemoglobin levels at the time of transplantation, which by itself increases the risk of PRBC transfusion[19].

Only 22.7% of kidney transplant recipients from living donors required a blood transfusion. This is likely due to the more prolonged cold ischemia time in deceased donors, which is responsible for initially suboptimal kidney function and a higher risk of delayed graft function[19]. Despite there may be other factors that we have not controlled for such as number of comorbidities, it seems that the kidney's capacity to generate erythropoietin in response to surgical trauma is crucial to avoiding severe or symptomatic anemia. Similarly to previously published data, we found no association between transfused patients and BPAR, development of donor-specific antibodies, or HLA sensitization[9,19,24]. This includes a recent metanalysis[25] that concludes otherwise, though by including in their analysis older populations[24] with less potent immunosuppression[26] and not only perioperative transfusion, but up to a year after transplantation[27]. The more recent studies on perioperative transfusions included in the metanalysis have the same immunological conclusion as ours[25]. Current treatment of blood products by blood banks, where white blood cells are almost entirely removed from PRBC units, significantly reducing HLA exposure, combined with modern immunosuppressive induction management, are probably responsible for this lack of risk[16-18]. Some authors state that hemoglobin levels are unreliable as they can be lower due to hemodilution in aggressive fluid resuscitation cases and higher in hemoconcentration instances when fluid resuscitation is insufficient[28]. However, in the case of KTx, false anemia due to hemodilution is unlikely. Recipients with immediate functioning grafts tend to be dehydrated due to polyuria, whereas fluids are restricted and closely controlled in those who are oliguric or have delayed graft function[29].

In our cohort, most (64.37%) of the PRBC units were prescribed as single units, with percentages similar (64%) to the improved reported values by programs where the PBM guidelines have already been introduced[30,31]. Nevertheless, the transfusion rate we observed (39%) is higher than many other surgical procedures classically associated with an increased risk for blood transfusions, such as radical cystectomy with urinary diversion (38%), open femoral fracture repair (29.5%), or open radical nephrectomy (2.6%)[32]. Thus, despite the previously shown difficulties related to patients with renal dysfunction, we firmly believe in implementing the PBM recommendation that the World Health Organization promotes to eliminate avoidable blood transfusions, given their scarcity and cost[30]. Moreover, the proposed three-pillar guideline has been successfully implemented by several surgical programs, treating patients before procedures to correct anemia if present, improving patients' fitness and tolerance to anemia, and reducing intraoperative bleeding, which further supports our belief in its effectiveness[11,28,33]. Pre-operatory anemia is the most important factor associated with blood transfusions, and its correction has been associated with a decrease in blood transfusions[6,30]. Iron deficiency, as defined in CKD patients[4,5], can be corrected by supplementing iron, as there is evidence that iron replenishment up to 15 minutes before major abdominal surgery is associated with a 60% reduction in blood transfusions[34]. The severity of anemia can also be reduced by adjusting ESA dosage to target the upper range of the recommended hemoglobin levels in CKD patients on the transplant waiting list[4,5]. Finally, the enrollment of patients on the waiting list in presurgical fitness programs can help improve their tolerance to anemia.

Another interesting finding is that KTx recipients who received more blood transfusions had a worse graft function 6 months after discharge. The causality of this association is unclear, as it may be due to better organ oxygenation in those who did not require any blood transfusion during the postoperative period, but this finding may also be explained by initially better-quality kidney grafts starting to produce endogenous erythropoietin faster and therefore have a better kidney function and higher hemoglobin levels with less blood transfusion requirements[35,36].

This study has many limitations. It is an observational study; therefore, no causal associations can be inferred. Also, data on ESA use before transplantation was unavailable, and transfusion practices were not protocolized making them variable among treating physicians. In addition, it is a single-center study, the number of included patients is limited, the follow-up time is short, and the extrapolation to other transplant units is questionable.

CONCLUSIONS

In conclusion, PBM guidelines should be applied to patients on the KTx waiting list and those scheduled to receive a transplant from a living donor. An ordered program will aid physicians in using blood products more efficiently and avoid potentially severe adverse effects.

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AUTHORS' CONTRIBUTIONS

FD, NE, BB, and DR-E conceived the study. MB also contributed to its conception. DR-E, AR, EC-P, BT, RM, and JC acquired the data. JJB performed the statistical analysis. DR-E, and JJB drafted and revised the paper. All Authors have revised the drafts and approved the final one.

ETHICAL CONSIDERATION

The Ethics Committee approved the protocol (HCB/2023/0172). Data collection has followed Regulation (EU) 2016/679 (General Data Protection Regulation), its subordinate national and regional laws, and the Declaration of Helsinki principles. The data are available upon reasonable request from the corresponding author. The clinical and research activities reported are consistent with the Principles of the Declaration of Istanbul outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

DISCLOSURE OF CONFLICTS OF INTEREST

MB received honoraria from Octhapharma and CSL Vifor. AC received honoraria from CSL Vifor, Astellas and GSK. The Authors have no conflicts of interest to declare.

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